

Clinical, Genetic and Magnetic Resonance Findings in an Infant Affected by Propionic Acidemia

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Abstract

Purpose: Report an infant patient of propionic acidemia with two mutations in the PCCB gene identified by genetic diagnosis.

Method: The patient received gas chromatograph-mass spectrometry and liquid chromatography-tandem mass spectrometry examination, electroencephalogram (EEG), MRI and genetic tests. He was diagnosed as propionic acidemia.

Results: The boy was admitted in hospital at 8 months of age because of dyspnea, depression, seizures. The EEG was abnormal. MRI showed abnormal signal in bilateral basal ganglia. The gas chromatograph-mass spectrometry and liquid chromatography-tandem mass spectrometry showed glycine, 3-hydroxypropionate, tiglylglycine, methylcitric acid, propionyl carnitine increased. The genetic tests demonstrated that the patient carried the mutations c.337C>T and c.1127 G>T in the PCCB gene. The mutations were inherited from his parents individually.

Conclusion: The patient carried two compound heterozygous mutations in PCCB gene which resulted in propionic acidemia. The metabolomics screen and brain MRI also played significant roles in the diagnosis of propionic acidemia.

Keywords: Propionic acidemia; Gene mutation; PCCB; MRI; Blood metabolomics screen; Organic acidemia

Case Report

Propionic acidemia (PPA) is an organic acidemia that can lead to metabolic acidosis and death. It is an autosomal recessive inherited disease caused by a defect of the mitochondrial protein propionyl-CoA carboxylase (PCC). PCC is a multimeric protein involved in the metabolism of branched-chain amino acids, odd-numbered chain length fatty acids and cholesterol. The enzyme consists of two non-identical subunits, α and β , encoded by the PCCA and PCCB genes, respectively. To date, a highly heterogeneous mutation spectrum in the PCCA gene has been reported, while a limited number of mutations accounts for most of the mutant alleles for the PCCB gene [1,2]. Patients with PPA show metabolic acidosis, hyperammonemia and hyperglycemia. There is a wide spectrum of clinical manifestations of propionic acidemia, including drowsiness, mental retardation, muscular hypotonia, vomiting, respiratory problems and so on.

Here we report an infant with propionic acidemia, who was definitely diagnosed by genetic test. The patient's disease was resulted from the compound heterozygous mutations in the PCCB gene.

The patient was admitted to the pediatric intensive care unit (PICU) at 8 months of age because of dyspnea, depression, and repetitive epileptic seizures. The patient had psychomotor retardation before. There was no family history of metabolic disorders.

Routine blood exam showed peripheral hypocytosis. Blood ammonia level was obviously increased to 142.6 $\mu\text{mol/L}$. The EEG was abnormal which showed diffuse slow wave of the background and multifocal spike or sharp waves were detected. Auditory evoked potentials showed bilateral central auditory nerve's damage. MRI scan showed bilateral and symmetrical hyperintensity of basal ganglia on T2-

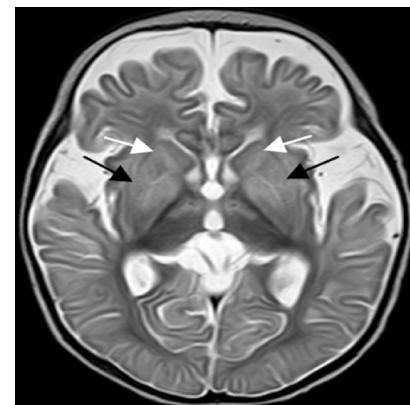


Figure 1: Brain MR images of the baby boy at the age of 8 months with propionic acidemia. T2-weighted cranial magnetic resonance image showed bilateral symmetrical increased signal in the basal ganglia, including lentiform nucleus (black arrows), the head of caudate nucleus (white arrows).

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weighted images (Figure 1) and decreased signal in T1-weighted images (Figure 2). The diffuse cortical atrophy and enlarged subarachnoid space were demonstrated. The diffusional weighted images (DWI) showed abnormal signal in the basal ganglia and the genu of the corpus callosum (Figure 3). The urine metabolic test showed glycine, 3-hydroxypropionate, tiglylglycine, methylcitric acid increased. The blood metabolic screen showed phenylalanine (Phe) (was 99.509), glycine (Gly)/alanine (Ala) (was 3.234), Phe/tyrosine (Tyr) (was 2.106), C3 (was 46.997), C5DC (was 0.096), C0/C16 (was 91.477), C3/C0 (was 2.764), C3/C2 (was 5.357), C3/C16 (was 252.865), C5DC/C16 (was 0.371), C8/C16 (was 0.932) increased; leucine (Leu)/Phe (was 0.671), valine (Val)/Phe (was 1.231), C4/C3 (was 0.006) decreased. Combined with the results of blood and urine metabolic screening, the patient was suspected to have PPA.

The patient's disease was resulted from the compound heterozygous

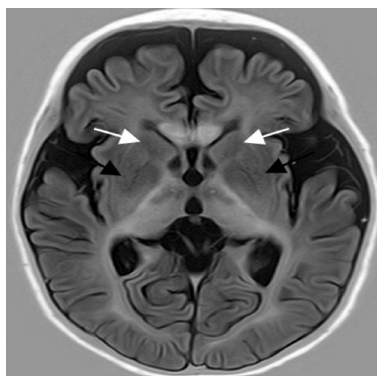


Figure 2: T1-weighted cranial magnetic resonance image showed bilateral symmetrical decreased signal in the basal ganglia, including lentiform nucleus (black arrows) and the head of caudate nucleus (white arrows). The enlarged subarachnoid space and lateral fissures suggested the cerebral atrophy.

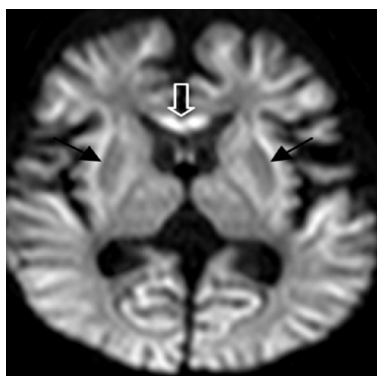


Figure 3: Diffusion-weighted image showed abnormal signal in the lentiform nucleus (black arrows) and the genu of the corpus callosum (empty arrow).

mutations c.337C>T and c.1127G>T in the PCCB gene (Table 1). The parents carried the mutations identified in the PCCB gene (Table 2). The mutation named c.337C>T inherited from her father was a nonsense mutation. The mutation named c.1127G>T was inherited from her mother. The compound mutations can cause the amino acid change.

Early effective fluid infusion, protecting of important organs, proper use of arginine to reduce the blood ammonia correction of electrolyte imbalance and acidosis effective antiepileptic drugs were helpful for saving life. Also, the patient received low protein and high calorie diet. After the prompt treatment, the epileptic seizures were controlled, and the serum biochemical parameters returned to normal. Blood ammonia level was decreased to 41.6 umol/L.

Discussion

Propionic acidemia is a rare genetic deficiency of the essential mitochondrial enzyme propionyl-CoA carboxylase, which leads to the accumulation of propionyl-CoA and metabolic by-products, including methylcitrate, 3-hydroxypropionate, tiglylglycine, and propionyl glycine in the mitochondria. These accumulations of by-products are neurotoxic which can cause neurologic damage. The clinical diagnosis is often delayed because of the insidious onset of symptoms. The metabolic disorder can lead to serious brain damage which may cause repetitive epileptic seizures and psychomotor retardation. Though the pathophysiological mechanisms are unknown, MR images can firstly detect the damage of the basal ganglia, which is the high metabolic rates area. The typical sign of our case was the abnormal signal in the globus pallidus, putamen, and head of the caudate nucleus. Also, the hypomyelination, white-matter atrophy could be revealed in the same time [3]. Magnetic resonance spectroscopy and diffusion weighted imaging may indicate some inherited metabolic diseases firstly and observe the changes after onset of therapy [4-6]. The MRI of the boy showed diffused cerebral atrophy due to delayed diagnosis and therapy of propionic acidemia which may suggest poor prognosis.

Conclusion

Both urine, blood metabolic tests and MRI examination have significant clinic value in diagnosis of Propionic acidemia. MRI examination can help to find the lesion site, but diagnosis and differential diagnosis should be made with the combination of metabolic screening, enzymological examinations and gene detection.

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Gene location	Chromosomal location	Nucleotide changes	Amino acid changes	rs code	Heterozygosis/homozygosis
PCCB	chr3:135975430	c.337C>T(E3)	p.113R>X	rs186031457	Heterozygosis
	chr3:136045681	c.1127G>T(E11)	p.376R>L	rs142982097	Heterozygosis

Table 1: Information of the proband's mutations identified in the PCCB gene.

No.	Gene location	Nucleotide changes	Amino acid changes	rs code	Heterozygosis/homozygosis
1*	PCCB	c.337C>T	p.113X	rs186031457	Heterozygosis
2*	PCCB	c.1127G>T	p.376L	rs142982097	Heterozygosis

Note: 1*: The proband's father; 2*: The proband's mother

Table 2: Information of the parents' mutations identified in the PCCB gene.

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