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Case Report

A case report of 3-hydroxybutyric aciduria with cerebellar ataxia

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Abstract: Aim: To report a case of 3-hydroxybutyric aciduria with cerebellar ataxia. Methods: Collect and review a case of 3-hydroxybutyric aciduria with cerebellar ataxia as initial manifestations. Results: The case was an adult female patient, who was examined and found signs of cerebellar ataxia and high levels of 3-hydroxybutyric acid, acetylacetate, 2-keto-3-methypentanoate, and 2-keto-isocaproate in acid. Conclusion The patient was diagnosed 3-hydroxybutyric aciduria with cerebellar ataxia.

Keywords: Ataxia, organic aciduria, 3-hydroxybutyric aciduria

Introduction

The disorder of organic acid metabolism is a rare disease and may be manifested by a variety of neurological-psychiatric symptoms as well as gastrointestinal conditions, metabolic disorder and other symptoms [1, 2]. With the clinical application of gas chromatography/mass spectrometry analysis, this disease has become increasingly known. In this paper, the abnormal organic acid metabolism and clinical manifestations were reported in a patient with 3-hydroxybutyric aciduria accompanied with cerebellar ataxia.

Clinical data

The case was a female patient aged 48 years with the admission number 422 ×××. She was admitted to the Department of Neurology at the Affiliated People's Hospital of Jiangsu University on March 24, 2014 due to "progressive unsteady gait and slurred speech for six months". This study was conducted in accordance with the declaration of Helsinki.

This study was conducted with approval from the Ethics Committee of the Affiliated People's Hospital of Jiangsu University. Written informed consent was obtained from all participants.

History of present illness

The patient reported an unsteady and slightly swaying gait from October, 2013, but the condition did not affect her walk. It was accompanied by bad pronunciation for some individual words without significant impact on her communication. A shaking walk and widened horizontal spacing between the feet were reported early in January, 2014 and affected her daily life, accompanied with a slowed speech rate with ambiguous pronunciation for most words. In March, 2014, the patient often fell during walks and needed to be supported by another person's hand; her family could not fully understand her words in most cases, which influenced communication. During the medical course, there was no dizziness, fever, drinking cough, difficulty swallowing, side limb numbness, shake in hands and head, meat twitching or muscle atrophy. The patient's diet and sleep were fair with normal feces and urine and no weight loss.

Past history and personal history

No special past history or history of contact to toxicants and radioactive substances were reported.

Family history

There was no family history of genetic diseases and similar diseases.

Physical examination

Body temperature 37.1°C, pulse 80 beats/min, respiration 18 times/times, blood pressure

120/80 mmHg (1 mmHg=0.133 kPa). No skin and mucous membrane abnormalities were reported, and superficial lymph nodes were not palpable. There were no abnormalities in her heart and lung auscultation, the abdomen was plain and soft without liver and spleen enlargement or lower extremity edema.

Neurological examination

The patient showed clear spirit, slurred speech, appropriate answers to questions and normal computing power. The two pupils were equal and round and sensitive to light with fair eyeball movements and without nystagmus and K-F ring. Bilateral nasolabial folds were symmetrical without abnormal facial sensation, showing normal audition and a middle result in Weber test. The soft palate elevation was powerful and the gag reflex was normal, with a centered uvula and lolling and without tongue muscle atrophy and tremor. The neck was soft without resistance; the limb muscle strength was Grade 5 without muscle atrophy, muscle bundle fibrillation; the muscle tension was not high with a slight knee hyperreflexia in the lower limbs. Pathological reflex was not found in both lower limbs. The result of left finger-to-nose test was positive (+), so was heel-knee-tibia test (+), ataxic gait and Romberg's sign (+); no abnormalities were reported in position sense, vibration sense or superficial sense; the meningeal irritation sign was negative (-).

Auxiliary examination

Blood routine

WBC, 5.2×109/L (reference value: 4.0~10.0×109/L); neutrophil count, 2.4×109/L (reference value: 1.6~7.5×109/L); neutrophils, 0.57 (reference value: 0.40~0.75); eosinophil count, 0.1×109/L (reference value: 0~0.5×109/L); eosinophils, 0.01 (reference value: 0.01~0.05); basophil count, 0×109/L (reference value: 0~0.01×109/L); basophils, 0 (reference value: 0~0.01); lymphocyte count, 1.5×109/L (reference value: 0.8~4.0×109/L); lymphocytes, 0.36 (reference value: 0.20~0.40); monocyte count, 0.2×109/L (reference value: 0.1~1.0×109/L); monocytes, 0.05 (reference value: 0.03~0.10). RBC, 4.28×1012/L (reference value: 3.55~5.55×1012/L); hemoglobin, 142 g·L-1 (reference value: 110~160 g·L-1); HCT, 35.5% (reference value: 35.0%~50.0%); MCV, 88.8 fL (reference value: 82.0~95.0 fL); MCH, 29.4 pg (reference value: 27.0~35.0 pg); MCHC, 331 g·L-1 (reference value: 320~360 g·L-1). MPV, 10.0 fL (reference value: 6.8~12.0 fL); PLT, 158×109/L (reference value: 100~300×109/L).

Urine routine

Yellow (normal: light yellow), clear (normal: clear). Creatinine, 0.50 mg·dL-1 (reference value: > 0 mg·dL-1); urinary cast, 0.27 (reference value: 0~2.40); pathological cast, 0/μL (normal: 0/μL); small round cells, 0/μL (normal: 0/μL); red blood cells, 10.0/μL (reference value: 0~18/μL); leucocytes, 4.4/μL (reference value: 0~23.0/μL); epithelial cells, 7/HP (reference value: 0~46/HP); occult blood (-); UBG (-); urorhodin (-); ketone body (-); protein (-); nitrite (-); glucose (-); leukocyte qualitation (-); pH 6.00 (reference value: 6.00~8.00); specific gravity, 1.009 (reference value: 1.005~1.030).

Stool routine

Yellow, soft, no blood, no mucus. Red blood cells 0/HP; white blood cells, 0/HP; phagocytes, 0/HP; no fat globules. No food residue. No ascaris eggs, hookworm eggs, whipworm eggs, tapeworm eggs, or schistosome eggs. Occult blood test (-).

Blood biochemistry

Total bilirubin, 10.80 μmol·L-1 (reference value: 2.10~17.30 μmol·L-1); direct bilirubin, 3.80 μmol·L-1 (reference value: 0~5.80 μmol·L-1); indirect bilirubin, 7.00 μmol·L-1 (reference value: 0~15.00 μmol·L-1); DBil/TBil, 0.35(reference value: 0~0.60); total protein, 63.90 g·L-1 (reference value: 60.0~80.0 g·L-1); albumin, 40.40 g·L-1 (reference value: 35.0~55.0 g·L-1); globulin, 23.5 g·L-1 (reference value: 25.0~36.0 g·L-1); A/G, 1.72(reference value: 1.00~2.50); AST, 22 U·L-1 (reference value: 0~40 U·L-1); ALT, 17 U·L-1 (reference value: 0~40 U·L-1); ALT/AST, 0.77; ALP 59 U·L-1 (reference value: 40~135 U·L-1); γ-GT, 38U·L-1 (reference value: 5~40 U·L-1); TBA, 2.40 μmol·L-1 (reference value: 0~18 μmol·L-1); prealbumin, 286 mg·L-1 (reference value: 200~450 mg·L-1); ADA, 3 U·L-1 (reference value: 0~20 U·L-1); BUN, 3.70 mmol·L-1 (reference value:

2.10~7.50 mmol·L-1); creatinine, 50 μmol·L-1 (reference value: 35~135 μmol·L-1); glucose, 4.41 mmol·L-1 (reference value: 3.80~6.10 mmol·L-1); uric acid, 246 μmol·L-1 (reference value: 145~428 μmol·L-1); triglyceride, 0.68 mmol·L-1 (reference value: 0.23~1.70 mmol·L-1); cholesterol, 4.56 mmol·L-1 (reference value: 2.80~5.46 mmol·L-1); HDL, 1.13 mmol·L-1 (reference value: 0.7~2.3 mmol·L-1); LDL, 2.42 mmol·L-1 (reference value: 0.2~3.1 mmol·L-1); apolipoprotein-A1, 1.1 g·L-1 (reference value: 1~1.6 g·L-1); apolipoprotein-B, 0.94 g·L-1 (reference value: 0.6~1.1 g·L-1); potassium, 4.22 mmol·L-1 (reference value: 3.5~5.1 mmol·L-1); sodium, 140.5 mmol·L-1 (reference value: 135~145 mmol·L-1); chlorine, 97.4 mmol·L-1 (reference value: 95~106 mmol·L-1); calcium, 2.22 mmol·L-1 (reference value: 2.20~2.75 mmol·L-1); phosphorus, 1.04 mmol·L-1 (reference value: 0.96~2.10 mmol·L-1); CO2CP, 26.2 mmol·L-1 (reference value: 23~31 mmol·L-1); LDH, 210 U·L-1 (reference value: 110~220 U·L-1); serum amylase, 90 U·L-1 (reference value: 20~220 U·L-1); creatine kinase, 60 U·L-1 (reference value: 10~110 U·L-1).

Coagulation function

Prothrombin time, 12.9 s (reference value: 9~13.3 s); international normalized ratio, 0.9 INR (reference value: 0.75~1.10 INR); APTT, 31 s (reference value: 20~40 s); fibrinogen, 4.12 g·L-1 (reference value: 2~4 g·L-1); thrombin time, 15.7 s (reference value: 14~21 s); D-dimer, 0.12 mg·L-1 (reference value: 0.10~0.55 mg·L-1). Folic acid, 20 ng·mL-1 (reference value: > 2.33 ng·mL-1); Vitamin B12, 210 pg·mL-1 (reference value: 180~914 pg·mL-1).

Tumor markers

CA125, 27.72 U·mL-1 (reference value: 0~35 U·mL-1); CA199, 16.74 U·mL-1 (reference value: 0~40 U·mL-1); CA153, 28.66 U·mL-1 (reference value: 0~30 U·mL-1); CA242, 6.07 U·mL-1 (reference value: 0~25 U·mL-1); CA50, 11.32 U·mL-1 (reference value: 0~20 U·mL-1); AFP, 1.43 ng·mL-1 (reference value: 0~20 ng·mL-1); CEA, 0.72 ng·mL-1 (reference value: 0~15 ng·mL-1).

Lactate levels

Lactate of resting state, 1.60 mmol·L-1; lactate after exercise, 1.51 mmol·L-1 (reference value: 1.2~2.1 mmol·L-1). Ceruloplasmin, 0.22 g·L-1 (reference value: 0.2~0.6 g·L-1).

Thyroid function

Free T_3, 5.38 pmol·L-1 (reference value: 3.1~6.0 pmol·L-1); Free T4, 13.11 pmol·L-1 (reference value: 7.86~17.41 pmol·L-1); total T_3, 1.83 nmol·L-1 (reference value: 1.34~2.73 nmol·L-1); total T4, 80.28 nmol·L-1 (reference value: 78.38~157.40 nmol·L-1); TSH, 1.11 μU·mL-1 (reference value: 78.38~157.40 μU·mL-1); TPOA, 1.1 U·mL-1 (reference value: 0~9 U·mL-1); TGA, 0.01 U·mL-1 (reference value: 0~4 U·mL-1); thyroglobulin, 3.28 ng·mL-1 (reference value: 1.15~131.00 ng·mL-1).

ECG

In normal range.

Imaging examination

① UCG: Left ventricle diastole dysfunction. ② Liver, gallbladder, pancreas and spleen B ultrasound: pancreas and spleen. ③ Brain MRI: (2013-11-27) Cerebellar atrophy, and lesions in pons and the right brachium pons; (2014-03-28) cerebellar atrophy, lesions in pons and bilateral brachia pons suggest progress compared to the conditions on 2013-11-27 without enhancement in contrast-enhanced MRI (**Figure 1**).

ATXN3 gene analysis

Gene analysis was detected by Molecular Genetics Lab, Institute of Neurology, Fudan University. The repetitions of ATXN3 gene exon 10 (CAG)n were < 44 times, and no abnormalities were indicated.

Peripheral SEM

Anisocytosis under the electron microscope with diameters of 5~7 μm, acanthocytes (-). Electron microscopic observation did not conform to acanthocytosis (Electron Microscopy Room, Shanghai Medical College of Fudan University).

Tandem mass spectrometry

No obvious abnormalities were reported in the detected amino acids and acyl carnitine (Lab of Endocrinology & Genetic and Metabolic Diseases, Shanghai Institute for Pediatric Research, Xin Hua Hospital Affiliated to Shanghai Jiao Tong University School of Medicine).

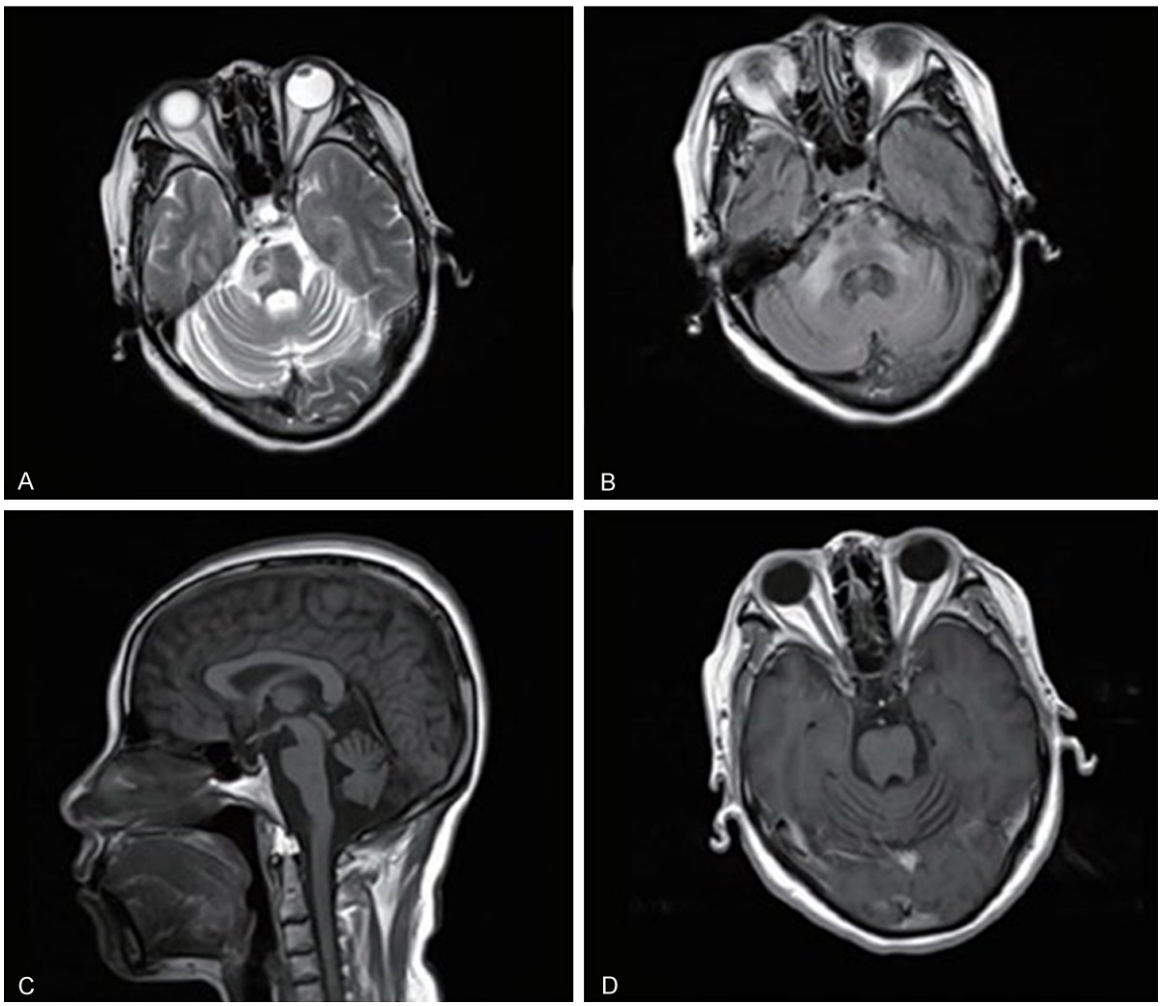

Figure 1. A: MRI-T2 weigh showed mixed signals in right pons; B: MRI-T2 weight showed signal in right brachium pons; C: Showed cerebellum atrophy; D: Contrast-enhanced MRI showed no enhancement.

Leukocyte lysosomal enzymatic analysis

β-galactosidase, 262.69 nmol·h^{-1}·mg^{-1} protein (reference value: 78.39~441.44 nmol·h^{-1}·mg^{-1} protein); ARSA, 169.1 nmol·17h^{-1}·mg^{-1} protein (reference value: 39.18~274.53 nmol·17h^{-1}·mg^{-1} protein); β-hexosaminidase, 1385.65 nmol·h^{-1}·mg^{-1} protein plasma (reference value: < 6138 nmol·h^{-1}·mg^{-1} protein plasma).

Urine GC/MS analysis

Significantly increased 3-hydroxybutyric acid, acetoacetic acid, 2-keto-3-methypentanoate, 2-keto-isocaproate-ox (**Table 1**).

Discussion

The disorder of organic acid metabolism may be caused by congenital accumulation of amino acid intermediate metabolites or metabolic disorders. Moreover, Vitamin metabolites, oxidative metabolites, tricarboxylic acid cycle metabolites, GABA metabolites and other metabolites may lead to more than 50 kinds of organic acid disease. It is more common in newborns and children, whereas it is rare for its onset in adulthood [1].

Hoffmann et al. [2] believe that the neurological manifestations of the disorder of organic acid metabolism mainly involve acute and sub-acute metabolic encephalopathy, chronic progressive psychomotor dysplasia, progressive cerebellar ataxia, muscle hypotonia and dystonia, tetraplegia or cerebral palsy, myopathy and (or) cardiomyopathy, megalencephaly, metabolic stroke, and epilepsy, etc [1, 2].

Table 1. GC/MS results of the urine in the case

Number	Test item	Result	Normal average	Normal low value	Normal high value	Result (Average)	Result (High value)
11	3-hydroxybutyric acid	406.6[1]	0.7	0	3.7	580.86	109.89
24	Acetoacetate	170.81[1]	0	0	0		
29	2-keto-3-methypentanoate	4.11[1]	0	0	0		
35	2-keto-isocaproate-ox	3.67[1]	0	0	0		

Notes: [1]Abnormal.

3-hydroxybutyric aciduria is a rare disease triggered by multiple semialdehyde dehydrogenase deficiencies. Its main clinical manifestations include atelencephalia, epilepsy, congenital malformations, and relapsed ketoacidosis [1, 3, 4].

Gibson et al. [5] found malonic semialdehyde dehydrogenase, methylmalonic semialdehyde dehydrogenase and ethylmalonic semi-aldehyde dehydrogenase deficiencies.

3-hydroxybutyric aciduria may be accompanied with multiple cerebral neurological congenital malformations, such as cerebral agenesis, microcephaly, toe (finger) flexion deformity, limb muscle hypotonia or infantile spasms, slow physical growth and development [3]. Boulat et al. [3] reported the case of a 2-year-old child who exhibited 15 minutes of upper extremity tonic-clonic seizures after vomiting, followed by lethargy. Hypoglycemia (3.4 $mmol \cdot L^{-1}$) was found, accompanied with ketosis and metabolic acidosis. The pneumonia was Grade 1. Normal conditions were restored on the follow-up after 3 months. However, the urine organic acids were abnormally increased, with a 3-hydroxybutyric acid level of > 11000 (reference value: 0~6), 3-hydroxypropionate of 1358 (reference value: 20~141) and 3-hydroxyisobutyrate of 10835 (reference value: 0~30), where the concentration unit was mmol/mol creatinine.

The incomplete metabolism of fatty acid in mitochondria produces ketone bodies, β-hydroxybutyric acid (also known as 3-hydroxybutyrate) and acetoacetate [6, 7]. When transferred by monocarboxylate transporter 1, the ketone bodies will travel through the blood-brain barrier and be metabolized into acetyl coenzyme A. Ketone bodies can also be the source of brain energy. For neonates and premature children, intracerebral ketone bodies can be utilized. In an experiment conducted upon newborn rats, 20% of the ketone bodies produced by the metabolism were used for intracerebral energy metabolism [8].

In the culture of hippocampal neurons, β-hydroxybutyrate protects hippocampal neurons from toxicity and damage caused by β-amyloid proteins (β-amyloid$_{1-42}$, Aβ$_{1-42}$) [6].

Reger et al. [9] indicate that the enhancement of blood β-hydroxybutyrate may improve the cognitive function in patients with amnestic mild cognitive impairment (MCI) and Alzheimer's disease (AD). According to the double-blind placebo-controlled trial (15 cases of AD patients, including 9 cases of Apoε4^{+}, 5 cases of MCI), where the oral medium chain triglyceride (MCT) had the trade name of Neo Bee 895(Stepan Inc)], and the placebo was long-chain triglyceride, the blood β-hydroxybutyrate of patients from the oral MCT experimental group achieved its peak level after 90 minutes (P=0.007). Alzeimer's Disease Assessment Scale Cognitive Subscale ADAS-cog was used to determine AD before treatment, and the cognitive function of 6 ApoEε 4^{-} patients (40%) was improved significantly (F=6.36, P=0.04). No differences in cognitive function were reported in MCI patients [6].

The study by Gilbert et al. [7] reported that the ketogenic diet of epilepsy patients during the medical course was comprised of high fat, moderate proteins and low carbohydrates. It can be used for the treatment of hunger-induced epilepsy or uncontrollable pediatric epilepsy. After 6 months of treatment with a ketogenic diet in 54 cases of epilepsy children, the control of epileptic seizures was associated with blood β-hydroxybutyrate level. Of the 54 patients whose β-hydroxybutyrate level appeared to be > 4 $mmol \cdot L^{-1}$ (< 5 $mmol \cdot L^{-1}$) during the follow-up for 3 to 6 months, the epileptic seizures of 42 patients were controlled to varying degrees. Eighty-two percent of patients

achieved the epileptic seizure control rate > 50%; 62% of them achieved the control rate of 90%; 43% achieved a control rate of 100%. Blood β-hydroxybutyrate levels were correlated with epileptic seizure control rates (Fisher's exact *p* values, *P*=0.039).

Because organic acid can be excreted in urine, relevant inherited metabolic diseases can be diagnosed by detecting the level of organic acid in urine. This method was firstly applied to clinical practice by K-Tanaka in 1966 [10]. As an extensive application of gas chromatography-mass spectrometry (GC-MS), it has been proven to be a reliable method for detecting organic acid [11]. However, there is no effective therapeutic method for the majority of organic acid disorders, so the treatment prognosis before the appearance of a neurological symptom is better, and for a patient highly likely to suffer from organic aciduria, dietary restriction, nutrition and energy supply, acidosis correction, L-carnitine and Vitamin B replenish, blood ammonia reduction with arginine etc. should be carried out [12]. A curative effect for a small part of diseases can be obtained by means of treatment; for example, Vitamin B12 has a significant effect on VB12-effective-type methylmalonic academia, and biotin has dramatic effectiveness on holocarboxylase synthetase deficiency [13].

The case in this study was a 48-year-old female with the main manifestations of progressive cerebellar ataxia within six months and absence of a family history. This case conformed to neither the clinical manifestations of such persistent and slowly progressive cerebellar ataxia among adults (such as the clinical manifestations of autosomal dominant hereditary cerebellar ataxia Type I, II, or III, etc.) nor the slowly progressive course of sporadic late-onset cerebellar ataxia. As a result, laboratory examination showed significantly increased 3-hydroxybutyrate, acetoacetate and other organic acids in the urine.

Further experiments were not performed due to the difficult conclusion considering increased organic acids like 3-hydroxybutyric acid were found in urine and accompanied the cerebellar damage. Combined with literature, it was speculated that the abnormal accumulation of organic acids including 3-hydroxybutyric acid and acetoacetic acid in vivo and in the brain might be caused by the lipodystrophy in mitochondria of the patient's cerebral and body cells or multiple semialdehyde enzyme deficiencies. Excess 3-hydroxybutyric acid will not protect nerve cells or be involved in energy metabolism of brain cells but, on the contrary, instead damage mitochondria or brain cells. Cerebellar cell damage and cerebellar atrophy then induced cerebellar ataxia.

Disclosure of conflict of interest

None.

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