CASE REPORT

Unusual presentation of two Chinese phenylketonuria sisters who were misdiagnosed for years

Xiaomei Liu, Hui Guo, Mahesh Dahal, Bingyin Shi

First Affiliated Hospital of Xi'an Jiaotong University Health Science Center, Xi'an, Shaanxi, China

Correspondence to
Professor Bingyin Shi,
shibingy@126.com

SUMMARY

Significant developmental delay was first noticed when both sisters were in their third year of life. However, no biochemical disorders were found through the routine biochemical tests, including liver and kidney function, lipoprotein, urine and blood cell count analysis. Progressively, both sisters exhibited odd behaviour, accompanied by personality changes and altered sleep rhythm and then were diagnosed as attention deficit hyperactivity disorder. In the eighth year, the younger sister began to take risperidone due to a presumed psychiatric disorder. Four months before attending our hospital, both sisters were diagnosed by MRI as having hereditary leukodystrophy. Nerve-nurturing treatment was tried, but without good outcome. They were then referred to our hospital for further consultation. After systematic examinations, it was confirmed that both the sisters were suffering from phenylketonuria. The symptoms were alleviated after dietary restriction of phenylalanine and symptomatic treatment.

BACKGROUND

It is well known that phenylketonuria (PKU) is one of the most common inborn errors of metabolism.¹ It is caused by dysfunction of the liver enzyme phenylalanine hydroxylase (PAH) or the enzymes related to tetrahydrobiopterin (BH4), leading to the amassing of phenylalanine in the blood, which causes damage to the brain.²⁻³ There are at least three striking redeemable distinctions of PKU: the metabolic disorder can be cured; diet regulation is the only means to control the disorder; and the disorder can be detected by newborn screening.

In this case report, we described two sisters with phenylketonuria with unusual presentation who were misdiagnosed for years. If the diagnosis had been made at an early stage of life, the damage to the newborn brain would have been avoided. PKU should be considered in patients with abnormal signal intensity in the white matter on brain MRI. Most importantly, screening tests should be implemented, which can prevent a delay in diagnosis of the disorder and subsequent irreparable brain damage.

CASE PRESENTATION

The reported cases were two Han Chinese patients born to non-consanguineous parents, who also have another two healthy girls. The birth history for both the sisters included full-term pregnancy with normal delivery, and they were breast-fed and given a normal infant diet. The family history was unremarkable for any related diseases.

The parents noticed a pronounced developmental delay and slow response, when the girls were about 3 years old. They were examined in the local hospital, with no significant positive findings. In the elder sister, the symptoms worsened, gradually causing joint pain and hindering gait coordination. The younger sister's condition was more serious; it manifested with obstinacy, grumpiness, aggression, change in character and paranoia. She refused to take food and change clothes, had sleep problems (nightmares), and had shortness of breath. Both the sisters did not have a history of convulsions, dizziness, headache, nausea, vomiting and changes in skin or hair colour, or urinary odour. Accompanied by their parents, the sisters sought help from many hospitals but with no positive results on routine tests. Six years later, the sisters had no alternative but to be treated for 'epilepsy' or 'hyperactivity behaviour'. They had to drop out from school. After that, the younger sister was suspected as having schizophrenia and was placed on risperidone 1 mg and trihexane 2 mg, once daily. Because of little improvement of her symptoms, her parents increased her dose of risperidone to 1.5 mg, twice daily. The elder sister did not receive any treatment during that period. In April 2011, both the sisters underwent MRI of the brain. MRI of the elder sister showed moderate-sized areas of hyperintensity, bilaterally in the parieto-occipital periventricular white matter (figure 1). In the MRI of younger sister, there were similar small areas of hyperintensity in the same regions (figure 2). At the same time, an MR angiography of the brain was performed for the younger sister and no abnormality was found. Based on these findings the two sisters had been diagnosed as having hereditary leukodystrophy and were treated with neurotrophic drugs and vitamins, but with sub-optimal outcomes.

Then they came to our hospital. The elder sister was 12 years old, 159 cm in height, and 38 kg in weight, expressionless and unresponsive to stimuli. The younger sister was 10 years old, 126 cm in height, and 35 kg in weight, obstinate, grumpy and uncooperative, with a fearful expression. Both the sisters had normal muscle tone and tendon reflexes, normal hair and skin colour, and their urines were without any peculiar odour. The remainder of the physical examination, including physical examination of the heart, chest, abdomen, external genital organs, etc, was unremarkable. Routine blood, urine and stool studies were normal. Liver function tests, kidney function tests, thyroid studies, electrolyte panel and lipoprotein tests were all within normal limits. ECG, abdominal ultrasound and X-ray of the chest showed no abnormalities.

To cite: Liu X, Guo H, Dahal M, et al. *BMJ Case Rep* Published online: [please include Day Month Year] doi:10.1136/bcr-2013-010270

Figure 1 MRI scan (T1-weighted) showing moderate-sized areas of hyperintensity bilaterally in the parieto-occipital periventricular white matter.

Sleeping EEGs showed mild-to-moderate abnormalities (a little unusual paroxysmal rhythm with middle–high amplitude in the frontal hemisphere). Ferric chloride test was positive, and the Matsumoto Institute of Life Science (MILS) international test showed that the phenylalanine in the urine exceeded the normal concentration range. The urine catecholamine and blood phenylalanine concentration (performed with MILS tandem mass spectrometry) was abnormally high, while the serum adrenocorticotrophic hormone (ACTH) and blood tyrosine concentration (performed with MILS tandem mass spectrometry) was normal (table 1). After treatment with strict dietary restriction of phenylalanine for 20 days, the characteristic pattern of urinary pterins and the activity of dihydropteridine reductase (DHR) in the red blood cells of the younger sister were both normal, while the elder sister did not undergo above tests due to the lack of a valid specimen.

DIFFERENTIAL DIAGNOSIS

Attention deficit hyperactivity disorder, psychiatric disorder, hereditary leukodystrophy, PKU.

Figure 2 MRI scan (T2 fluid-attenuated inversion recovery) showing areas of hyperintensity bilaterally in the parieto-occipital periventricular white matter.

Table 1 Laboratory findings of the two sisters

Laboratory items	Elder sister	Younger sister	Reference range
Serum ACTH (pg/mL)	14.19	39.76	5.00–60.00
Urine catecholamine (nmol/24 h)	13.29	28.37	94.50–238.30
Concentration of blood phenylalanine (μmol/L)	543.07	740.10	20.00–63.20
Concentration of blood tyrosine (μmol/L)	32.57	35.00	8.00–68.50

ACTH, adrenocorticotrophic hormone.

TREATMENT

The diagnosis was confirmed as PKU and the patients were placed on a dietary restriction of phenylalanine.

OUTCOME AND FOLLOW-UP

Seven months after being discharged from the hospital, the elder sister gradually walked with a steady gait, and her joint discomfort was reduced significantly. Her menstrual cycle became regular. She was to return to class in September 2011, 1 year after dropping out from school, resuming her studies in her primary school at grade 5. The younger sister started to be receptive to advice and cooperated with the dietary treatment. She gradually showed willingness to be clean and tidy, and her paranoia was improving. However, there was no improvement in her aggressive behaviour, which prevented her from rejoining school. Both of the sisters did not suffer from other related illnesses after the initiation of treatments.

DISCUSSION

PKU is one of the few curable inborn errors of metabolism. The critical point is early diagnosis. PKU can be detected by newborn screening. It was reported that of 19 million newborns screened from 1985 to 2007 in China, 1638 were identified as having PKU, giving a prevalence of 1 in 11 572.⁴ In China, newborn screening was started in Shanghai in October 1981. Presently, almost all provinces of China have launched newborn screening programmes for PKU.^{4–6} However, the number of newborns screened accounts for only 25% of the live births officially reported in China in 2007.⁴ High screening rates are only seen in a small number of economically developed regions, such as Zhejiang province (94.55%).⁷ Accordingly, the management for newborn screening should be strengthened and more financial support should be offered to underdeveloped regions and low-income families.

Early detection and early treatment of PKU allows patients to have normal intelligence and lead a normal life, while in the absence of an accurate diagnosis, no basis exists for selecting a proper treatment. Furthermore, any delay in the diagnosis of PKU can lead to permanent brain damage and other long-term sequelae. Neuroimaging studies demonstrate that for most patients with PKU, profound and irreversible intellectual disability occurs if there is no dietary restriction of phenylalanine.⁸ Moreover, the high-signal intensity in the periventricular white matter in most patients with PKU can extend into the subcortical and frontal regions in more severe cases.⁹ These two sisters are prime examples.

Because these patients had normal hair and skin colour, along with no unusual urine odour, the diagnosis of PKU was not considered in the past 7 and 9 years. In these two sisters, it was the normal blood tyrosine concentration and the unsuppressed tyrosine hydroxylase that maintained the melanin production which is directly related to the hair/skin colour. It is the atypical

clinical presentation that caused a delay in diagnosis. We did not check the activity of PAH level. Probably, the PAH activity of the two atypical patients was slightly higher than typical patients with PKU.

In addition to MRI, which suggested leukoencephalopathy, these two sisters with learning disabilities were earlier misdiagnosed as having hereditary leukodystrophy. As we know, leukoencephalopathy can be divided into two types: primary and secondary. For the secondary type, besides the usual causes including infections, poisoning, degeneration and trauma of the central nervous system, there are some infrequent causes such as PKU, hereditary tyrosinemia and Hartnup disease, which can damage the central nervous system and make changes to the white matter.^{10 11} In these two sisters, the abnormality in MRI of the brain is actually due to hyperphenylalaninaemia rather than hereditary leukodystrophy.

The probable reasons of misdiagnosis are as follows: there were no changes in hair or skin colour, or urine odour; the tests performed in the previous years were all normal except for MRI, which implied leukoencephalopathy. In addition, the lack of treatment response cannot rule out the diagnosis of hereditary leukodystrophy, as there is no specific treatment for hereditary leukodystrophy, and the organ damage had already been long-standing.

Learning points

- ▶ The index of suspicion needs to be raised for this easily treatable phenylketonuria disease, especially for the patients with neuropsychiatric manifestation and without hair or skin colour change.
- ▶ There needs to be more concentrated efforts to make newborn screening tests more widely available in China, especially in the underdeveloped and rural areas.
- ▶ Get more detailed information on family history in your clinical work when you are confused.

Acknowledgements The authors would like to thank Professor Richard Bae for helpful suggestions on Medical Literature writing.

Contributors XL, HG, MD and BS have made a similar individual contribution to the conception and design, acquisition and interpretation of the data; drafting the article and revising it critically for important intellectual content; and final approval of the version published.

Competing interests None.

Patient consent Obtained.

Provenance and peer review Not commissioned; externally peer reviewed.

REFERENCES

- 1 Leandro J, Saraste J, Leandro P, *et al*. The G46S-hPAH mutant protein: a model to study the rescue of aggregation-prone PKU mutations by chaperones. *Mol Genet Metab* 2011;104(Suppl):S40–4.
- 2 Huttenlocher PR. The neuropathology of phenylketonuria: human and animal studies. *Eur J Pediatr* 2000;159(Suppl 2):S102–6.
- 3 Moyle JJ, Fox AM, Arthur M, *et al*. Meta-analysis of neuropsychological symptoms of adolescents and adults with PKU. *Neuropsychol Rev* 2007;17:91–101.
- 4 Zhan JY, Qin YF, Zhao ZY. Neonatal screening for congenital hypothyroidism and phenylketonuria in China. *World J Pediatr* 2009;5:136–9.
- 5 Mak CM, Ko CH, Lam CW, *et al*. Phenylketonuria in Hong Kong Chinese: a call for hyperphenylalaninemia newborn screening in the Special Administrative Region, China. *Chin Med J (Engl)* 2011;124:2556–8.
- 6 Lee HC, Mak CM, Lam CW, *et al*. Analysis of inborn errors of metabolism: disease spectrum for expanded newborn screening in Hong Kong. *Chin Med J (Engl)* 2011;124:983–9.
- 7 Maitusong R, Japaer R, Zhao ZY, *et al*. Newborn screening in Zhejiang, China. *Chin Med J (Engl)* 2012;125:702–4.
- 8 Mitchell JJ, Trakadis YJ, Scriver CR. Phenylalanine hydroxylase deficiency. *Genet Med* 2011;13:697–707.
- 9 Anderson PJ, Leuzzi V. White matter pathology in phenylketonuria. *Mol Genet Metab* 2010;99(Suppl 1):S3–9.
- 10 El-Karakasy H, Fahmy M, El-Raziky M, *et al*. Hereditary tyrosinemia type 1 from a single center in Egypt: clinical study of 22 cases. *World J Pediatr* 2011;7:224–31.
- 11 Broer S, Palacin M. The role of amino acid transporters in inherited and acquired diseases. *Biochem J* 2011;436:193–211.

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