Brain & Development 38 (2016) 807–818

BRAIN & DEVELOPMENT
Official Journal of the Japanese Society of Child Neurology

www.elsevier.com/locate/braindev

Original article

Clinical and genetic analysis of two Chinese infants with Mabry syndrome

Jiao Xue, Hui Li, Yuehua Zhang, Zhixian Yang *

Department of Pediatrics, Peking University First Hospital, Beijing, China

Received 28 February 2016; received in revised form 5 April 2016; accepted 12 April 2016

Abstract

Objective: Hyperphosphatasia mental retardation syndrome (Mabry syndrome) is an autosomal recessive disorder. We aim to analyze two Chinese patients diagnosed as Mabry syndrome.

Methods: The clinical manifestations, diagnosis and treatment were observed in two patients. Genetic analysis including *PIGV* and *PIGO* was examined.

Results: Two patients were diagnosed as Mabry syndrome clinically and genetically. Developmental delay, hyperphosphatasia and seizures were presented in both of them. Typical facial dysmorphism and hypoplastic terminal phalanges were only found in one. Some novel presentations including congenital laryngeal cartilage softening, inguinal hernia, broken palmprint, optic atrophy and skeleton dysplasia such as carpal age delay and metaphysis anomalies were observed in two patients. Molecular genetic analysis revealed compound heterozygous mutations of *PIGV* or *PIGO* in our patients, including c.615C > G (p.Asn205Lys) and c.854A > G (p.Tyr285Cys) of *PIGV* in patient 1, and c.458T > C (p.Phe153Ser) and c.1355_1356del (p.Ala452Glyfs*52) of *PIGO* in patient 2. Additionally, a heterozygous c.2926G > A (Asp976Asn) of *PCDH19* was identified in patient with *PIGV* mutations, the causative gene of Epilepsy and mental retardation limited to females (EFMR).

Conclusion: To our best knowledge, this is the first time to report Chinese patients diagnosed as Mabry syndrome. For the *PCDH19* mutation in our patient carrying *PIGV* mutations, due to lacking characteristics of EFMR and the ambiguity results in pathogenicity analysis, we were not sure how much pathogenic role *PCDH19* mutation shared with *PIGV* mutations in this disease. The novel mutations of *PIGV* and *PIGO,* and novel clinical manifestations reported here might expand the genotype and phenotype spectrum of Mabry syndrome.

Keywords: Hyperphosphatasia; Cognitive disability; Seizures; *PIGV* gene; *PIGO* gene

1. Introduction

Hyperphosphatasia mental retardation syndrome (HPMR, OMIM 239300) is a rare disorder first described in 1970 by Mabry et al. [1], which was proposed be called Mabry syndrome in 2010 by Thompson et al. [2]. It was identified by the core trio of symptoms consisting of developmental disability, seizures and hyperphosphatasia [2]. In addition to the core signs, a recognizable facial gestalt and brachytelephalangy might also suggest the diagnosis [2–5]. Recently, the largest reported cohort to date significantly extended the range of manifestations to multiple congenital malformations, such as Hirschsprung disease, vesicour-

* Corresponding author at: Department of Pediatrics, Peking University First Hospital, No.1, Xi'anmen Street, Xicheng District, Beijing 100034, China. Tel.: +86 10 83573082; fax: +86 10 66134261.
E-mail address: zhixian.yang@163.com (Z. Yang).

http://dx.doi.org/10.1016/j.braindev.2016.04.008

eteral and renal anomalies, and anorectal malformations [6].

Multiple homozygous or compound heterozygous mutations in genes that encode molecules of the glycosylphosphatidylinositol (GPI) anchor biosynthesis and remodeling pathway, such as *PIGV*, *PIGO*, *PIGL*, *PIGW*, *PGAP2* and *PGAP3*, have recently been identified in Mabry syndrome [7–12]. And up to now, only more than twenty patients in the world have been diagnosed genetically [3,5–10]. Among them, *PIGV* and *PIGO* were the two most common genes, which were first identified by Krawitz et al. in 2010 and 2012, respectively [7,8]. Here, we report two Chinese patients diagnosed as Mabry syndrome, including one with *PIGV* mutations, and another one with *PIGO* mutations. And simultaneously, a heterozygous *PCDH19* mutation was found in our patient carrying *PIGV* mutations.

2. Patients and methods

2.1. Case reports

2.1.1. Patient 1

Patient 1 was a female born from unrelated parents. Threatened absorption appeared at 3 months pregnancy. The delivery was uncomplicated and she was born at term. Birth weight (3500 g) and head circumference were in the normal range. She was diagnosed congenital laryngeal cartilage softening at birth and was continuously supplemented calcium and cod liver oil. The left inguinal veducible hernia was found at her age of 1 month, and no treatment measures were taken.

The patient developed seizures at the age of 2 months, showing breathholding, purple lips and squint, which ceased for few days after calcium supplementation. However, seizures recurred two months later, manifesting vomit, convulsions, limbs stiffness and facial cyanosis for less than ten seconds, 20–30 times per day at most. The use of pyridoxine (100 mg/day) through intravenous was successful in controlling the seizures in hospital. While on the 7th days after discharging from hospital, seizures recurred again without oral pyridoxine. Then, phenobarbital, topiramate and clonazepam were used together, but no effective was observed in suppressing the seizures. At her age of 7 months, oral pyridoxine (120 mg/day) was administered, together with topiramate and clonazepam unchanged, which dramatically ended her seizures for a few weeks. After pyridoxine dose was reduced arbitrarily by parents, seizures recurred again and could not controlled by a combination of oral pyridoxine (30 mg/day), topiramate, levetiracetam, valproate and valgabatrin. Adrenocorticotropic hormone was used intravenously when she was 15 months old, the frequency and severity of seizures decreased but still existed. At her age of 1.5 years, pyridoxine was added to 120 mg/day without seizures controlled. At the last follow up (at her 2.5 years old), seizures still occurred occasionally, and ketogenic diet was used persistently without obvious effect.

The girl's intelligence and motor development were delayed and severe muscular hypotonia presented continuously. She had no speech skills and couldn't control her head stably until now. Acquired microcephaly had been recognized in the process of her development, with a head circumference of 42 cm at age of 8 months and then 43 cm at age of 14 months.

Dysmorphic features (Fig. 1A) included apparently hypertelorism, long and upslanting palpebral fissures, a short nose with broad nasal bridge and nasal tip, a tented upper lip with downturned corners of the mouth, and a high-arched palate. She had broken palmprint of both hands (Fig. 1B). Clinically, shortness of the fifth digits distal phalanges (Fig. 1C) was demonstrated but unidentified radiologically. Mild nail hypoplasia of thumb (Fig. 1D) was presented. And clinodactyly appeared in her feet. Hypertrichosis was observed mainly on forehead and back.

Serum alkaline phosphatase (ALP) level was elevated with 850 IU/L and 739 IU/L (normal range: 50–350 IU/L) at age 4.5 and 5 months respectively, and was still elevated with 943 IU/L (normal range: 50–240 IU/L) at age 18 months.

Electroencephalography (EEG) examinations showed hypsarrhythmia or arrhythmic and asynchronous slow and sharp waves, multi-focal spikes and polyspikes close to hypsarrhythmia especial at sleep from 5 months age to 2.5 years old (Fig. 2). However, physicians and parents never noticed epileptic spasms through clinical observation. During the several weeks when seizures were controlled by pyridoxine, EEG was not reexamined to evaluate the efficacy. After using adrenocorticotropic hormone, EEG had a transient improvement (Fig. 2B). Magnetic resonance imaging (MRI) showed frontal–temporal subarachnoid widened at her age of 7 months. Periventricular leukomalacia, corpus callosum atrophy, delayed myelination and bilateral frontal brain outside clearance widened appeared at 10 months (Fig. 3A and B). Ocular fundus examination showed optic atrophy. Chromosome karyotype, plasma amino acid and organic acid analysis were all normal.

2.1.2. Patient 2

Patient 2 is a 21-month-old male born to nonconsanguineous parents after a 38-week gestation via Cesarean section with no asphyxia. Birth weight was 4200 g and head circumference was in the normal range. Both the pregnancy and neonatal course were unremarkable.

The patient went to see a doctor for uncontrolled his head stably and lacking response to sound and objects at 5.5 months old. Physical examination revealed hypertonia of limbs and a head circumference of 44 cm. At his age of 6 months, seizures started after receiving routine