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Late-diagnosed phenylketonuria mimicking x-linked adrenoleukodystrophy with heterozygous mutations of the PAH Gene: A case report and literature review

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ABSTRACT

Phenylketonuria (PKU) is a prevalent inherited metabolic disorder caused by a phenylalanine hydroxylase (PAH) or tetrahydrobiopterin (BH4) deficiency, which leads to the accumulation of phenylalanine (PHE). High blood levels of PHE have a toxic effect on the brain and are associated with several neurological signs. Most cases of PKU are identified during infancy, and diagnosis of PKU in adult is rare. Here, we describe a 29-year-old patient with progressive dementia and muscular weakness mimicking X-linked adrenoleukodystrophy. Haematological tests revealed high PHE levels (966.67 μmol/ L, normal 20.00–120.00 μmol/L) and his gene test showed compound heterozygosity for c.740 G > T and c.728 G > A of PAH gene mutations, suggesting a diagnosis of PKU. His condition had controlled partly but not significantly improved with appropriate treatment. Our patient is the first case of late-diagnosed PKU with definite heterozygous PAH gene mutations reported in China albeit he had milder symptoms than the previous reported cases around world. Although late-diagnosed PKU is rare, this diagnosis should be considered for patients presenting with leukoencephalopathy accompanied by common neurological signs.

1. Introduction

Phenylketonuria (PKU) is an autosomal recessive disorder characterised by the accumulation of phenylalanine (PHE) resulting from a phenylalanine hydroxylase (PAH) deficiency [1]. The disorder was first described in two siblings by Asbjörn Fölling in 1934 [2–4]. PKU was the first inborn error of metabolism disease identifiable through population-based newborn screening (NBS) programmes [5]. The incidence of PKU varies from 1:10,000 to 1: 16,000 in different geographic regions [1,6]. Because of the high incidence of PKU and good prognosis after diagnosis and treatment, newborns have undergone systematic screening for PAH deficiency since mid- to late-1960 s in North America and in the United Kingdom and the early 1970 s in the some of the developed countries [4]. Although most countries have adopted NBS programmes, lack of coverage and unreliable test results in some regions can result in missed diagnoses. Generally speaking, PKU is a childhood disorder. However, rare cases of PKU patients are diagnosed in adulthood, which resembles other neurological disorders, have been reported [7–13]. Here, we describe a patient with late-diagnosed PKU mimicking X-linked adrenoleukodystrophy with a heterozygous mutation of the PAH gene, and discuss previously reported cases identified in a literature review.

2. Patients and methods

We describe the clinical symptoms, neuroimaging, gene test results and blood PHE levels of our patient at diagnosis. We also search PubMed database (http://www.ncbi.nlm.nih.gov/pubmed) concerning adult-onset PKU or late-diagnosed PKU published between 1993 and 2016 (using “adult-onset”, “late-diagnosed”, “late diagnosis”, “phenylketonuria” and “PKU” as keywords). The demographic and medical characteristics of the 11 patients identified, including our case, are summarised in Table 1.

3. Results

3.1. Case presentation

A 29-year-old unmarried Chinese male presented with progressive dementia and left limb weakness for about one year, which had worsened during the past two months. He had light black hair, left-sided talipes varus and high body mass index (BMI = 28.40). Neurological

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Table 1
A summary of adult-onset or late-diagnosed patients with PKU.

Source	Country	Sex	Age of onset(y)	Clinic symptoms	Neuroimaging	CSF	Phe level at diagnosis (μmol/L)	Gene mutation	Prognosis
Ishimaru et al	Japan, 1993	M	36	Red hair, gray eyes, impaired gait and visual IQ = 68	Leukoencephalopathy (MRI)	Normal	1663	NA	PHE-restricted diet, no recovery
J Weglage et al.	Germany, 2000	F	45	Brisk reflexes, spastic tetraparesis, dementia, tremor and ataxia	Leukoencephalopathy (MRI)	Normal	882	R408 W/R68S	PHE-restricted diet, almost complete recovery.
S Kasim et al.	Germany, 2001	F	57	Spastic paraparesis, brisk reflexes, ankle clonus and an upgoing left toe, cognitive impairment, IQ = 108	Normal (MRI)	OB(+)	2153	R158Q/IVS12 + 1G > A	Protein restricted diet, partial improvement.
Jousserand et al.	France, 2009	M	55	Musty body odour, brisk reflexes, spastic paraparesis, mental retardation	Leukoencephalopathy (MRI)	Protein 0.58 g/L	1140	I65 T/R252W	Protein-restricted diet
L Daelman et al.	France, 2014	F	47	Parkinsonism, tremor, epilepsy, mental retardation	Normal (MRI)	NA	2358	IVS4 + 5G > T/P281L	Levodopa, no specific diet
Narayanan et al.	UK, 2014, two siblings	M	40	Tonic clonic seizures and learning difficulties	Normal (CT)	NA	1451	NA	PHE-restricted diet
		M	42	Learning difficulties	NA	NA	1670	NA	PHE-restricted diet
Rosini et al.	Italy, 2014	F	46	Dementia, inability to walk, aphasia, prosopagnosia, extrapyramidal signs, brisk tendon reflexes and visual impairment	Leukoencephalopathy (MRI); decreased NAA/Cr ratio (MRS)	Tau protein 997 pg/ml(NV < 275)	947	IVS10-11G > A/ IVS4 + 4A > G	PHE-restricted diet, rapid improvement
J Papassin et al.	France, 2015	F	20	Light skin and hair, IQ < 65	Leukoencephalopathy (MRI)	NA	1687	Homozygote mutation	No specific diet
Tufekcioglu et al.	Turkey, 2016	M	59	Blurred vision, cognitive problems, gait difficulty, brisk reflexes, Parkinsonism. MMSE 25/30	Leukoencephalopathy (MRI)	Protein 61 mg/dl	1075	NA	PHE-restricted diet, significant improvement
Current case	China, 2016	M	29	Dementia, weakness, ankle clonus, knee clonus and left talipes varus. MMSE 27/30, MoCA 19/30	Leukoencephalopathy (MRI)	Pressure 210/ 150mmH_2O	966.67	G247 V/R243Q	Protein-restricted diet, partial improvement

M: male; F: female; OB: Oligoclonal Bands; NA: not available; MRS: MR spectroscopy; NAA/Cr ratio: N-acetyl-aspartate/ creatine ratio; NV: Normal value.