SHORT REPORT

Phenylketonuria presenting in adulthood as progressive spastic paraparesis with dementia

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Abstract

A 57 year old woman living independently in the community presented with four years of progressive spastic paraparesis and dementia. An extensive evaluation for the usual causes of these difficulties was unrevealing, but her serum phenylalanine concentration was markedly elevated and genetic analysis demonstrated mutations in the phenylalanine hydroxylase gene consistent with classic phenylketonuria. A protein restricted diet was associated with improvement in her condition. Although untreated phenylketonuria is typically associated with severe neurological dysfunction beginning in early childhood, this case shows that disability may be delayed until adulthood.

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Phenylketonuria is an autosomal recessive disorder caused by deficiency of the enzyme phenylalanine hydroxylase, which normally converts phenylalanine to tyrosine.[1–3] Serum phenylalanine concentrations exceeding 1200 µmol/l are usually diagnostic of phenylketonuria whereas concentrations of 400–800 µmol/l typically reflect partial deficiency of phenylalanine hydroxylase or defects in the metabolism of its cofactor tetrahydrobiopterin.[3] Patients with untreated phenylketonuria most often present in the first year of life with developmental delay, profound mental retardation, and difficult behaviours. Many also develop pyramidal or extrapyramidal dysfunction.[4–7] The neurobehavioural abnormalities can be prevented by early dietary restriction of phenylalanine, but relaxation of the diet after childhood is suspected to be the cause of deterioration later in adulthood, most often characterised as progressive spastic tetraparesis.[8] We describe an untreated patient with phenylketonuria who presented in adulthood with progressive spastic paraparesis and dementia.

Case report

A 57 year old woman was evaluated for 4 years of slowly progressive impairment of gait and cognitive dysfunction. She had a normal neurodevelopmental history, but received average to low average grades in school. She completed 2 years of secretarial school, but never found employment. She never obtained her driving licence, dated, or married. Instead, she lived with her parents and took care of her ailing father for several years before his death. Her father was diagnosed as having Parkinson's disease with dementia in his 6th decade, because of akinesia, bradykinesia, and impaired gait without tremor. He responded well to levodopa and died 10 years after the onset of illness. Her one younger brother had severe cognitive and behavioural problems as a young child and had been diagnosed with phenylketonuria. Now in his 5th decade, he is mentally retarded but has no apparent difficulty with his gait. The patient and her brother had shared the same paediatrician, who never suspected that she could also have phenylketonuria.

Physical examination disclosed fair hair and skin with light blue eyes. Cranial nerve examination was normal. She had a spastic paraparesis with brisk reflexes, ankle clonus, and an upgoing left toe. She required a walker for safe ambulation. Arm strength was normal, but arm reflexes were very brisk with increased tone. She had no involuntary movements and coordination was normal.

A mental status examination showed a fully alert and cooperative patient with flattened affect and a tendency towards slow and methodical responses to questions and execution of tasks. Attention was normal as assessed by forward and backward digit spans. She scored 29/30 on the mini mental state examination, and her new adult reading test score was consistent with a premorbid estimated full scale IQ of 108. New verbal learning and delayed recall scores were also normal. However, recognition memory was poor, as judged by a score on the recognition trial of the Rey auditory verbal learning test that placed her more than 8 SD below the mean for age and sex. She also displayed marked psychomotor slowing, producing an average of 7.7 words a minute on a verbal fluency test, placing her at the 22nd percentile for age, sex, and educational level. Her score for the trail making test (parts A and B) put her at the zero percentile. In addition, visuoconstructional abilities were poor. She made errors drawing a simple clock face and scored at less than the 10th percentile copying the Rey-Osterrieth complex figure. Arithmetic abilities were impaired with an age corrected score of 6.0 on the arithmetic

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Table 1   Phenylketonuria presenting in adulthood

	Presenting complaint	Examination	MRI	CSF	*Serum phenylalanine (µmol/l)	Response to dietary phenylalanine restriction
Current case	Progressive gait and cognitive impairment	Spastic paraparesis with cognitive decline	Normal	Oligoclonal bands	2153	Partial recovery
Weglage et al[12]	Progressive gait and cognitive impairment	Spastic paraparesis with cognitive decline	White matter plaques consistent with dysmyelination	Normal	882	Almost complete recovery
Ishimaru et al[13]	Progressive gait and visual impairment	Spastic paraparesis with visual loss	White matter plaques consistent with dysmyelination	Normal	1663	No recovery

*Normal range 25–81 µmol/l.

portion of the Wechsler adult intelligence scale (WAIS- III).

The following tests were normal: serological tests for syphilis, folate, and vitamin B12, thyroid function tests, sedimentation rate, antinuclear antibodies, rheumatoid factor, anti-Ro, anti-La, antiphospholipid antibodies, immunoelectrophoresis, HTLV-1, vitamin E, very long chain fatty acids, α-fetoprotein, lactate, ammonia, and peripheral blood smear. The CSF had oligoclonal bands but a normal immunoglobulin index. Visual evoked responses, somatosensory evoked responses, and nerve conduction studies were normal. Magnetic resonance imaging of the head, cervical spine, and thoracic spine were normal. In particular, there was no abnormality of the white matter. A non-fasting serum phenylalanine was 2153 µmol/l (normal 25–81 µmol/l), with a simultaneous tyrosine of 41 µmol/l (normal 20–108 µmol/l). Repeat fasting serum phenylalanine and tyrosine were 1862 and 35 µmol/l, respectively. Molecular genetic studies of blood samples from the two siblings showed that they were both compound heterozygotes for the common mutations IVS12 +1g>a, and R158Q. This genotype is sometimes associated with small amounts of residual enzyme activity but is typically associated with the phenotype of classic phenylketonuria.[9]

The classic phenylketonuria diet was not feasible, so she was instead encouraged to follow a protein restricted diet by eliminating all meats and severely limiting all dairy products. Within 4 months she was ambulating without her walker, although objective changes could not be detected on neurological examination. Her mother also reported improvement in her mental abilities, but this could not be verified since she declined follow up neuropsychological testing.

Discussion

It seems very likely that the progressive neurological dysfunction in this case resulted from phenylketonuria rather than another coincidental condition. The serum phenylalanine concentrations and genotype were indicative of classic phenylketonuria, and investigations for other potential causes for progressive spastic paraparesis with dementia were negative. The neurological features also resemble those of patients with phenylketonuria who followed a phenylalanine restricted diet as children but developed neurological deterioration as adults after relaxation of the diet,[8] and a protein reduced diet resulted in partial improvement. This case demonstrates three important points:

(1) neurological dysfunction in phenylketonuria may first become apparent during adulthood; (2) the same phenylalanine hydroxylase genotype may produce very different clinical phenotypes; (3) the clinical phenotype may resemble other more common neurological diseases, such as multiple sclerosis.

PHENYLKETONURIA PRESENTING IN ADULTHOOD
It is widely recognised that many inherited disorders that typically affect children may also present in adults. Two recent reviews summarised many paediatric diseases that may present in adulthood, although neither included phenylketonuria.[10 11] A review of the literature disclosed two other patients with untreated phenylketonuria who did not develop neurological dysfunction until adulthood. One report described a 45 year old woman who presented with progressive spastic tetraparesis and dementia, a picture very similar to that of the current patient.[12] However, that patient had a milder variant of the disease, with serum phenylalanine concentrations only moderately above the threshold for dietary intervention (table 1). The other report described a 32 year old man who developed paraparesis with increased limb tone and progressive visual impairment over a period of 4 months.[13]

Early studies describing the natural history of untreated phenylketonuria anecdotally recognised the existence of rare patients with normal cognition and no neurological abnormalities during childhood.[1–3 5] A screening study of 28 000 cases from a Massachusetts clinic disclosed three patients with phenylketonuria who were living in the community,[14] and a review of the literature disclosed at least eight additional cases of phenylketonuria with normal intelligence.[15 16] The existence of these rare cases, together with the phenomenon of late neurological deterioration in phenylketonuria, suggests that it should be added to the list of paediatric diseases that may first become apparent in adulthood.

GENOTYPE-PHENOTYPE DISCORDANCE
This case also shows that the same genotype may produce very different clinical outcomes. Several other studies have also documented appreciable variations in the clinical phenotype among untreated members of the same family who presumably carried the same mutations.[2 3 15] Although the genotype is likely to have a strong influence on the phenotype, these cases demonstrate an important role for multifactorial influences. Recent studies have indicated that clinical heterogeneity may reflect not only differences in residual phenylalanine

hydroxylase, but other aspects of phenylalanine metabolism such as uptake into the brain or responsiveness to the tetrahydrobiopterin cofactor.[3 9 17 18 19]

DIFFERENTIAL DIAGNOSIS OF ADULT ONSET PHENYLKETONURIA

In our patient, the clinical presentation of progressive spastic paraparesis with dementia provided no pathognomonic features that pointed specifically to the diagnosis of phenylketonuria. The differential diagnosis for progressive spastic paraparesis includes multiple sclerosis, familial spastic paraparesis, amyotrophic lateral sclerosis, Chiari malformation or syringomyelia, compression of the spinal cord due to malignancy or orthopaedic disease, ischaemia or vascular malformations of the spinal cord, vitamin B12 deficiency, infections such as HTLV-1 or HIV, or rare genetic diseases such as Friedreich's ataxia, adrenoleukodystrophy, metachromatic leukodystrophy, or Krabbe's disease.[20]

The most common presentation for late deterioration in phenylketonuria is progressive spastic paraparesis with cognitive decline,[8] a presentation that could be readily mistaken for multiple sclerosis. In addition, the brain MRI in two of the three published cases of adult onset phenylketonuria demonstrated white matter plaques similar to those seen in multiple sclerosis, and one of the three patients had oligoclonal bands in the CSF (table 1). Misdiagnosis of adult onset phenylketonuria as multiple sclerosis may lead to treatment with immunosuppressant drugs, when dietary alterations are probably more appropriate. Dietary restriction of phenylalanine prevents the neurobehavioural consequences of typical childhood onset phenylketonuria and may be beneficial in adult patients with phenylketonuria who develop neurological deterioration after relaxation of the diet.[8] Because of the implications for therapy, patients who present with unexplained spastic paraparesis should have a serum amino acid screen if such screening was not provided during childhood.

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