J Neurol (2014) 261:2446–2448
DOI 10.1007/s00415-014-7492-7

LETTER TO THE EDITORS

Adult-onset phenylketonuria revealed by acute reversible dementia, prosopagnosia and parkinsonism

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Received: 3 April 2014 / Revised: 2 September 2014 / Accepted: 3 September 2014 / Published online: 31 October 2014

Dear Sirs,

Phenylketonuria (PKU) is an autosomal recessive disorder caused by deficiency of phenylalanine hydroxylase (PAH) enzyme [1], usually manifesting in infancy; however, rare cases of adult onset of PKU symptoms have been described [2–6].

A 46-year-old female, with mild learning difficulties (middle-school degree achieved), was observed for rapidly progressive dementia, walking difficulties and visual impairment started 1 month before, at the end of 6-month unbalanced diet for slimming. Her older sister, presenting with fair hair and skin (similarly to their unaffected mother), mental retardation and spastic tetraparesis, was diagnosed with PKU in infancy. Patient's newborn screening was reported as negative. Her physical examination disclosed fair hair with blue eyes. Neurologic examination showed inability to walk, aphasia, prosopagnosia, extrapyramidal signs and brisk tendon reflexes. Fundoscopy revealed pale optic disks. Brain MRI evidenced diffuse bihemispheric white matter hyperintensity, mild cortical atrophy, and decreased *N*-acetyl-aspartate/creatine (NAA/Cr) ratio at MR spectroscopy (Fig. 1a). Electroencephalogram showed diffuse slowing of cerebral biorhythms. Among serum and CSF testing, CSF total TAU protein was increased (997 pg/ml, nv $<$ 275), beta-amyloid was 529 pg/ml, (nv $>$ 600), phosphorylated-TAU was normal (21 pg/ml, nv $<$ 50). Amino acid analysis evidenced increased phenylalanine (Phe) (serum 947 μmol/L, nv 37–94, urinary 49 mmol/mol-creatinine, nv 2–19), with normal tyrosine. Molecular analysis of the proband and her sister confirmed a compound heterozygosity for the mutations IVS10-11G>A/IVS4+4A>G of PAH gene, reported with classical PKU phenotype. Immediately after Phe-restricted diet with amino acid supplementation introduction (daily Phe intake: 600 mg), patient showed rapid improvement; 6 months later (still under Phe-restricted diet), only mild cognitive deficit and visual reduction remained, despite unvaried Phe levels (serum 868 μmol/L, urinary 55 mmol/mol-creatinine). One-year brain MRI and MR spectroscopy follow-up showed marked reduction of white matter abnormalities and increased relative NAA/Cr ratio (Fig. 1b).

Adult-onset PKU represents an uncommon event after the late 1960s, since newborn screening identifies the affected individuals; however, up to 10 % false negatives have been reported before the recent use of tandem-mass spectroscopy method. Few patients with cognitive, motor and visual disturbances were described with adult onset of PKU symptoms [2–6]; diffuse white matter abnormalities have been reported [3–5], either related to hypomyelination or intramyelinic edema [7]. Clinical and MRI changes are often reversible after therapy [8]. In our patient, the learning difficulties may have been a not-recognized disease sign that should have been evaluated and treated before; during the acute phase, beside dementia and extrapyramidal changes, she showed prosopagnosia, as a prominent sign. Brain MRI evidenced mild cortical atrophy, unusual for the age. H1-MR spectroscopy showed different NAA/Cr ratio before and after diet, without increased choline/creatine (Cho/Cr) ratio: this finding,

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