Malignant Phenylketonuria (PKU) Due to Dihydropteridine Reductase (DHPR) Deficiency

Abstract:

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DHPR deficiency is a rare autosomal recessively inherited metabolic disorder of tetrahydrobiopterin (BH4) regeneration. Clinical symptoms may comprise microcephaly, developmental delay, ataxia and seizures. BH4 is the co-factor for the enzyme phenylalanine (Phe) hydroxylase (PAH), and for tyrosine and tryosine hydroxylases, both of which are essential for serotonin and dopamine biosynthesis. We present four patients in two families who are being treated at the National Centre for Inherited Metabolic Disorders of the Children’s University Hospital. We have identified a homozygous mutation, c.353C>T, in the DHPR (QDPR) gene which, to the best of our knowledge, has not been previously described.

The mainstay of treatment is a life-long Phe-restricted diet together with supplementation of L-dopa and 5-hydroxytryptophan (5-HT) and folic acid. In Ireland, there is neurological comorbidity in our adult DHPR patients, although the overall outcome is satisfactory and one affected female has three healthy children.

Methods

Ethics approval and patient consent were obtained for this study. We retrospectively collected anonymized data from our patients with DHPR deficiency who had been diagnosed and treated at the NCIMD from 1966 until 2014, using medical charts and the laboratory database. Descriptive statistics were performed using MS Excel 2010.

Case 1

This is a 28-year-old woman from the Irish Traveller population. She has been treated from day 20 of life following abnormal NBS. Work-up for PKU which included measurements of amino acids (Phe 133nmol/l), pterins and DHPR in blood revealed an absence of DHPR enzyme activity. She was started on a Phe-restricted diet together with L-dopa/carbidopa (ratio 4:1), 5-HT and folic acid (Table 1). Developmental assessment showed language delay and mild motor deficits. At 26 years of age, psychological assessment showed that she had an IQ of 51 indicating an intellectual ability within the Exceptionally Low Range. At age 20, she gave birth to her first child. During pregnancy, her Phe levels were mostly in the desired range of 116-150 µmol/l. The baby was born by emergency LSCS due to foetal distress. The baby’s NBS screening was normal. Aged 23 years, she had a miscarriage at 14 weeks gestation. In a non-pregnant state, her elevated prolactin levels of 610-6577 mU/l (normal range 200-400) may reflect adherence issues in taking the medications. At 24 years of age, she gave birth to her second child. During this pregnancy, she had elevated Phe levels in the range of 271-599 µmol/l requiring hospital admission. At 25 years of age she had a third child. Phe levels were monitored according to our policy for PKU patients with a target range of 120-400 µmol/l in childhood; neurotransmitter supplements were adjusted according to CSF levels (Figure 1) and body weight. At 12 years of age, psychology assessment showed mild speech delay and mild motor deficits. At age 15 years showed an IQ within the Mild General Learning Disability range. During childhood, his Phe levels were mostly in the desired range of 150-250 µmol/l. His baby was born vaginally. During this pregnancy, his Phe levels were mostly in the desired range of 150-250 µmol/l. The baby was born by emergency LSCS due to foetal distress. The baby’s NBS screening was normal.

Case 2

This is a male patient who was identified with high Phe levels on high-risk NBS. His sister (case 1) is the index case. Absence of DHPR enzyme activity in blood confirmed the diagnosis biochemically. After molecular genetic testing became available to us, we could demonstrate pathogenic c.353C>T mutation in the DHPR (QDPR) gene in this family. The boy was started on a Phe-restricted diet, L-dopa/carbidopa, 5-HT and folic acid. CSF neurotransmitter metabolite concentrations subsequently increased to near normal levels (Figure 1). He had mild speech delay and an episode of intracranial calcifications. Treatment comprises a Phe-restricted diet along with L-dopa, 5-HT and folic acid supplementation. In this study, we report on diagnosis, management and clinical outcome in four DHPR-deficient patients. Diagnosed in Ireland on NBS for PKU, they represent only 0.56% of our total cohort of 718 PKU patients being treated at the NCIMD.

Case 3

The third patient is a 17 months old boy. He presented with high Phe levels on NBS and was admitted to the NCIMD at 10 days of age. On admission his plasma Phe level was 1688 µmol/l and he underwent work-up for PKU including blood Phe levels and pterins. He was subsequently started on a Phe-restricted diet. Within the first month he was diagnosed with DHPR deficiency (DHPR activity < 0.1 µmol/min/g). The diagnosis was also confirmed genetically. He was started on L-dopa/carbidopa (2-8 mg/kg/day), 5-HT (2-7 mg/kg/day) and folic acid (10 mg/day). His Phe levels are within therapeutic limits so far. Serum prolactin concentrations came down with treatment (max. 1129 µmol/l prior to treatment, min. 186 µmol/l whilst on treatment). His development is normal.

Case 4

This baby girl is the sister of case 3. She was diagnosed on high-risk NBS on day 3 of life with a Phe level of 668 µmol/l. Her maximum Phe level was 1198 µmol/l on day 8 of life before treatment was fully implemented. Her initial prolactin level was 2212 mU/l; it came down after she had been commenced on medications. Since day 9 of life, her Blood Phe levels were within therapeutic limits thus far. She is homosygous for the same pathogenic c.353C>T mutation in the DHPR gene. She was started on a Phe-restricted diet, L-dopa/carbidopa, 5-HT and folic acid. CSF neurotransmitter metabolite concentrations subsequently increased to near normal levels (Figure 1). He had mild speech delay and an episode of intracranial calcifications. Treatment comprises a Phe-restricted diet along with L-dopa, 5-HT and folic acid supplementation. In this study, we report on diagnosis, management and clinical outcome in four DHPR-deficient patients. Diagnosed in Ireland on NBS for PKU, they represent only 0.56% of our total cohort of 718 PKU patients being treated at the NCIMD.

Abstract:

Phenylalanine (Phe) hydroxylase (PAH) is a key enzyme in amino acid metabolism, converting Phe into tyrosine, using tetrahydrobiopterin (BH4) as its co-factor. Defects in BH4 metabolism, including dihydropteridine reductase (DHPR) deficiency, are referred to as malignant or atypical phenylketonuria (PKU) as distinct from classical PKU which refers to a defect in PAH apo-enzyme. DHPR is involved in a salvaging process of BH4. There are other BH4-dependent enzymes involved in neurotransmitter synthesis including tyrosine hydroxylase, which converts tyrosine to L-dopa and tryptophan hydroxylase, which converts tryptophan to 5-hydroxy tryptophan (5-HT). Ireland was the first country worldwide to have a national Newborn Bloodspot Screening (NBS) Programme, including PKU, commencing in February 1966. Similar to patients with classical PKU, patients with atypical PKU due to DHPR deficiency present with elevated Phe levels on NBS. In general, classical PKU is characterized by neurotoxicity due to excessively elevated Phe concentrations, leading to severe mental retardation, microcephaly, and epilepsy if left untreated. Patients with malignant PKU due to DHPR deficiency may also present clinically with microcephaly, hypotonia, mental retardation and seizures. In DHPR deficiency there is not only an accumulation of Phe but also a profound deficit in the neurotransmitters dopamine and serotonin. There can be also alterations in the CNS folate status along with intracranial calcifications. Treatment comprises a Phe-restricted diet along with L-dopa, 5-HT and folic acid supplementation. In this study, we report on diagnosis, management and clinical outcome in four DHPR-deficient patients. Diagnosed in Ireland on NBS for PKU, they represent only 0.56% of our total cohort of 718 PKU patients being treated at the NCIMD.
QDPR gene. At her most recent visit, she was clinically well and neurologically asymptomatic.

**Discussion**

All our patients with DHPR deficiency presented with raised Phe levels on NBS. In principle, a very low/absent DHPR enzyme activity in blood in the setting of an elevated Phe level confirms the diagnosis biochemically. Molecular genetic testing is available. In addition to Phe-restricted diet, patients with DHPR deficiency need life-long L-dopa/carbidopa and 5-HT as well as folic acid supplements to prevent/reduce severe neurological symptoms. In addition to neurotransmitter studies in CSF for monitoring, serum prolactin measurement was introduced at the NCIMD in 2006 which is a sensitive marker for hypothalamic dopamine content and, therefore, a suitable biomarker for optimal dosage of L-dopa in DHPR-deficient patients. Taken together, DHPR deficiency is an extremely rare metabolic disorder. In Ireland to date, only members of the Irish Traveller population have been affected, a population constituting <1% of the total Irish population, in which a high rate of consanguinity is a common finding. All four patients harbour the same pathogenic c.353C>T mutation in the QDPR gene that, to the best of our knowledge, has not yet been described. Despite the low frequency, malignant PKU or DHPR deficiency has to be considered in each newly diagnosed PKU patient as approx. 2% of all patients with high Phe levels have an underlying disorder of BH4 metabolism. Following the identification of an index case in the family, early high-risk NBS is recommended for future pregnancies. An early diagnosis soon after birth enables early initiation of treatment with the best possible outcome. There is neurological comorbidity in our adult patients, although the overall outcome is so far satisfactory.

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**References**


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