Dihydropyrimidine Dehydrogenase Deficiency: A Baby Boy with Ocular Abnormalities, Neonatal Seizure and Global Developmental Delay

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Case Report

A post-term Pakistani male infant of 2,940 grams was delivered by Caesarean section after an uneventful pregnancy. He is the second child of consanguineous parents who are first cousins. Both his parents and his 4-year-old sister are all along healthy. He was transferred to our neonatal unit soon after delivery because of respiratory distress. Physical examination on admission revealed several subtle dysmorphic features, namely left low set ear, wide anterior fontanel, sacral dimple and undescended left testis. He was also found to have paucity of spontaneous movement, generalised hypotonia and absent reflexes. Chest examination showed subcostal insucking but his chest was clear on auscultation. Liver was palpable at 2 cm below right costal margin and spleen was not enlarged. Cardiovascular examination showed no abnormality. Ophthalmological examination revealed micro-cornea, nystagmus and hypoplastic macula. He was treated as suspected sepsis with antibiotics initially but cultures from blood, gastric lavage and cerebrospinal fluid (CSF) yielded no growth.

He had twitching of four limbs and eye deviation since Day 2 of life. He was treated with loading lose of phenobarbitone for control of repeated seizures. Multiple anticonvulsants were subsequently added for poor seizure control. Electroencephalogram (EEG) showed sharp waves over bilateral frontal lobes especially over right anterior and temporal regions. Brainstem auditory evoked potential (BAEP) study showed no response indicating severe bilateral hearing loss. Visual evoked response (VEP) was normal. Neurological assessment at 7 months old still showed generalised hypotonia and motor developmental delay.

Computed tomography (CT) scanning of brain on Day 3 showed slightly prominent right lateral ventricle and suspicion of microgyria. Magnetic resonance imaging (MRI) of brain performed on Day 13 revealed mildly prominent right lateral ventricle without CSF outflow obstruction. The myelination was commented to be...
appropriate to age. MRI brain repeated at 6 months old showed prominent sulcal spaces and ventricles and the white matter showed marked delay in myelination. Magnetic resonance spectroscopy (MRS) of brain performed at the age of 7 months depicted diffuse neuronal loss as indicated by relative decrease of N-acetyl aspartate and increase of choline levels. Elevated glutamate/glutamine were consistently demonstrated in the deep gray matter and parietal white matter and abnormal accumulation of lipid and lactate were also noted. Each of these findings is rather non-specific but when combined, they are consistent with hypoxic encephalopathy.

Biochemical examination of the patient’s urine sample by gas chromatography-mass spectrometry (GC-MS) showed thymine-uraciluria and the presence of abnormal metabolite 5-hydroxymethyluracil. Subsequent plasma pyrimidines profile also revealed significant elevations of thymine and uracil which all support the diagnosis of dihydropyrimidine dehydrogenase (DPD) deficiency, an autosomal recessive inborn error of pyrimidine metabolism. Both patient’s mother and elder sister were also diagnosed to have DPD deficiency in view of increased concentrations of thymine and uracil in their urine samples during family screening.

Further molecular analysis of the DPD gene using polymerase chain reaction (PCR) and restriction fragment length polymorphisms (RFLP) tests on a common splice mutation site leading to 165 bp skipping of exon 14 was performed for proband and his parents. Proband and his mother were proven to be homozygous for G→A mutation in this splice-donor site. Although patient’s father had no thymine-uraciluria, he was found to be heterozygous for the same mutation. DPD gene analysis was not performed for patient’s elder sister as she had left our locality at that time but she is expected to be homozygous for this splice donor site point mutation in view of her thymine-uraciluria and the molecular genetics findings of her parents and sibling.

Discussion

DPD is the initial and rate-limiting step in pyrimidine catabolism which catalyses the NADPH-dependent reduction of uracil and thymine to 5,6-dihydrouracil and 5,6-dihydrothymine respectively. These metabolites are finally converted to \( \beta \)-alanine or \( \beta \)-aminoisobutyric acid, ammonia and carbon dioxide through the action of dihydropyrimidinase and ureidopropionase (Figure 1).

DPD deficiency is an autosomal recessive disease characterised by the presence of thymine-uraciluria and variable clinical phenotypes. Human DPD gene had been mapped to chromosome 1p22. Measurement of uracil and thymine in amniotic fluid has been used as markers for prenatal diagnosis of DPD deficiency.

Patients with either complete or partial deficiency of this enzyme are both at risk of developing severe toxicity or

![Figure 1](catabolic_pathway.png)  
**Figure 1** Catabolic pathway for pyrimidines and 5-fluorouracil. (DPD: Dihydropyrimidine dehydrogenase; DHPase: Dihydropyrimidinase).
even death after anti-neoplastic agent 5-fluorouracil (5FU) administration as DPD accounts for around 85% of the metabolism of 5FU. No specific drug or dietary therapy is available for this enzyme deficiency to date.

DPD deficiency was first postulated as an inborn error of pyrimidine metabolism by van Gennip et al (1981) in a child with speech delay, seizure and behavioural problems. Most of the early reported paediatric cases were Dutch and the common clinical features were convulsion, hypertonicity, microcephaly and in some patients, mental retardation. Van Gennip et al (1994) commented that seizures or epileptic attacks were reported in 7 out of the 12 and mental retardation in 5 out of 12 previously reported Dutch patients with DPD deficiency. Other symptoms like microcephaly, motor retardation, autism and growth retardation were less frequent. Christensen et al (1998) found different clinical presentations in three Danish patients with DPD deficiency all homozygous for the same splice-donor site mutation – one with delay in motor development and seizure, one with mild speech and mental developmental delay and the other with normal psychomotor development and growth at the age of 7 months but was found to have DPD deficiency in urine screening of metabolic diseases as she was lethargic at Day 2 of life.

Patients with DPD deficiency have variable clinical presentations but neurological abnormalities are common in previously reported cases. Out of 22 patients with complete DPD deficiency, 45% had convulsion, motor delay and mental retardation, 18% had growth retardation, 18% had autism, 14% had microcephaly, 14% had dysmorphism and 23% had ocular abnormalities. β-alanine, one of the end products of pyrimidine catabolism, is a structural analogue of γ-aminobutyric acid (GABA) and glycine which are the major inhibitory neurotransmitters in the central nervous system. Animal studies have been demonstrated that β-alanine could activate glycine and GABA\textsubscript{A} receptors as effective as glycine and GABA in central nervous tissue.

β-alanine is also a potent blocker of GABA uptake into glia cells. After synaptic release, GABA is transported into presynaptic endings and into glia cells where some of the neurotransmitter is metabolised by GABA transaminase. GABA uptake blocker such as β-alanine could therefore increase the availability of GABA in presynaptic endings and potentiate the GABA-mediated inhibition in the nervous system and hence suppressing epileptiform activity. Reduced level of β-alanine in patients with DPD deficiency may explain some neurological symptoms (e.g. convulsive disorder) observed in these patients.

On the other hand, accumulation of pyrimidine bases is also thought to be responsible for neurotoxicity (e.g. seizures, lethargy and hyperactivity) seen in patients with DPD deficiency after cancer treatment with 5FU.

Ocular abnormalities were found in 23% (5/22) patients with complete DPD deficiency. Reduced β-alanine level in DPD deficiency may alter the GABA\textsubscript{A} receptor regulation in the visual system and this may explain the observed ocular abnormalities in these patients.

Van Kuilenburg et al had identified seven different mutations, including one splice-site mutation, two deletions and four missense mutations after studying 17 families presenting 22 patients with complete DPD deficiency. The most common (47%) mutation in these 17 families accounted for DPD deficiency was G→A point mutation in the invariant splice donor site leading to the skipping of exon 14 [DPYD*2A] and this is also the mutation found in our reported cases. However, no clear correlation between genotype and phenotype could be established.

Clinical phenotype of DPD deficiency often begins in early childhood. Our patient had ocular abnormalities (micro-cornea, nystagmus and hypoplastic macula), generalised hypotonia, neonatal seizure and developmental delay since early neonatal period. Multiple anticonvulsants were given because of difficult seizure control. However, proband's mother and elder sister, who are also homozygous for the same splice-donor site mutation, are healthy so far. The variability of clinical phenotypes in patients with the same mutation indicates that other factors may play a role in clinical manifestation of this disorder.

The actual incidence of this defect could be underestimated as many asymptomatic patients may be unaware of their underlying condition. In fact, it was estimated that as high as 3% of Caucasian population could be heterozygous for the mutant DPD gene (DPYD) alleles and up to 1% Caucasian population could be homozygous for DPYD mutations. Screening for the presence of the G→A splice-site mutation [DPYD*2A] in a limited number of individuals of various nationalities had revealed heterozygous state for this mutation in around 4% of the Finnish population and in approximate 5% of the Taiwanese population but none in British, Japanese, African-American and Dutch populations.

As patients with DPD deficiency could be easily detected by determination of the pyrimidine organic bases (i.e. uracil, thymine and their degradation products) in urine, screening for these defects should be indicated for those with any
cerebral dysfunction symptoms and for those patients who are going to be treated with the anti-neoplastic agent, 5FU.

References