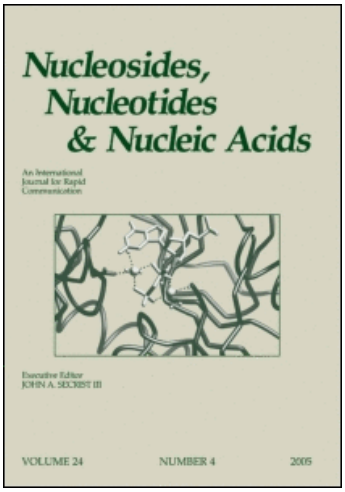

Nucleosides, Nucleotides and Nucleic Acids
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713597286

A Neonate with Recurrent Vomiting and Generalized Hypotonia Diagnosed with a Deficiency of Dihydropyrimidine Dehydrogenase

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To cite this Article Brussel, W. , van Kuilenburg, A. B. P. and Janssens, P. M. W.(2006) 'A Neonate with Recurrent Vomiting and Generalized Hypotonia Diagnosed with a Deficiency of Dihydropyrimidine Dehydrogenase', Nucleosides, Nucleotides and Nucleic Acids, 25: 9, 1099 — 1102
To link to this Article: DOI: 10.1080/15257770600894063
URL: http://dx.doi.org/10.1080/15257770600894063

Nucleosides, Nucleotides, and Nucleic Acids, 25:1099–1102, 2006

ISSN: 1525-7770 print / 1532-2335 online
DOI: 10.1080/15257770600894063

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A NEONATE WITH RECURRENT VOMITING AND GENERALIZED HYPOTONIA DIAGNOSED WITH A DEFICIENCY OF DIHYDROPYRIMIDINE DEHYDROGENASE

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□ *Deficiency of dihydropyrimidine dehydrogenase (DPD) is a rare inborn error of pyrimidine metabolism. To date, only about 50 patients are known worldwide. The clinical picture is varied and is not yet fully described. Most patients are diagnosed at the age of 1–3 years. We present a patient diagnosed 8 weeks postpartum.*

The female patient presented in the first 3 days after birth with agitation, choking, and vomiting. Six weeks later, the patient presented again with vomiting and insufficient weight gain. Metabolic screening of urine showed a strongly increased excretion of uracil and thymine, with no other abnormalities. This suggested a deficiency of DPD which was confirmed by enzyme analysis in peripheral blood mononucleair (PBM) cells (patient: activity <0.01 nmol/mg/h; controls: 9.9 ± 2.8 nmol/mg/h). The patient was homozygous for the IVS14+1G>A mutation.

MRI of the brain showed some cerebral atrophy; myelinization appeared normal. Many patients with DPD-deficiency suffer from convulsions and mental retardation, some show microcephaly, feeding difficulties, autism, and hypertonia. Our patient showed feeding difficulties and in the second half-year she developed slight motor retardation and generalized hypotonia. Further observation of the development of the patient may shed more light on the relationship between clinical symptoms and DPD deficiency. DPD deficiency may present in newborns with vomiting and hypotonia as the main symptoms.

Keywords Neonate; Vomiting; Hypotonia; DPD deficiency

INTRODUCTION

Deficiency of dihydropyrimidine dehydrogenase (DPD) is a rare autosomal recessive inborn error of pyrimidine metabolism (McKusick 274270).

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Approximately 50 patients have so far been described.[1] DPD catalyses the initial and rate-limiting step in the reduction of the pyrimidine bases uracil and thymine to dihydrouracil and dihydrothymine, respectively. The clinical picture of DPD-deficiency varies and is not yet settled. Patients may present with neurological symptoms during the first year of life, showing mental and motor retardation, epileptic insults, growth retardation, failure to thrive, microcephaly, hypertonia, and autism.[1] However, DPD deficiency may also be asymptomatic manifesting only later in life as severe toxicity after treatment with the chemostatic drug 5-fluorouracil. Most patients are diagnosed at the age of 1–3 years. Rarely, head imaging abnormalities have been described, showing diffuse cerebral atrophy and white matter hyperintensity.[2] It is presumed that some of the clinical abnormalities seen in DPD deficient patients result from altered homeostasis of ß-alanine and β-aminoisobutyric acid, the degradation products of the uracil and thymine, respectively.[3] Beta-alanine is supposed to be a neurotransmitter while β-aminoisobutyric acid is a partial agonist of the glycine receptor.

MATERIALS AND METHODS

The concentrations of the pyrimidine bases, uracil and thymine in urine were determined using HPLC electrospray tandem mass spectrometry, as described before.[4] The activity of DPD was determined in PBM cells using radiolabeled thymine followed by separation of radiolabeled thymine from radiolabeled dihydrothymine using reversed-phase HPLC.[5] DNA was isolated from granulocytes and PCR amplification of all 23 coding exons and flanking intronic regions of the DPD gene was carried out using intronic primer sets, as described before.[6]

RESULTS

The female patient described, was delivered after an uncomplicated pregnancy, had good Apgar scores and a normal birth weight. The parents were nonconsanguineous. A tent-shaped mouth and thick hair were noted. During the first 3 days the girl showed agitation, choking, and vomiting.

Six weeks later the patient presented again with vomiting and insufficient weight gain. Standard laboratory investigations, electroencephalography, gastroscopy, and distal oesophagus biopsies showed no abnormalities. Metabolic screening in urine obtained 8 weeks postpartum, however, showed a significantly increased excretion of uracil and thymine (888 and 628 μmol/mmol creatinine, respectively; reference values 11.8 $\pm$ 9.1 μmol/mmol creatinine and 0.5 $\pm$ 0.6 μmol/mmol creatinine), with no detectable levels of 5,6-dihydrouracil and 5,6-dihydrothymine. This is compatible with DPD deficiency, which subsequently was confirmed by

enzyme measurement and mutation analysis. The enzyme activity in PBM cells was <0.01 nmol/mg/h (controls 9.9 ± 2.8 nmol/mg protein/h). The analysis of the DPD gene showed that the patient was homozygous for the IVS14+1G>A mutation. This mutation leads to skipping of exon 14 immediately upstream of the mutated splice donor site in the process of DPD pre-mRNA splicing. As a result the mature DPD mRNA lacks a 165 nt segment encoding the amino acids 581–635. Analysis of the prevalence of the various mutations among DPD patients has shown that the IVS14+1G>A mutation is by far the most common one.[1]

Subsequent metabolic investigations showed that the level of β-alanine was in the normal range, in the patients urine (2.9 μmol/mmol creatinine; reference value 2.4 ± 3.0 μmol/mmol creatinine), as well as in plasma (2.9 μmol/l; reference value 3.8 ± 2.9 μmol/l). The level of β-aminoisobutyric acid was markedly decreased in urine (1.1 μmol/mmol creatinine; reference value 14.8 ± 11.7 μmol/mmol creatinine) and in serum (0.1 μmol/l; reference value 2.3 ± 1.9 μmol/l).

An MRI of the brain at the age of 5 months showed abnormally prominent sulci and ventricles on the T2-weighted axial images, suggesting cerebral atrophy. There was a right sided cyst in the basal ganglia between the claustrum and hippocampus. Myelinisation appeared normal and no white matter pathology was seen.

During the first 12 months of life weight gain of the girl has been steady but subnormal (−1.5 SD); the growth of the head is normal (±0 SD). Neurological examination shows mild general hypotonia and at 12 months of age she is not able to sit without support and crawling is not shown. There is still regular vomiting and she is drooling a lot. At one year of age eruption of teeth has not yet occurred. She suffered a viral upper airway infection at the age of 10 months and a viral gastrointestinal infection at 12 months, both illnesses associated with an increase in vomiting.

DISCUSSION

Vomiting was the only clinical symptom when the patient presented at 6 weeks of age, and this remained during the first year of life. It is uncertain whether the vomiting is related to the enzyme deficiency; the finding of a DPD-deficiency in our patient may also be unrelated to the mild motor retardation and generalized hypotonia. It should be noted that asymptomatic individuals with DPD-deficiency have been diagnosed, mostly at much older ages than our patient.[1,7] Because there are unaffected individuals, including asymptomatic siblings with biochemical and molecular findings similar to affected patients, it appears that DPD deficiency is a necessary, but not the sole factor, for the development of clinical abnormalities.[1,7] Besides vomiting our patient had mild dysmorphic features and later motor

delay and hypotonia. The MRI of the brain of our patient did show abnormalities, similar to the abnormalities described in other patients with DPD deficiency.[2]

The mechanism of neurological injury in DPD deficiency has not been clarified. The levels of β-alanine and β-aminoisobutyric acid, the degradation products of uracil and thymine, situated behind the DPD-block, showed a pattern very similar to that described in other patients with DPD-deficiency (i.e., a low-normal level of ß-alanine and a strongly decreased level of ß-aminoisobutyric acid in plasma), with the alterations in plasma being more pronounced than in urine.[3] The presence of significant residual amounts of ß-alanine, despite the complete block at DPD, has been explained by the existence of alternate pathways for the synthesis of ß-alanine.[3] This might also explain the large phenotypical variability of patients with DPD-deficiency The clinical development will be followed which may shed more light on the relationship between DPD deficiency, brain MRI pathology, and other clinical symptoms.

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