UvA-DARE (Digital Academic Repository)

Partial epilepsy in a girl with a symptom-free-sister: first two Finnish patients with dihydropyrimidine dehydrogenase deficiency

Holopainen, I.; Pulkki, K.; Heinonen, O.J.; Nanto-Salonen, K.; Haataja, L.; Greter, J.; Holme, E.; van Kuilenburg, A.B.P.; Vreken, P.; van Gennip, A.H.

DOI

[10.1023/A:1005399131620](https://doi.org/10.1023/A:1005399131620)

Publication date

1997

Published in

Journal of inherited metabolic disease

[Link to publication](#)

Citation for published version (APA):

Holopainen, I., Pulkki, K., Heinonen, O. J., Nanto-Salonen, K., Haataja, L., Greter, J., Holme, E., van Kuilenburg, A. B. P., Vreken, P., & van Gennip, A. H. (1997). Partial epilepsy in a girl with a symptom-free-sister: first two Finnish patients with dihydropyrimidine dehydrogenase deficiency. *Journal of inherited metabolic disease*, 20, 719-720.
<https://doi.org/10.1023/A:1005399131620>

General rights

It is not permitted to download or to forward/distribute the text or part of it without the consent of the author(s) and/or copyright holder(s), other than for strictly personal, individual use, unless the work is under an open content license (like Creative Commons).

Disclaimer/Complaints regulations

If you believe that digital publication of certain material infringes any of your rights or (privacy) interests, please let the Library know, stating your reasons. In case of a legitimate complaint, the Library will make the material inaccessible and/or remove it from the website. Please Ask the Library: <https://uba.uva.nl/en/contact>, or a letter to: Library of the University of Amsterdam, Secretariat, Singel 425, 1012 WP Amsterdam, The Netherlands. You will be contacted as soon as possible.

UvA-DARE is a service provided by the library of the University of Amsterdam (<https://dare.uva.nl>)

CASE REPORT

Partial epilepsy in a girl with a symptom-free sister: First two Finnish patients with dihydropyrimidine dehydrogenase deficiency

I. Holopainen^{1*}, K. Pulkki², O. J. Heinonen^{2,6}, K. Näntö-Salonen³, L. Haataja¹, J. Greter⁴, E. Holme⁴, A. B. P. van Kuilenburg⁵, P. Vreken⁵ and A. H. van Gennip⁵

Departments of ¹Pediatric Neurology, ²Clinical Chemistry and ³Pediatrics, Turku University Central Hospital, Kiinamyllynkatu Turku, Finland; ⁴Department of Clinical Chemistry, Sahlgrenska University Hospital, Gothenburg, Sweden; ⁵Academic Medical Centre, Departments of Pediatrics and Clinical Chemistry, Amsterdam, The Netherlands; ⁶Sports Medical Research Unit, Department of Physiology, University of Turku, Turku, Finland

*Correspondence: Department of Pediatric Neurology, Turku University Central Hospital, Kiinamyllynkatu 4-8, FIN-20520 Turku, Finland

Dihydropyrimidine dehydrogenase (EC 1.3.1.2; DPD) is the rate-limiting enzyme in pyrimidine catabolism converting the pyrimidine bases thymine and uracil to their dihydro derivatives (Webster et al 1995). DPD deficiency (McKusick 274270) has so far been reported in about 30 patients, most of them children (Webster et al 1995). The clinical phenotype is variable. Affected individuals have in many cases been detected when they have been investigated because of unspecific neurological symptoms. In some patients, symptoms have been induced by 5-fluorouracil, an anticancer drug which is also metabolized through DPD. We describe the first two Finnish cases of DPD deficiency: a girl whose first symptom was status epilepticus at the age of 7 years, and her so far symptom-free 5-year-old sister.

A 7-year-old girl was admitted to Turku University Hospital because of unconsciousness. She is the elder of two children of nonconsanguineous healthy Finnish parents. She was born at term after a normal pregnancy, and her growth and psychomotor development were normal. On admission, she was reacting to pain but needed assisted ventilation. Her EEG showed a generalized slowing of background activity but no irritative features or local abnormalities. Routine clinical laboratory parameters, spinal fluid analysis, and brain CT were normal. No infectious agents were found. She recovered in 24 hours without any symptoms, and the episode was tentatively classified as status epilepticus. After 3 weeks, she was admitted to the hospital for further examinations. In the ward she had her first partial, secondarily generalized epileptic attack. EEG recording indicated an irritative activity in the right occipital region. Her brain MRI was normal. Antiepileptic medication with oxcarbazepine was started, and she has been without seizures since then.

Urinary organic acids were analyzed by gas chromatography-mass spectrometry after solid-phase extraction and thymine and uracil concentrations by cation exchange chromatography using UV detection (van Gennip et al 1995). A urine sample from the patient indicated increased concentrations of thymine and uracil (163 and 191 µmol/mmol creatinine, respectively), and serum concentrations of thymine (22 µmol/L) and uracil (23 µmol/L) were also elevated. The symptom-free sibling also had increased levels of

thymine (227 $\mu\text{mol}/\text{mmol}$ creatinine) and uracil (275 $\mu\text{mol}/\text{mmol}$ creatinine) in her urine, and the plasma concentrations of thymine (25 $\mu\text{mol}/\text{L}$) and uracil (18 $\mu\text{mol}/\text{L}$) were increased. Her mother and father had nondetectable serum concentrations of thymine, and very low levels of uracil (0.40 and 0.15 $\mu\text{mol}/\text{L}$, respectively). Their urine samples contained trace amounts of thymine and uracil (the father had uracil) $\sim$ (6 $\mu\text{mol}/\text{mmol}$ creatinine). DPD activities (nmol/mg protein per h) in cultured skin fibroblasts were as follows: the patient and her sister nondetectable; mother 0.66; father 0.51; controls ($n=16$) 1.00 ± 0.76 (mean $\pm$ SD). The molecular analysis of DPD gene was carried out as described recently (Vreken et al 1996), and indicated that both sisters were homozygous for G $\rightarrow$ A mutation in an invariant splice-donor site. As expected, both parents were heterozygous for this mutation.

Although the clinical manifestations of DPD deficiency are unspecific and variable, the majority of patients have convulsive disorders or a family history of epilepsy (Webster et al 1995). Epilepsy usually appears during the first decade. The mode of inheritance of DPD deficiency is autosomal recessive. The gene frequency is not known, but based on the Dutch experience it may be rather high (van Gennip et al 1995). The mutation leads to skipping of the 165 nt exon immediately upstream of the splice-donor site in the process of DPD pre-mRNA splicing. As a result, the mature DPD mRNA lacks a 165 nt segment encoding amino acid residues 581–635. The resulting mutant DPD protein has no detectable residual activity (Vreken et al 1996). The same mutation has also been found in two homozygous, unrelated Dutch patients and in a patient from Denmark (Vreken et al 1996), suggesting homogeneity in DPD-deficient patients in northern Europe.

REFERENCES

- van Gennip AH, van Lenthe H, Abeling NGGM, Bakker HD, van Kuilenburg ABP (1995) Combined deficiencies of NADPH- and NADH-dependent dihydropyrimidine dehydrogenases, a new finding in a family with thymine-uraciluria. *J Inher Metab Dis* **18**: 185–188.
- Vreken P, van Kuilenburg ABP, Meinsma R, et al (1996) A point mutation in an invariant splice donor site leads to exon skipping in two unrelated Dutch patients with dihydropyrimidine dehydrogenase deficiency *J Inher Metab Dis* **19**: 645–646.
- Webster DR, Becroft DOM, Suttie DP (1995) Hereditary orotic aciduria and other disorders of pyrimidine metabolism. In Scriver CR, Beaudet AL, Sly WS, Valle D, eds. *The Metabolic and Molecular Bases of Inherited Disease*, 7th edn. New York: McGraw-Hill, 1777–1837.