A Retrospective Study of a Patient with Homozygous Form of Acute Intermittent Porphyria

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Summary: In 1964 a child with an exceptional form of porphyria was described; she excreted persistently excessive amounts of delta-aminolaevulinic acid, porphobilinogen and uroporphyrin in her urine from early childhood. The biochemical profile resembled that of acute intermittent porphyria (AIP). The child died at the age of 8 years. Reinvestigation of some urine samples by HPLC revealed differences in comparison with urines of other patients with AIP. The clinical picture characterized by porencephaly and severe retardation in development was completely different from that of AIP. Her mother suffered from AIP but the father never had attacks. Investigations on blood and urine samples of the father showed that he also was affected. Due to the early onset in the index patient, its persistent character, and the fact that both parents are affected we postulate retrospectively to have diagnosed a case of homozygous or a double heterozygous AIP, hitherto undescribed.

Acute intermittent porphyria (AIP) is a dominant, autosomal, inherited disorder characterized by a diminished porphobilinogen deaminase activity (PBG deaminase, EC 4.3.1.8). PBG deaminase catalyses the condensation of four PBG molecules into a symmetrical head-to-tail arrangement, thus forming the tetrapyrrole, hydroxymethylbilane. Uroporphyrin III synthase (EC 4.2.1.75) converts this latter compound into the cyclic tetapyrrole, uroporphyrinogen III. Four other enzymes convert uroporphyrinogen III into haem (Jackson et al., 1967; Jordan and Berry, 1980; Wright and Lim, 1983).

Affected heterozygous individuals still have enough PBG deaminase activity left to ensure the production of the required amount of haem, and in general no striking overproduction of the precursors delta-aminolaevulinic acid (ALA), PBG and the

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porphyrins is observed. The majority of these subjects remain clinically latent in spite of the dominant character of the defect.

However, under circumstances when increased haem production is required, due to a sudden need for cytochrome P450 oxidase, these individuals may exhibit acute attacks, leading to abdominal pain and neuropsychiatric manifestations (Walsh, 1984). Attacks are precipitated by drugs, particularly barbiturates, sulphonamides and also by alcohol, infection, fasting or endocrine factors.

During attacks the disease can be diagnosed easily on the basis of increased urinary levels of ALA, PBG and porphyrins. During the latent phase these may barely be elevated, or even may be normal. Then the assay of PBG deaminase activity in erythrocytes may reveal the presence of the disorder. However, in practice there appears to be an overlap between relatively low PBG deaminase activities without AIP and relatively high activities in affected individuals (Bottomley et al., 1981). In such cases the only way to prove AIP definitively is the investigation of genetic material of the patient by tracing the defective gene coding for PBG deaminase by means of restriction fragment length polymorphism (RFLP), or by means of sequencing (Llewellyn et al., 1987).

The prevalence of AIP in the population is, due to the occurrence of many latent cases, not precisely known. In certain parts of the world, e.g. in Lapland, the incidence of AIP is as high as 1 : 1000, whereas in general it is estimated to be in the order of 1 : 10000 (Kappas et al., 1983). One can deduce from this figure that the chance for the occurrence of homozygous or double heterozygous AIP must be extremely rare.

In 1964 a child with severe neurological abnormalities on a basis of porencephaly, and biochemically with a persistent porphyria of the AIP type, was observed (Villeneuve et al., 1964). The girl died at the age of 8 years. From early childhood her urine contained excessive amounts of uroporphyrinogens, uroporphyrins, PBG and ALA. As at that time possibilities to explore her case were limited, no conclusions could be made as to the exact nature of her disease. However, some urine samples of this patient were stored at \(-20^\circ C\). Recently these samples were reinvestigated by modern analytical techniques. Also blood and urine samples of her parents and other relatives (two brothers and a sister) were investigated. Results reported in the present paper revealed that both parents were affected with AIP. We postulate that this unique patient may represent the homozygous or double heterozygous form of AIP.

**PATIENT AND FAMILY**

The index patient was a girl, born in 1953; pregnancy and delivery were uneventful, and apart from a peculiar pale red coloration of her diapers, noticed by her mother, she showed no abnormalities during the first 6 months of life. At the age of 8 months she developed a cyst just above the nose, which initially was treated with penicillin, but later on built up again. After inspection the cyst appeared to have grown into the frontal cranial cavity. During operation of the cyst it was noticed that her brain was abnormally small. After the operation she showed no further mental development. At the age of 5 years she was readmitted for her mental retardation and neurological aberrations, and the urine was screened for inherited metabolic diseases. Porphyria was observed; urinary analysis performed on several occasions, over a period of 3