Molecular abnormalities of the responsible enzymes for each type of acute porphyria have accumulatively been determined. Although enzyme defects in the heme synthetic pathway are different in the 4 types of porphyria (porphobilinogen deaminase for acute intermittent porphyria (AIP), coproporphyrinogen oxidase for hereditary coproporphyria (HCP), protoporphyrinogen oxidase for variegate porphyria (VP) and δ-aminolevulinic acid dehydratase (ALAD) for ALAD deficiency porphyria), the clinical features during an acute attack are similar and to date the primary treatment is very much the same (1, 2). Since linkage between enzyme defects and clinical manifestations has not been fully elucidated, the radical therapy for acute attack has not been established.

Therefore, prevention is the most important. Fortunately, a number of risk factors have been known experimentally and clinically. All relatives at risk should be tested by the screening methods available for each type of porphyria (3). For these carriers avoidance of known or theoretically risky drugs, and prompt treatment of intercurrent diseases including infections and other causes of stress are very important. Generous intake of carbohydrates may also prevent minor attacks (1, 2).

Traditional symptomatic therapy has been insufficient in severe cases, resulting in a high mortality. Accordingly, fundamental therapy based on pathogenesis has been eagerly investigated.

During the past several decades, therapies for acute attacks bordering on the radical have been developed. δ-aminolevulinic acid (ALA) toxicity through δ-aminolevulinic acid synthase (ALAS) induction and heme deficiency related to heme enzyme defect are two major rationales of the pathogenesis (1, 2). Therefore, many trials have targeted these points. So far increased glucose supplementation and hematin infusion have had beneficial results.

An increased amount of glucose intake suppresses ALAS activity (the so-called “glucose effect”) (4), leading to reduction in ALA, porphobilinogen (PBG) and porphyrins excretion, and ameliorates porphyria symptoms. The efficacy of glucose, however, is limited to mild cases.

Hematin is more potent than an increased amount of glucose to alleviate an acute episode and thus should be administered in more severe cases. Lyophilized hematin (Panhematin, Abbott Laboratories, North Chicago, IL, USA) in North America and heme-arginate (Normosang, Medica Pharmaceutical Co., Ltd., Helsinki, Finland) in Europe are available (1, 2). Two to four mg/Kg of hematin is infused intravenously for 30–60 minutes, every 12 hours. This manipulation always decreases hepatic ALAS (the house-keeping type) activity, ameliorating hepatic overproduction of ALA and PBG, and improves porphyria symptoms (1, 2, 5). The effect is sometimes drastic but is of short duration. So, hematin should be administered for at least 3 days. However, hematin dissolved in isotonic solution is quickly polymerized, and has a propensity for adverse effects, such as phlebitis, thrombophlebitis, coagulopathy or hemolysis (6). When an excess amount of hematin is infused, transient renal failure may occur. All these adverse effects occur frequently (about 50%) (1) and therefore the patient should be carefully observed during hematin therapy. Heme-arginate in albumin solution is stable and has only a few such side effects (7). However, both hematin preparations provide a good substrate for hemeoxygenase, which may reduce the effect of hematin. In addition, findings that both heme preparations have possible risks of viral infection because of its source of blood and the fact that these are not available in Japan, limit the long-term use of hematin. Another heme-related compound is tinoporphyrin, which is not degraded by hemeoxygenase and suppresses ALAS activity and ALA and PBG excretion in experimental porphyria (8). Clinical evaluation will soon be proven.

A recent treatment trial for acute porphyria is cimetidine, an H2 receptor antagonist. The benefit of this drug for acute attacks, especially for severe cases, is equivocal. However, it is helpful for mild attacks, better than glucose therapy and may play a role in prophylaxis of acute attacks (9). Cimetidine is also effective for clinical symptoms and porphyrin metabolism in erythropoietic protoporphyria and porphyria cutanea tarda (10). Thus, the drug may act on both house-keeping and erythropoietic types of ALAS, but the precise mechanism is still unknown. This drug may be cost-effective and an easily administered alternative to hematin, but beneficial results are variable and therefore the optimal dosage and duration of the treatment with cimetidine have not yet been determined.

Another treatment option of acute porphyria has been endocrine manipulation. Women who experience repeated attacks during their perimenstrual period have sometimes benefited from contraceptives, which suppress ovulation and cyclical sex hormone production (11). However, steroid treatment itself, especially progesterone, may also exacerbate porphyria symptoms. In 1984 Anderson et al (12) introduced a safe applicable treatment using long acting luteinizing-hormone releasing hormone (LHRH) analogue for perimenstrual attacks of AIP patients. Repeated administration of the agent appears to desen-
sitize the effect of LHRH on the pituitary, thereby abolishing cyclical secretion of luteinizing-hormone (LH) and follicle-stimulating hormone (FSH), and ovulation. Beneficial effects are marked for clinical symptoms as well as preventing acute attacks and decreasing porphyrin production. These results are confirmed by further case reports in 17 AIP (13–19) and 1 VP (16) patients. The agent can be applied intranasally or subcutaneously, and is a reliable contraceptive and can presumably be easily continued for several years. And it is available in Japan. Recently, Yamamori et al (20) reported in this journal that the drug is of marked benefit in one HCP patient.

During treatment for 5 years, the patient did not experience a cyclical attack except for one minor episode. She also noted osteoporosis due to marked deficiency of estrogen 4 and a half years after the initiation of LHRH analogue therapy. Osteoporosis has been widely observed in other cases, but it is the only serious adverse effect during long-term LHRH analogue therapy. Another warning which must be given concerning the initial and inevitable agonistic action of LHRH analogue is that it can lead to acute attacks. Fortunately, the cases reported did not experience this side effect, but several cases noted minor climacteric symptoms.

Although the beneficial effects are limited in women, this easily available LHRH analogue may provide a new approach in the management of acute porphyria.

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References