CASE REPORT

Premenstrual attacks of acute intermittent porphyria: hormonal and metabolic aspects – a case report

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Abstract

We report the case of a 38-year-old woman with acute intermittent porphyria (AIP). Following the observation of an acute AIP attack in the patient’s father, the diagnosis was established after genetic and biochemical examinations. At the age of 29, eight months after delivery of her first and only child, the patient was hospitalized due to a first proven attack of AIP. In the following years she suffered several premenstrual AIP attacks, with clinical symptoms ranging from abdominal pain to paralysis. One attack was accompanied by an increased urinary catecholamine output, strongly indicating adrenergic hyperactivity. The precipitation of acute episodes by secretion of gonadotrophins and a severe hyponatraemia due to a syndrome of inappropriate anti-diuretic hormone secretion indicated hypothalamic involvement in the pathogenesis of AIP. This patient has experienced an evolution of treatment regimens. At first, acute attacks were treated by i.v. hypertonic glucose. Afterwards propranolol was instituted as a maintenance therapy. Later on, i.v. injections of haem arginate were very successful in resolving acute AIP episodes. However, until therapy with an LHRH analogue was started, the patient continued to suffer premenstrual AIP attacks. These LHRH analogues cause hypothalamic inhibition of gonadotrophin secretion, with stabilization of endogenous ovarian steroid production at a low level, and therefore may be effective in preventing acute exacerbations of this disease. Since this patient went on a fixed regimen of an LHRH analogue combined with the lowest dose oestrogen patch her quality of life has improved substantially and she has not required hospitalization, now for over 3 years.

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Introduction

Acute intermittent porphyria (AIP), the major type of hepatic porphyrias, is an autosomally dominant inherited disorder (1). The prevalence of gene carriage is estimated at 1/10 000, but the case prevalence is only 1–5/100 000. It results from mutations in the gene encoding for uroporphyrinogen I synthetase, previously called porphobilinogen (PBG) deaminase, causing a decreased activity of this third enzyme in the haem biosynthetic pathway (1). This partial block not only interferes with the negative feedback regulation of hepatic amino-laevulinic acid synthetase (ALAS), which is the first and rate-controlling enzyme, resulting in a secondary overproduction of delta-aminolaevulinic acid (δ-ALA) and PBG, but also accounts for the normal or only slightly increased urinary and faecal porphyrins (1).

AIP is marked biochemically by the increased urinary excretion of the porphyrin precursors PBG and δ-ALA, giving the urine a reddish-brown colour. Patients with AIP usually present with a wide variety of signs and symptoms. These include tachycardia, severely increased arterial blood pressure and absent deep tendon reflexes. Symptoms range from abdominal pain, vomiting and constipation to seizures, paresis and frank paralysis. Abdominal pains can be so severe as to mimic appendicitis or acute abdomen (2).

The metamorphosis of AIP from a latent disorder of metabolism into a severe clinical syndrome, sometimes even life-threatening (2), is a puzzling and important feature of this disease. Acute attacks are often precipitated by exposure to certain drugs (e.g. barbiturates, oral contraceptive agents and sulphonamide antibiotics), cyclical hormonal changes in women, fasting or alcohol intake and/or by infections. Endogenous steroids are important determinants of disease activity, as indicated by the female preponderance of clinical disease, the rarity of attacks before puberty or after middle age, and the frequent occurrence of premenstrual attacks in women affected by AIP (3).
To prevent acute attacks of AIP one should avoid triggering factors. Acute attacks can be treated by oral or i.v. glucose administration (300–500 g/day) and/or the administration of haematin or haem arginate (165 mg/day) (4, 5). Propranolol (3 × 20 mg/day) can be used to treat symptoms of adrenergic hyperactivity associated with AIP (6).

Since there exists a group of young women suffering monthly premenstrual porphyric crisis, the use of luteinizing hormone-releasing hormone (LHRH) analogues was introduced by Anderson et al. (7).

**Case report**

We describe the history of a 38-year-old woman with AIP. Following the observation of an acute attack of AIP in the patient’s father, she was screened for having this autosomally dominant inherited disorder. Analysis of urinary haem precursors and of faecal porphyrins revealed a significantly elevated level of δ-ALA up to 8.6 mg/g creatinine (normal: ≤ 5 mg/g creatinine). Moreover, measurement of uroporphyrinogen I synthetase activity in erythrocytes (79.1 pmol/mg protein per 30 min) demonstrated a decreased activity (normal: >100 pmol/mg protein per 30 min), reflecting the primary genetic defect of AIP and establishing the diagnosis. At that time the patient was 22 years of age.

At the age of 29, eight months after delivery of her first and only child, the patient was hospitalized due to increasing pain sensations at the lumbar region, severe abdominal pain, vomiting, restlessness and a progressively increasing fatigue. The painkillers she took in that period aggravated the situation. A physical examination revealed a blood pressure of 150/105 mmHg, a regular heart rate of 76/min, normal heart sounds and auscultation of the lungs. Pulpation of the abdomen was painful. Her urine had a dark-reddish appearance. Urine examination for the presence of porphyrins confirmed the diagnosis of an acute attack of AIP. I.v. hypertonic glucose administration (300 g/day), ispaghul mucilago to resolve the faecal impaction and propranolol (3 × 20 mg/day). A carbohydrate-rich diet and the use of propranolol was subsequently advised.

Only 3 months later the patient was readmitted to the hospital because of another premenstrual AIP attack. I.v. injections of haem arginate (Normosang: 165 mg/day) during 6 consecutive days alongside i.v. hypertonic glucose infusions resulted in a spectacular biochemical and clinical improvement.

The patient continued to suffer several premenstrual AIP attacks, which required hospitalization and were successfully treated by i.v. haem arginate injections.

At the next admission it was decided to start with triptorelin, an LHRH analogue (Decapeptyl: 3.75 mg/2 ml, i.m., every 4 weeks), in addition to classical treatment approaches. This option was taken because of the menses-related exacerbations of AIP. The benefits of treatment were carefully weighed against potential adverse effects of oestrogen suppression. Before starting with the LHRH analogue, a pregnancy test, a PAP smear, a gynaecological ultrasound, a peripheral blood examination and measurement of bone mineral density were done. These held no contra-indications. The follicular phase levels of oestradiol (158 pg/ml; normal: 30–120 pg/ml), progesterone (0.42 ng/ml; normal: 0.26–1.2 ng/ml), luteinizing hormone (LH) (9.5 mU/ml; normal: 1.0–7.8 mU/ml), follicle-stimulating hormone (FSH) (3.4 mU/ml; normal: 0.9–17.8 mU/ml), testosterone, sex hormone binding globulin, δ4-androstenedione, dihydroepiandrostenedione sulphate and prolactin were also determined, resulting all in normal values, except for the slightly increased oestradiol and LH levels.

Because of the well-known adverse effects of LHRH analogues, it was decided to add the lowest dose oestrogen patch (Systen Patch TTS 3.2 mg/16 cm²,

normal electrolytes, normal liver function tests, and a normal thyroid function. Increased concentrations in the 24 h urine collection of PBG (142 mg/24 h (normal: 0–2 mg/24 h)), and δ-ALA (42.7 mg/24 h (normal: 1.3–7.0 mg/24 h)) were compatible with the diagnosis of an acute premenstrual attack of AIP. On 2 consecutive days urine was collected to detect catecholamines, and showed an increased urinary excretion of free catecholamines with levels up to 197 and 152 μg/day (normal: <115 μg/day), total metanephrines up to 1267 and 1433 μg/day (normal: <900 μg/day) and vanillylmandelic acid up to 24.6 and 21.7 mg/day (normal: <10 mg/day), all indicative of adrenergic hyperactivity. Plasma renin activity was normal. X-ray of the abdomen revealed faecal impaction at the level of the colon. The presence of a phaeochromocytoma was excluded by scanning of the adrenal glands by CT and a clonidine suppression test. An ECG was normal, as were the results of an eye fundus and of an electromyographic examination. When the patient was discharged from the hospital her kidney function was completely normalized with a creatinine of 1.0 mg/day. Therapy consisted of i.v. hypertonic glucose administration (300 g/day), ispaghul mucilago to resolve the faecal impaction and propranolol (3 × 20 mg/day). A carbohydrate-rich diet and the use of propranolol was subsequently advised.

The patient continued to suffer several premenstrual AIP attacks, which required hospitalization and were successfully treated by i.v. haem arginate injections.
The patient continued to use the LHRH analogue combined with the lowest dose oestrogen patch for a period of 17 months. During this entire period she required no hospitalization. This treatment regimen resulted in a decrease of the levels of oestradiol, progesterone, LH and FSH measured in the follicular phase: 15 pg/ml, 0.23 ng/ml, 2.2 mU/ml and 1.7 mU/ml respectively.

Table 1 shows the effect of haem arginate and of triptorelin on urinary δ-ALA as a marker of activity of AIP and on different haemostatic factors.

Three months after an attempt to stop the LHRH analogue treatment regimen, however, she was again admitted to the hospital. Another 5 months later the patient was hospitalized once more due to another premenstrual attack of AIP. A physical examination revealed only a severe hypertension of 160/110 mmHg and a tachycardia of 110 beats/min. Laboratory investigation showed a normal peripheral haematogram, a slightly impaired kidney function with a creatinine of 1.5 mg/dl, normal liver function tests, a slight hypokalaemia of 3.2 mmol/l (normal: 3.5–5.0 mmol/l) and a severe hyponatraemia of 112 mmol/l (normal: 135–148 mmol/l). Urinary sodium excretion was very high (111 mmol/l; normal: < 20 mmol/l), serum osmolality was low (234 mosmol/kg; normal: 275–305 mosmol/kg) and urinary osmolality was normal (433 mosmol/kg; normal: 50–1200 mosmol/kg). The level of urinary δ-ALA reached up to 54 mg/24 h (normal: 1.3–7.0 mg/24 h). Measurement of serum cortisol, adrenocorticotrophin (ACTH) and a 24-h cortisoluria showed no abnormal results. The levels of catecholamines in the 24-h urine collection were also normal. Based on the available data, we assume that this attack of AIP was accompanied by a severe hyponatraemia due to the syndrome of inappropriate anti-diuretic hormone (ADH) secretion (SIADH). The levels of total and low-density lipoprotein (LDL)-cholesterol were slightly increased (236 and 168 mg/dl respectively). This attack was treated by fluid restriction to correct the hyponatraemia, i.e., hypertonic glucose infusion and haem arginate injections, and therapy with triptorelin was restarted. Since this treatment option was restarted the patient has not required hospitalization, and this for 3 years.

**Discussion**

This patient was screened for gene carriage of AIP following the observation of an acute AIP attack in her father. Analysis of urinary haem precursors and determination of uroporphyrinogen I synthetase activity in erythrocytes established the diagnosis. Identification of asymptomatic children who have inherited AIP is an important aspect of the management of the disease in these families and requires enzymatic or DNA methods (8, 9).

Eight months after delivery of her first and only child the metamorphosis of AIP from a latent disorder of metabolism into a clinical syndrome became apparent. Among women with AIP a group exists whose clinical symptoms are precipitated by menses or pregnancy, as was the case here (3). Endogenous steroids are important determinants of disease activity since they might compromise haem biosynthesis through cytochrome P450 induction, resulting in a haem-deficient state and subsequently triggering acute attacks. The patient's first acute attack was aggravated by exposure to analgesics, probably by inducing the metabolism of cytochrome P450.

The severity of attacks can be classified according to Dhar et al. (10): this patient had one class B attack with creeping paralysis, and several acute episodes with class A severity. The pathophysiology of the neurological manifestations of AIP is not yet clearly understood (11). Neurological manifestations may be explained by a deficiency of haem and a corresponding deficiency of cytochrome P450 in neural tissues (4). Another hypothesis is that the porphyrin precursor δ-ALA may be neurotoxic, since acute attacks only occur when excretion of porphyrin precursors is increased (12).

Hypothalamic activity plays an important role in the pathogenesis of AIP. In the first place, secretion of gonadotrophins or their secondary effects may be involved in precipitating acute episodes of AIP. In the second place, disorders of ADH secretion can be present. Severe hyponatraemia can occur due to the SIADH provoked by AIP (11, 13, 14). Also the findings of
tachycardia, hypertension, constipation and an increased urinary excretion of catecholamines in our patient, which are indicative of adrenergic hyperactivity, might result from abnormalities in hypothalamic control of the autonomic nervous system (3, 15). Thus hypothalamic involvement certainly applies to this patient. In addition, there is an influence of the hypothalamus on growth hormone, abnormal lactation and defective ACTH secretion (16–18). AIP also shows a number of other endocrine and metabolic complications. These include dyslipidaemia with an increased level of total and LDL-cholesterol, disturbances in glucose tolerance and hyperinsulinism, and disturbances of haemostasis and fibrinolysis. Apart from a slightly elevated increase in cholesterol and plasminogen activator inhibitor no other abnormalities were detected despite thorough investigation. Moreover, Table 1 shows that coagulation parameters improved as well after haem therapy as after treatment with an LHRH analogue. To the best of our knowledge, we are the first to describe this finding.

To prevent acute attacks of AIP one should avoid exogenous triggers such as certain drugs, alcohol and fasting. Acute AIP attacks are treated with i.v. glucose administration (300–500 g/day) and increased carbohydrate intake. I.v. administration of haematin or haem arginate is also used to treat acute episodes in porphyric patients. Glucose and haematin/haem arginate (165 mg/day) act by suppressing the activity of ALAS and subsequently lowering the elevated concentrations of δ-ALA and PBG in plasma and urine (5, 19, 20). Haematin might also be able to correct intraneuronal haem deficiency. A possible side-effect is the occurrence of severe phlebitis after i.v. administration of haematin, which does not occur with haem arginate. It may be as safe as isotonic glucose and is certainly easier to administer than hypertonic glucose solutions. It may also be cost-effective because it considerably shortens the required time of hospitalization (21). Our patient responded spectacularly to haem arginate administration.

Propranolol (3 × 20 mg/day) is another possibility to treat symptoms of adrenergic hyperactivity in AIP, because it seems to decrease the induction of ALAS (6, 15). Since attacks of AIP can be precipitated by hormonal factors, devastating the lives of young women suffering monthly premenstrual porphyric crisis, many treatment regimens were tried. The tolerance to exogenous, even low-dose steroids appears to be highly variable in women with AIP (22). Some authors describe successful treatment with low-dose hormonal oral contraceptives for the prevention of clinical symptoms of AIP (3), while others report that administration of hormonal oral contraceptives can precipitate acute attacks (23). It would be important to analyse whether the type, the dose or the route of administration of pharmacological compounds can exacerbate the disease.

Another risk associated with the use of hormonal oral contraceptives is liver damage (24). This is particularly important since AIP patients, especially women, seem to have an increased risk of developing hepatocellular carcinoma (HCC). Liver cirrhosis appears to be more common in AIP patients and may be a preliminary stage of HCC. Therefore, the use of oral hormonal contraceptives is not advisable in women with AIP. Andersson et al. (25) even recommend that all AIP gene carriers aged 55 years or more should be screened for HCC. Experience with danazol, a derivative of 17α-ethyl testosterone, which suppresses gonadotrophin and oestrogen release, was discouraging. Danazol proved to be a steroidal inducer of ALAS, causing clinical exacerbations of AIP (26).

Recently the use of LHRH analogues was introduced. These LHRH analogues cause, after an initial period of stimulating gonadotrophin secretion, a down-regulation of pituitary function, namely reducing secretion of LH and of FSH, if regularly given (7, 27). As a consequence oestradiol and progesterone levels fall, as in our patient, reaching menopausal levels if a sufficiently large dose is given. This suggests that hypothalamic inhibition of gonadotrophin secretion, with stabilization of endogenous ovarian steroid production at a low level, may be effective in preventing acute exacerbations of this disease. Possible side-effects consist of flushing, vaginal dryness, decreased breast size, decreased libido, coronary artery disease and bone demineralization (28–30). In our patient, so far, treatment with an LHRH analogue combined with the lowest dose oestrogen patch has proved to be an excellent regimen, since she has not suffered any attacks during those periods. A gynaecological ultrasound and bone mineral density scan and in addition hormonal dosages are repeated annually during this treatment regimen.

Raloxifene, a selective oestrogen receptor modulator which appears not to be metabolized by the cytochrome P450 pathway, might be useful in future treatment regimens. It looks promising since it seems to have oestrogen-like effects on bone and lipid and oestrogen antagonist-like effects on uterine and breast tissues (31). However, assessment of any treatment in AIP is very difficult, not only because of the variability of disease activity between and within subjects, but also because of the very small number of patients affected.

**Conclusion**

AIP is an infrequently encountered genetic disease. The tragedy is that even today there are still many patients who suffer from this disorder, but are not aware of it and keep having symptoms. In addition, physicians often do not immediately recognize this disorder and proper treatment is delayed. The need for good information is very important, since it is the unknown nature of this disease which holds dangers of missed or wrong diagnosis and treatment. Because AIP is a relatively rare disorder, not enough support is available to study it.
in detail. This case showed the whole spectrum of clinical symptoms and the evolution of treatment regimens. Now our patient is being treated by means of an LHRH analogue combined with the lowest dose of oestrogen patch, substantially improving her quality of life, since she does not suffer premenstrual exacerbations of AIP any more. Close follow-up is mandatory to detect the slightest adverse effect of these drugs and to be alert for abnormalities associated with AIP.

References


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