Acute intermittent porphyria treated by testosterone implant

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Summary: The hereditary disorder acute intermittent porphyria is potentially fatal. Many more females present with active disease than males and some have attacks related to their menstrual cycle and pregnancy. We present a female patient who was diagnosed while pregnant at 19 years. She subsequently developed life-threatening attacks pre-menstrually at 24 years; these were associated with weight loss. Initial treatment was with high calorie feeding via a naso-gastric tube, followed by a gastrostomy. Subsequent gonadotrophin suppression with intranasal leuteinizing hormone-releasing hormone analogue (buserelin) thrice daily met with limited success. We implanted 100 mg of testosterone subcutaneously in November 1989. The buserelin was discontinued in January 1990 and menses returned 3 months later. There have been no serious attacks since then. Repeat implantation was performed at 6 monthly intervals until her present pregnancy. Baseline biochemical parameters have remained high and unaltered despite treatment although the testosterone has clearly had a marked clinical benefit, without side effects.

Introduction

Acute intermittent porphyria (AIP) is an autosomal dominant disorder of haem metabolism. The biochemical abnormality is a 50% reduction in the activity of the enzyme porphobilinogen (PBG) deaminase. The rate-limiting step in this pathway is the enzyme aminolaevulinic acid (ALA) synthase. This is thought to be controlled by negative feedback of free haem (Figure 1). AIP sufferers have raised urinary levels of the porphyrin precursors PBG and ALA. Only about 10% of persons inheriting the defect will develop the clinical disease, which is characterized by intermittent attacks of abdominal pain, vomiting, peripheral neuropathy and psychosis. Attacks are thought to be caused by neuronal dysfunction, possibly caused by ALA (which rises even higher during attacks), or by cytochrome deficiency secondary to relative lack of intracellular haem¹ (Figure 1). The disorder is potentially life-threatening.

Many factors influence the occurrence and frequency of attacks. Apart from low weight, drugs and other illness, hormonal factors are clearly

important. Apparently spontaneous attacks in women are about five times more common than in men. Attacks are more common pre-menstrually and during pregnancy, and almost unheard of before puberty and after the menopause.

Our patient, who presented with pre-menstrual attacks, has been treated apparently successfully with testosterone implants. Other treatments including gonadotrophin down-regulation with intranasal buserelin had failed.

Case report

A female born in 1963 was diagnosed aged 19 while pregnant, when urine left standing near a window became port-wine coloured. She developed acute attacks pre-menstrually at the age of 24 years which were followed by weight loss from 40 to 36 kg. Initial treatment was with dietary supplementation by naso-gastric tube and subsequent gastrostomy to induce weight gain. This was successful only initially but when pre-menstrual attacks recurred a 'medical menopause' was induced with intranasal buserelin (a gonadotrophin-releasing hormone analogue). The incidence and severity of attacks fell dramatically for a time but after 8 months the attacks returned despite continuing amenorrhoea. These were again severe and necessitated hospital admission.

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Figure 1 The relationship between the clinical symptoms, haem, the cytochromes, ALA synthase, 5β steroids and the possible effects of testosterone in acute intermittent porphyria.

Our extensive experience of low-dose testosterone implantation in women with the pre-menstrual syndrome, the low incidence of side effects, and the inference from the known sex difference in the incidence of attacks that androgens may protect affected males, led us to implant 100 mg of testosterone sub-cutaneously in November 1989. The normal male replacement dose is 800 mg. Two months later the busserlin was discontinued. Regular menstruation returned 3 months later with normal luteal phase progesterone measured in one cycle. Repeat hormone implantation was carried out in May and October 1990. The patient remained symptom free for 14 months apart from three mild attacks, two of which were pre-menstrual and one with no obvious precipitant.

She did not report any side effects of treatment with testosterone and became neither hirsute nor virilized. Neither busserlin nor testosterone affected the baseline levels of urinary PBG or ALA which have remained grossly elevated (range 94–694 and 212–376 $\mu\text{mol}/24\text{ h}$, normal less than 40 and 16 $\mu\text{mol}/24\text{ h}$, respectively). The patient remained underweight with a body mass index of approximately 15 kg/m^2 , but nevertheless became pregnant with her third child. During this pregnancy she has had two further mild attacks of nausea and vomiting which settled with conservative treatment.

Discussion

The most obvious hormonal feature in the luteal phase of the cycle is the high circulating level of progesterone. One of the 5β metabolites of progesterone (5β pregnanedione) with its angulated chair shape is porphyrinogenic under experimental conditions whereas its planar epimer 5α pregnandione is not.³

AIP sufferers are known to be distinguished from those with latent AIP by a deficiency of hepatic 5α reductase⁴ with consequent increased production of porphyrinogenic 5β steroid metabolites. Testosterone is also metabolized by 5α reductase to the more active androgen 5α dihydrotestosterone. In the patient's case, testosterone therapy seems to have had a marked clinical benefit suggesting that an androgenic environment is at least partially protective against attacks, even in the presence of normal luteal phase progesterone levels. 5α reductase is known to be induced by androgens,⁵ and this effect might be relevant by reducing the production of 5β pregnanedione and other 5β steroids (Figure 1). Alternatively we speculate that androgens may act later in the pathway either directly or indirectly to stimulate haem production which is necessary to maintain intracellular levels of a range of cytochromes and their dependent enzymes (Figure 1).

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