Acute intermittent porphyria treated by testosterone implant

M.W. Savage, P. Reed, S.L. Orrman-Rossiter, C. Weinkove and D.C. Anderson

University of Manchester, Department of Medicine and Endocrinology, and Chemical Pathology, Hope Hospital, Salford M6 8HD, UK

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 leutening 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 haem (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.
Normal haem biosynthesis

Glycine + Succinyl CoA

ALA synthase
(Rate limiting)

Negative feedback

ALA

PBG

PBG deaminase

Intermediate porphyrinogens

Haem

Cytochromes

Normal neuronal function

PBG = Porphobilinogen
ALA = Aminolaevulinic acid

Acute intermittent porphyria

Glycine + Succinyl CoA

ALA synthase

ALAS

5β Steroids

Reduced negative feedback

PBG deaminase activity reduced by 50%

Intermediate Porphyrinogens

Haem

Cytochromes

(Deficient)

Symptoms

Postulated effect of androgens

Glycine + Succinyl CoA

ALA synthase

5β Steroids

Less 5β Steroids

Testosterone

Increased negative feedback

PBG deaminase

Intermediate porphyrinogens

Haem

Reduced cytochrome deficiency

Fewer symptoms

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.

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 pregnanediol) with its angulated chair shape is porphyrinogenic under experimental conditions whereas its planar epimer 5α pregnan-dione is not. 3

AIP sufferers are known to be distinguished from those with latent AIP by a deficiency of hepatic 5α reductase 4 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 pregnanediol 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).
References

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