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Case report

Placental sulphatase deficiency

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INTRODUCTION

Placental sulphatase deficiency/congenital ichthyosis is an X-linked inborn error of metabolism which was first described in 1969 by France and Liggins.[1] It is an enzymatic defect affecting steroid metabolism, clinically manifested by diminished oestrogen production during fetal life and by congenital ichthyosis post-natally. This disorder has a reported incidence of between 1 : 6,000 and 1 : 10,000 males.

CASE HISTORY

A 33-year-old woman presented at the Jubilee Maternity Unit, Belfast City Hospital, at 27 weeks' gestation and this was confirmed by ultrasonic scan. Her weight was 68.8 kg, blood pressure 110/80 mm Hg, haemoglobin 14.2 g/dl, blood group O (Rhesus-negative), and no atypical red cell antibodies were detected. The patient claimed to smoke 15 cigarettes per day. She had previously had a 12-week spontaneous abortion followed by a successful pregnancy. Throughout that pregnancy she was recorded as losing weight; labour was induced at 41 weeks and five days, and after an eight-hour labour she had a forceps delivery of a 2750 g female infant.

In her present pregnancy she was reviewed at 32 weeks' gestation and then two weeks later when, because of a weight loss of 2 kg and proteinuria, she was admitted for fetal assessment. Ultrasonic scan, cardiotochography, maternal kick-chart, haemoglobin and serum human placental lactogen were all satisfactory. A midstream sample of urine showed a significant urinary tract infection which required treatment. The urinary oestriol/creatinine ratio was reported as 0.9 nmol/μmol (normal >5); this was repeated and was consistently low (Fig. 1).

In view of the markedly low urinary oestriol results, the diagnosis of placental sulphatase deficiency was raised. Further enquiry revealed a family history of 'dry skin' affecting only male members (Fig. 2). Deficiency of the sulphatase enzyme was confirmed by the intravenous administration of 50 mg dehydroepiandrosterone sulphate (DHEAS), an oestrogen precursor. Serum oestradiol was measured at 5, 10, 15, 20, 30, 60 and 120 minutes following this and revealed no change from the pre-injection level of 5.0 nmol/l. Twenty-four hours later, 50 mg of dehydroepiandrosterone (DHEA) was administered intravenously. This compound does not require a sulphatase enzyme and serum oestradiol rose from the base line of 5.0 nmol/l to a maximum 175 nmol/l after only 10 minutes. Following this, serum oestradiol declined slowly to 50 nmol/l after 2 hours. This significant rise in serum oestradiol following the injection of DHEA but not that of DHEAS was evidence that there was placental sulphatase deficiency.

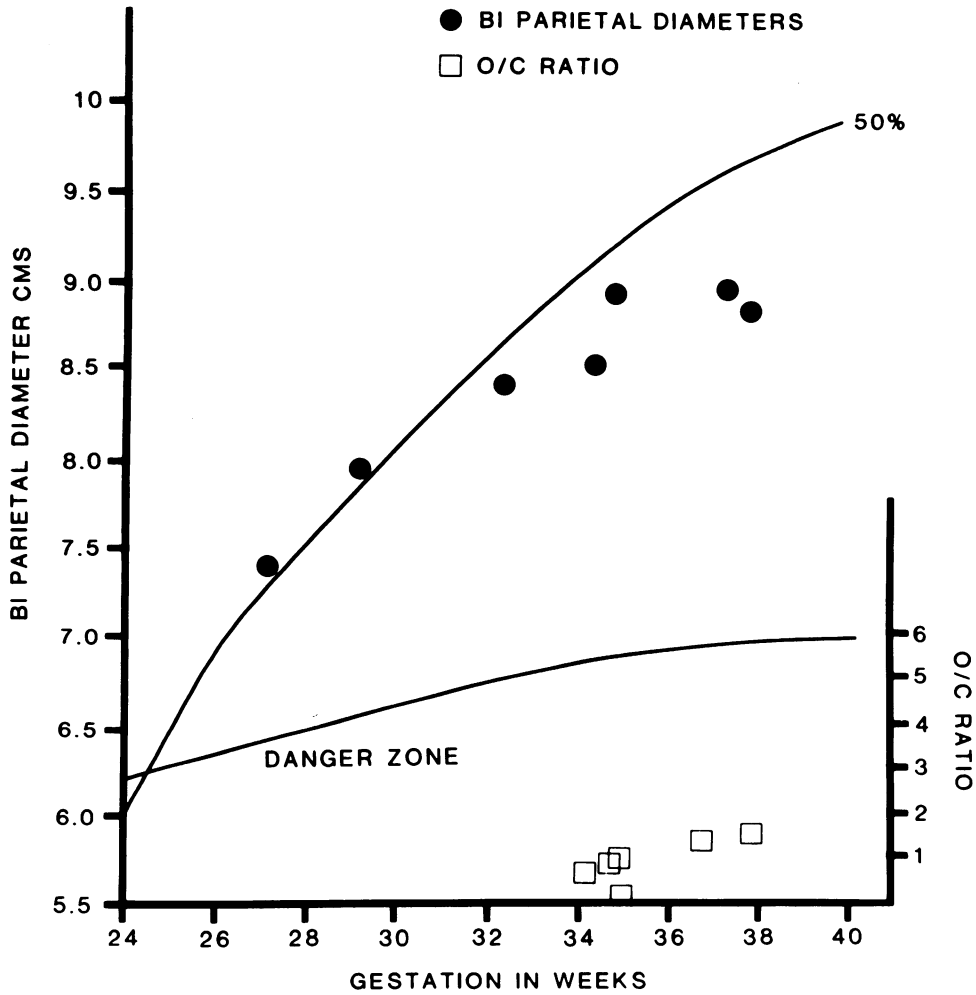

FIGURE 1. Urinary oestriol/creatinine (o/c) ratio and fetal bi-parietal diameter from week 24 to 38.

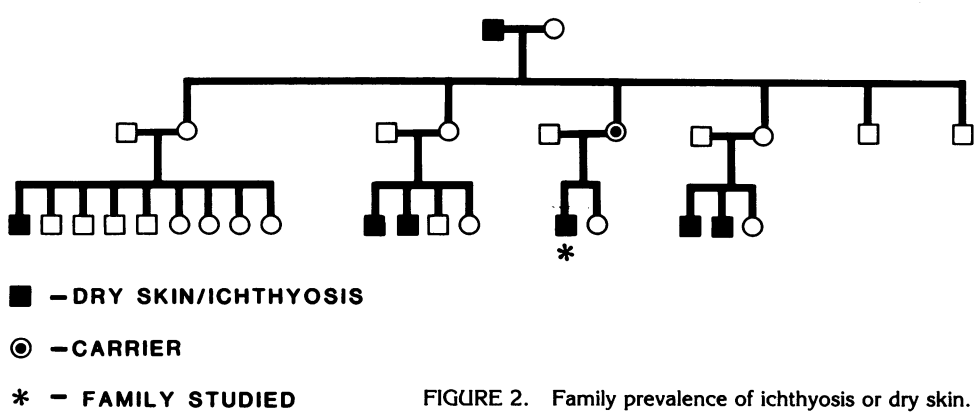

FIGURE 2. Family prevalence of ichthyosis or dry skin.

Ultrasonic scan was unsuccessful in determining the sex of the fetus. The patient was allowed to go home and was reviewed weekly. She was re-admitted at 37½ weeks' gestation, having lost a further 2 kg. Her blood pressure had risen to 140/90 mm Hg and proteinuria persisted. Serial ultrasonic scans demonstrated intrauterine growth retardation (IUGR) with an estimated fetal weight of 2 kg. Repeated urinary oestriol/creatinine ratios (O/C) remained low. It was decided to terminate the pregnancy by forewater amniotomy and intravenous syntocinon infusion. She laboured slowly at first, with a long latent phase of five hours, and required a lumbar epidural anaesthetic. Following this the cervix soon reached full dilatation. Because of fetal distress, she had a forceps delivery of a healthy male infant weighing 2125 grams. He showed no skin abnormality at birth but by the age of six weeks he was already developing severe ichthyosis.

The placenta was retained and removed manually. A specimen of one cotyledon was frozen and sent for enzyme analysis. The results confirmed a sulphatase deficiency with normal microsomal and lysosomal enzymes.

DISCUSSION

The human placenta in isolation is incapable of oestrogen synthesis without assistance from the fetal liver and the adrenal cortex. DHEAS is the major oestrogen precursor produced by the fetal and maternal adrenal glands. It is converted by the enzyme 3 ß-hydroxysteroid sulphatase which removes the sulphate group, leaving the neutral C-19 steroid nucleus which is then aromatised to oestrogen.

Prenatally, steroid sulphatase deficiency leads to reduced oestrogen production in spite of which pregnancy continues and is often prolonged. No antenatal danger has yet been shown and the low oestrogens themselves are not an indication for early interference. However, in this case, concomitant intrauterine growth retardation pointed to the need for induction. The low level of oestrogen, as in the anencephalic fetus, often delays the onset of labour, especially in the primigravida.[2] The cervix is slow to dilate, with an increase in cervical dystocia, which leads to a higher rate of Caesarean section.

Postnatally the enzyme deficiency caused an accumulation of cholesterol sulphate in the blood, cornea and skin leading to the development within the first year of ichthyosis and corneal opacities.

The genetic locus for this condition is found on the short arm of the X-chromosome at the Xg blood group locus and is one of the few genes that is not subject to inactivation. This family's pedigree is consistent with X-linkage. The prenatal diagnosis of sulphatase deficiency must be considered when urinary oestrogens are found to be low. There are many causes, such as drug therapy (using corticosteroids, antibiotics, meprobamate, mondelamine) acute urinary tract infections, anencephally, congenital adrenocortical hypoplasia and incorrect 'dates' which can lead to a reduction in urinary oestrogens. If these are excluded, sulphatase deficiency can be isolated as in this case by loading the patient with DHEAS and DHEA and following the subsequent oestradiol responses.[5] After delivery, the placenta can be analysed for deficient 3 ß-hydroxysteroid sulphase.[3] Affected individuals with X-linked ichthyosis will have a marked (15 to 30 times) elevation of serum cholesterol sulphate.[4] Therapeutically some relief is obtained from topical urea preparations. Genetic counselling and reassurance remain important in the management of patients with this disorder.

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