X-linked ichthyosis

A sulphatase deficiency

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SUMMARY In 3 pregnant women oestrogen excretion in the urine was very low. The pregnancies were otherwise uncomplicated and the 3 infants, boys, were normal at birth, but later developed ichthyosis of the X-linked inherited type. Histochemically, the placenta in each case showed deficiency in arylsulphatase-type C activity. In all three children the skin showed the same enzyme deficiency. In the skin of 9 other unrelated (adult) patients with proved X-linked inherited ichthyosis vulgaris, arylsulphatase C activity was deficient. Skin from 5 normal adults and 5 normal children showed arylsulphatase C activity to be present. It is concluded that a sulphatase deficiency is a factor in the causation of ichthyosis of the X-linked inherited type.

A very low oestriol level in the urine of a pregnant woman may have a variety of causes; severe intrauterine growth retardation, fetal death, iatrogenic effects (antibiotics and other drugs), fetal adrenal hypoplasia, anencephaly, fetal hepatitis, or placental sulphatase deficiency. 16 cases of placental sulphatase deficiency have been described, all reportedly in normal healthy boys. The sulphatase deficiency is the result of an X-linked recessive gene (France and Liggins, 1969; Cedard *et al.*, 1971; Fliegner *et al.*, 1972; Oakey *et al.*, 1974; Tabei and Heinrichs, 1976).

We describe 3 children with placental sulphatase deficiency. The children were normal at birth, and developed ichthyosis of the X-linked type at 2-8 months. This association has not previously been reported.

Case reports

Case 1. In 1970 a healthy 23-year-old primipara gave birth to a slightly dysmature girl who subsequently developed normally. In the 33rd week of her second pregnancy in 1974, the urine oestrogen levels were estimated because of suspected intrauterine growth retardation. Total oestrogen excretion was 10 $\mu\text{mol}/24\text{h}$ (2.7 ng/24h) (range 32-179 $\mu\text{mol}/24\text{h}$; 8.7-48.7 ng/24h; mean 115

$\mu\text{mol}/24\text{h}$; 31.3 ng/24h). Pregnanediol excretion was 72 $\mu\text{mol}/24\text{h}$ (23 mg/24h) (range 75-213 $\mu\text{mol}/24\text{h}$; 24-68 mg/24h; mean 144 $\mu\text{mol}/24\text{h}$; 46 mg/24h). At 39½ weeks a healthy boy was born, weighing 2700 g. Placenta weight 350 g. The baby was screened after birth for abnormalities of adrenal function. Blood sugar and electrolytes: normal, 17-oxosteroids: normal. Cortisol on day 3: 0.60 $\mu\text{mol}/\text{l}$ (21.7 $\mu\text{g}/100\text{ ml}$). At 3 months the baby was found to have ichthyosis, with sparing of the bodyfolds. It was learned that the mother's brother suffered from the same condition; the mother herself had no such symptoms. The clinical appearances and family history made the diagnosis of X-linked type of ichthyosis vulgaris probable. The early onset supported this diagnosis as the dominant type of ichthyosis vulgaris develops at a later age.

Case 2. In 1971 a healthy 28-year-old primipara gave birth at 42 weeks to a boy weighing 4500 g; he remains normal and has no skin disease. A girl with multiple congenital malformations was born in 1973; she died within 24 hours. In 1975 the mother had her third pregnancy; at 36 weeks an extremely low urine total oestrogen was recorded, 14-20 $\mu\text{mol}/24\text{h}$ (3.8-5.4 ng/24h). Pregnanediol excretion: 74-125 $\mu\text{mol}/24\text{h}$ (23.7-40 mg/24h). Induction of labour at 40 weeks with oxytocin failed. At 42 weeks a caesarean section was performed for fetal distress, and a normal boy delivered, birthweight 3320 g. Placenta weight 600 g. Tests of his adrenal function

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proved normal. Blood sugar, electrolytes, and 17-ketosteroids: normal. Cortisol excretion, 0.59 $\mu\text{mol/l}$ (213 $\mu\text{g}/100\text{ml}$) on day 2. After 2 months he developed ichthyosis vulgaris, which, on the same grounds as Case 1, was classified as the X-linked type; the mother, herself free of symptoms, had a brother suffering from ichthyosis vulgaris (Fig. 1).

Case 3. At 34 weeks of pregnancy the urine total oestrogen was measured in a 24-year-old primipara because of signs of toxæmia, and proved to be extremely low: 14 $\mu\text{mol}/24\text{h}$ (3.8 ng/24h). At 39 weeks a boy was delivered by forceps on account of fetal distress, with meconium staining. Birthweight 2740 g. Placenta weight 480 g. The baby was normal except for signs of mild dysmaturity. When he was 9 months old, ichthyosis became conspicuous on both legs with sparing of the popliteal fossae (Fig. 2). The scales were brown as seen in X-linked ichthyosis vulgaris, but the trunk showed only a slight whitish scaling. The mother had first noticed this condition when the child was 6 months old. X-linked type of ichthyosis vulgaris was probable, but because of the unusual distribution and the absence of other affected relatives the diagnosis was less certain than in Cases 1 and 2.

All three children remain in good health. The skin disease is varying in severity, but is easily controlled with simple ointments.

Enzyme studies

Antenatal diagnosis of placental sulphatase-deficiency was performed with a tolerance test. 100 mg dehydroepiandrosteronesulphate in 30 ml

Fig. 1 Case 2, age 2 months.

Fig. 2 Case 3, age 8 months.

0.65% NaCl was administered intravenously to the mothers of Cases 2 and 3; there was no rise in urine total oestrogen. In the mother of Case 3 the effect of giving the unconjugated dehydroepiandrosterone was also studied and this resulted in a rise in urine total oestrogen as expected (to be published).

Like France *et al.* (1973) we found an arylsulphatase-type C deficiency in placental tissue but, while they used a biochemical method, we used a histochemical method based on the work of Koudstaal (1975). Arylsulphatase C was not demonstrable histochemically in the trophoblast cells of the 3 placentae, whereas 14 control placentae of varying degrees of maturity did show cytoplasmic reactivity (Figs 3a, b) (Jöbsis *et al.*, 1976). A series of enzymes was also tested for histochemical activity, including 3 β -hydroxysteroid dehydrogenase and the lysosomal arylsulphatase A and B; all showed a normal cytoplasmic reaction in the trophoblast cells of the 3 placentae.

In the skin of the 3 children the same selective arylsulphatase C deficiency was found in the granular layer where the enzyme is normally found (Figs 4a, b). The skin of 5 children of the same age and of 5 adults served as controls. In the skin of 9 adolescent or adult patients with unmistakable X-linked ichthyosis vulgaris, arylsulphatase C activity was absent.

Discussion

Placental sulphatase deficiency is rare, about 1 : 5000 (Oakey *et al.*, 1974) as is X-linked ichthyosis, about 1 : 6000 in the United Kingdom (Wells and Kerr, 1966). A chance association of the two conditions in our 3 cases is therefore unlikely.

It is of interest that no skin disorder was noted in any of the other 16 reported cases of placental sulphatase deficiency. This may in part be due to the rather late onset of the ichthyosis, which moreover fluctuates and may, if mild, be easily overlooked. It is also noteworthy that most of the earlier 16 cases have come from hot and sunny parts of the world, where X-linked ichthyosis is known to be less severe.

France *et al.* (1973) showed by biochemical methods that both steroid-sulphatase and arylsulphatase C were deficient in placentae with an inability to desulphatise. Shapiro and Weiss (1977) mentioned the deficiency of steroid-sulphatase in the fibroblasts of a patient with the same enzyme deficiency in his placenta. It is not yet clear according to France *et al.* (1973) whether we are dealing with a group of specific enzymes not functioning properly, or with a single nonspecific enzyme. But since steroid-sulphatase and arylsulphatase C are not the

same enzyme (France *et al.*, 1973) it seems more probable that several related enzymes are not functioning properly.

The two conditions are perhaps closely located on the X chromosome. If so, there may exist patients with only one of the two illnesses—e.g. normal

Fig. 3 Placenta of Case 3 (a) compared with that of a normal control (b) of similar maturity. Histochemical test for arylsulphatase C performed concurrently and with identical technique. Trophoblast shown clearly in control, but is unstained in the placenta of Case 3. $\times 140$.

Fig. 4 Skin of Case 3 at 2 months (a) compared with that of a normal control (b). Histochemical technique as in Fig. 3. The granular layer of the patient's epidermis fails to stain, compared with control. (In (a) there is also nonspecific perinuclear oedema in the epidermis, but the interposition of a semipermeable membrane between section and medium precludes sharper definition here as in Fig. 3). $\times 140$.

oestriol excretion during pregnancy and a boy with X-linked ichthyosis, or the converse, abnormal excretion of oestriol owing to placental sulphatase deficiency and a boy with normal skin. The last might be represented among the 16 cases in which no skin disorder was mentioned.

Our 9 adult or adolescent patients with X-linked ichthyosis vulgaris were also negative for arylsulphatase C activity in skin. This suggests at least a firm linkage between the skin disorder and this histochemical phenomenon. They were born, however, many years ago when the desulphatising capacity of placentae was unstudied.

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