Earlier studies, such as that by Hodgman *et al.*,⁵ in which the diagnosis was not based on SP urine culture would not now be accepted. In studies in which the diagnosis of bacteriuria was based on SP urine culture, Pendarvis *et al.*⁷ found 10% of preterm babies who had weekly cultures had bacteriuria, Zies *et al.*⁸ found 5.6% of preterm babies had bacteriuria, and Edelman *et al.*⁴ found bacteriuria in 2.4–3.4% of preterm babies. The incidence in our series which may well be zero is much lower. This may be due to the fact that in our unit ill babies and babies suspected, or at risk, of developing infection are treated promptly with antibiotics and were excluded from the study.

We feel that as it is often difficult to obtain a clean urine specimen in a small baby and as the incidence of asymptomatic bacteriuria in healthy preterm infants is so low, routine screening for this is not justified. In order to detect asymptomatic bacteriuria before renal damage has occurred, babies need to be screened after the newborn period. We also endorse the statement by Edelman *et al.*⁴ that a bag specimen can only show the absence of bacteriuria; confirmation of bacteriuria must always be based on culture of SP urine.

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Pituitary cretinism in two sisters

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SUMMARY Two sisters with cretinism are reported. Each showed low levels of serum triiodothyronine, thyroxine, and thyroid-stimulating hormone (TSH). In the elder sister, serum TSH did not increase after administration of thyrotropin-releasing hormone. We conclude that cretinism in these 2 sisters was due to TSH deficiency. This is the second report of 'familial' pituitary cretinism (TSH-deficient congenital hypothyroidism).

Congenital pituitary hypothyroidism is thought to be rare. 15 cases have been reported,^{1–11} nearly all of them sporadic. In each the diagnosis was confirmed

by low serum thyroid-stimulating hormone (TSH) being determined by radioimmunoassay. Among these cases was one familial case: that of 2 sisters with cretinism due to TSH deficiency.⁴ This is the second report of familial pituitary cretinism.

Case report

The 2 children were among 6 of 2nd-cousin parents (Fig. 1). Their brothers were reported to be growing and developing normally and their mother was clinically euthyroid with normal concentrations of serum triiodothyronine (T3), thyroxine (T4), and TSH.

Fig. 1 Pedigree of a family with pituitary cretinism

Case 1. A 4-month-old girl was admitted to this hospital because of poor weight gain. She had been born at term after a normal pregnancy weighing 3.2 kg. Prolonged neonatal jaundice was not noticed. At 2 months she had been noted to have an umbilical hernia and was seen by a doctor, who also drew attention to her retarded growth. She had severe constipation, moving her bowels every 7 to 10 days. She was referred to our hospital.

On examination her poor growth and lack of development were obvious with weight 3140 (-4.9 SD) g, height 47.7 (-8.4 SD) cm. She had the features typical of cretinism with a husky voice, dry and coarse skin, and myxoedema. No thyroid gland was palpable.

Serum T3 was <0.05 ng/ml (0.077 nmol/l), T4 <0.5 μ g/100 ml (6.44 nmol/l), and TSH 2.8 μ U/ml. Serum cholesterol was 495 mg/100 ml (12.8 mmol/l). Thyroxine binding globulin (TBG) capacity was 29.4 μ g/100 ml (378.7 nmol/l). Antithyroid antibodies were negative. A 24-hour 131 I-uptake was low, and no thyroid gland was seen on the scintigram. Administration of TSH, 5 units daily for 4 days, increased the 24-hour 131 I-uptake to 12% and it was clearly shown by scintigraphy that our patient had a thyroid gland in normal position. Serum T3 and T4 also increased after TSH stimulation, to 0.6 ng/ml (0.92 nmol/l) and 0.7 μ g/100 ml (9.0 nmol/l) respectively. Serum TSH remained low after administration (7 μ g/kg) of thyrotropin-releasing hormone (TRH) (Fig. 2). No secretion of growth hormone (GH) was detected after administration of arginine (0.5 g/kg). Serum electrolytes, fasting blood sugar, blood urea nitrogen (BUN), uric acid, creatinine, alkaline phosphatase were normal.

Fig. 2 (Case 1). Serum TSH response to TRH, with normal control, showing absence of rise in serum TSH.

Serum lactic dehydrogenase (LDH) was 380 mU/ml, glutamic-oxalacetic transaminase (GOT) was 400 mU/ml, and glutamic-pyruvic transaminase (GPT) 150 mU/ml. X-ray of skull was normal. Bone age was less than 3 months in the wrist.

Case 2. A 2-month-old girl, a younger sister of Case 1, was admitted to this hospital because of poor weight gain and lethargy. She had been born at term with a weight of 3.8 kg. Her mother had proteinuria and oedema at 7 months of pregnancy. She had had an episode of asphyxia at birth and needed resuscitation. Neonatal jaundice was not severe nor was it prolonged. At 30 days the baby developed respiratory arrest suddenly after feeding and was resuscitated. She was severely constipated. The clinical features of this baby were so similar to those of her elder sister that she was referred to our hospital.

On examination growth retardation was obvious, weight 2.9 (-4.2 SD) kg, and height 46 (-5.0 SD) cm. She also had the features typical of cretinism with husky voice, coarse skin, and myxoedema. No thyroid gland was palpable. Physical findings in the chest and abdomen were within normal limits.

Serum T3 was 0.3 ng/ml (0.46 nmol/l), T4 1.2 μ g/100 ml (15.4 nmol/l), and TSH <1.25 μ U/ml. Cholesterol was 470 mg/100 ml (12.1 mmol/l). TBG capacity was 18 μ g/100 ml (231.8 nmol/l). Anti-thyroid antibodies were negative. Serum electrolytes, fasting blood sugar, BUN, uric acid, creatinine,

alkaline phosphatase, LDH, GOT, and GPT were normal. Skull x-ray was normal. This baby unfortunately died of aspiration pneumonia on the 8th day of the hospital course. Necropsy could not be performed.

Discussion

Two sisters with cretinism are reported. They were the children of 2nd-cousin parents. Their mother was euthyroid and their four elder brothers had no apparent hypothyroidism.

Before treatment with thyroid hormone, Case 1 showed a very low serum TSH with resultant low concentrations of serum T3 and T4. Administration of TRH produced no increase in serum TSH. In the younger sister the function of the hypothalamic-pituitary-thyroid axis could not be studied in detail because she died of aspiration pneumonia. Serum TSH was undetectable however, with low concentrations of serum T3 and T4, as in Case 1. In addition, it was clearly demonstrated by scintigraphy that the elder sister had a thyroid gland in normal position, and that it was able to respond to TSH, as shown by the rise in serum T3 and T4 after administering TSH. We conclude that hypothyroidism in these 2 sisters was due to TSH deficiency, also termed familial pituitary cretinism.

About 10–15% of patients with combined anterior pituitary hormone deficiency apparently first have isolated pituitary hormone deficiency.¹² GH secretion is generally impaired in the presence of hypothyroidism, so isolated TSH deficiency may be misdiagnosed as combined TSH and GH deficiency. In our case, there was no increase in serum GH after arginine infusion before treatment with thyroid hormone. Further evaluation of the secretory reserve of GH and other anterior pituitary hormones will be necessary after normal thyroid function has been achieved.

The aetiology of pituitary cretinism is not clear. It is in most cases sporadic and affects both sexes. About half the cases are seen in childhood with mild symptoms of hypothyroidism.^{3 6–8 10–11} Embryonal and fetal factors may be involved. Genetic factors

seem likely to play an important role in the occurrence of familial pituitary cretinism because these patients and the two reported by Miyai *et al.*⁴ had characteristics in common—female sex, progeny of 2nd-cousin parents, and severe signs of cretinism in the neonatal period.

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