heterozygote for 7,8-dihydrobiopterin synthesis deficiency as the parents of a child affected by malignant hyperphenylalaninaemia (Case 2, Table),[1 5] have similar very low biopterin levels (1979, unpublished data).

This case shows that a low serum *C. fasciculata* activity together with high serum phenylalanine concentration does not necessarily mean that the child is affected by a malignant hyperphenylalaninaemia unless chromatographic analysis of the serum also shows lack of 7,8-dihydrobiopterin. It also demonstrates that transient hyperphenylalaninaemia is a heterogenous condition and can be caused by reduced biosynthesis of 7,8-dihydrobiopterin.

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Familial thyroid ectopy and hemiagenesis

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SUMMARY Two siblings had sublingual thyroid glands and hypothyroidism. A third sibling had a left lobe agenesis of the thyroid, but normal function of the gland. This is the second such family to be described.

The ectopic position of the thyroid gland is not an uncommon anomaly, with an incidence of about 1 in 4000 of all thyroid diseases.[1] Generally only one sibling is affected but familial occurrences have occasionally been reported.[2–5] This anomaly is the most frequent cause of hypothyroidism in babies, with an incidence of between 36 and 68%.[6–7] A family is described with 3 affected siblings; 2 siblings had sublingual thyroids and the third had hemiagenesis of the gland.

Case reports

Case 1. A 4-year-old girl was examined because of stunted growth and slow physical and psychomotor development. She was the product of a term, uncomplicated pregnancy and delivery. There was no

Table *Clinical, hormonal, and biochemical findings in 3 children with familial thyroid ectopy*

Case	*Sex*	*Age (years)*	*Height age (years)*	*Bone age (years)*	*TSH (mg/ml)*	*T_4I (μg/ml)*	*T_3(%) retention*	*FTI unit*	*PBI (μg/100ml)*	*Cholesterol (mmol/l)*	*Thyroidal uptake % 2h*	*^{131}I 24h*	*Thyroid scan*
1	F	4	2·4	1·5					4·2	4·8	13	16	Sublingual
2	F	3·6	2·6	1·6					4·8	7	7	13	Sublingual
3	M	3	3·4	2·6	0·85	4·6	42	4	4·5	4·2	10	26	Agenesis of left lobe
Normal values					<1	2·5–8	39–55	2·6–9	4–8	4·6–8·5·	12±4	34±12	

Conversion: traditional units to SI—T_4I: 1 μg/100 ml ≈ 12·87 nmol/l, PBI 1 μg/100 ml ≈ 78·8 nmol/l, cholesterol 40 mg/100 ml ≈ 1 mmol/l.

consanguinity in the family. No abnormality was found until age 3 years. During her fourth year, the mother observed a progressive retardation in the somatic growth and in intellectual performance.

The diagnosis of hypothyroidism was established, based on delayed bone age as shown on *x*-rays, retarded growth (<3rd centile), and low ^{131}I uptake. Scan of the thyroid showed a sublingual position of the gland. Results of the thyroid function tests are given in the Table. Treatment with desiccated thyroid extract was started and changed later to L-thyroxine. After 8 years of treatment our patient is normally developed, the height >25th centile, and the bone age has caught up with chronological age.

Case 2. The 3½-year-old sister of Case 1 was examined for stunted growth and constipation. She too had been born after an uneventful pregnancy and delivery, and no problems had been encountered during the neonatal or infantile period. The physical examination was normal except for her height, which was <10th centile.

Hypothyroidism was suggested by the growth and bone age retardation, and the low ^{131}I uptake by the thyroid (Table). Again the scan showed the ectopic, sublingual position of the thyroid gland. L-thyroxine was given for replacement therapy, and now, after 7 years of treatment at age 10½ years, she is a perfectly developed girl and her height has reached the 50th centile.

Case 3. A 3-year-old brother of Cases 1 and 2 was normally developed and without symptoms related to the thyroid gland. He was examined during the investigation of the entire family and although clinical and laboratory findings were normal (Table), the thyroid scan showed left hemilobar agenesis.

Both parents and 2 more siblings were found to be normal in all the tests. The maternal grandmother has been treated for thyrotoxicosis.

Discussion

Although ectopic thyroid glands have been reported,[6 8–9] familial thyroid ectopy is rare and only 3 such families have been thoroughly documented.[4–5]

In many children the ectopic, underdeveloped thyroid can supply the metabolic needs of the organism up to a certain age, and signs of hypothyroidism may appear late when the requirements for thyroid hormones are increased.[7] Therefore, various degrees of hypothyroidism, from barely detectable to severe cretinism, have been described in the presence of ectopic thyroid tissue.[10–11] Little *et al.*[7] suggested the name 'cryptothyroidism' for ectopically situated thyroid glands, by analogy with cryptorchidism.

The family described by Orti *et al.*[4] was similar to ours: 2 siblings with sublingual thyroids and one with hypoplasia of a thyroid lobe. Kaplan *et al.*[5] described 2 siblings with sublingual thyroids, with slight hypothyroidism in one and no clinical signs in his brother. The estimation of basal serum thyroid stimulating hormone (TSH) was of value for the early detection of incipient hypothyroidism. Our patients were diagnosed at a time when only protein-bound iodine (PBI), ^{131}I uptake, and scanning of the thyroid could be tested. However, the low ^{131}I uptake, retarded bone age, growth retardation, and the ectopically-situated thyroids leave no doubt about the diagnosis of hypothyroidism, confirmed by the result of thyroid hormone therapy. The brother, who only had agenesis of the left lobe of the thyroid, was perfectly compensated, as shown by his normal development, normal PBI, thyroxine, triiodothyronine, Sephadex uptake, and TSH.

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Control of life-threatening bleeding by combined plasmapheresis and immunosuppressive treatment in a haemophiliac with inhibitors

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SUMMARY Life-threatening lingual haemorrhage was successfully treated in a 3-year-old haemophiliac who had a high level of inhibitor in his plasma. Repeated plasma exchange with high-dose factor VIII concentrate led to a cessation of bleeding. Immunosuppressive treatment introduced at the time of plasmapheresis and carried out for 6 weeks seems to have prevented the return of the inhibitor.

The presence of inhibitors in patients with severe haemophilia A presents a serious clinical problem. Patients who had previously been well managed on 'average' replacement therapy, fail to respond to large doses of factor VIII concentrates. About 10% of haemophiliacs eventually develop inhibitors although the time they take to do so varies.[1] Attempts at overcoming this problem started soon after it became recognised. Approaches have been found to be beneficial by some and ineffective by others. The use of high-dose factor VIII concentrates with concomitant immunosuppression was advocated by Nilsson and Hedner.[2] Several authors have reported success with the use of activated or nonactivated prothrombin complex concentrates.[3] Others have failed to confirm these findings, and furthermore have warned of the possibility of severe untoward effects—such as disseminated intravascular coagulation—after the use of such compounds.[4]

Plasmapheresis as a prompt measure for the control of severe bleeding has been successfully tried at a number of centres for haemophiliacs.[5-6] In some of these patients plasmapheresis was followed by short-term immunosuppressive treatment. In most patients however, the inhibitor level returned to pre-treatment values within days or weeks of plasmapheresis. Continuous flow plasmapheresis has been suggested for adult patients but these instruments are expensive and somewhat difficult to use with small children.

We report a case of haemophilia A with inhibitors in a 3-year-old boy, who had repeated life-threatening bleeding from his tongue. Bleeding was successfully controlled by 'conventional' plasma exchange with factor VIII concentrate and fresh frozen plasma. Immunosuppression, introduced at the time of plasmapheresis, seems to have led to the disappearance of the factor VIII inhibitor.

Case report

There was no history of haemophilia in the family of our patient nor was there history of any other bleeding disorder. Our patient's mother subsequently was found to be an asymptomatic carrier for haemophilia A. The patient was first investigated for suspected haemorrhagic disorder when he had prolonged bleeding after a diphtheria-pertussis-tetanus vaccination. The diagnosis of haemophilia A was established at age 4 months. Factor VIII level was found to be less than 1%. He repeatedly received cryoprecipitate and transfusions for gum and nose bleeds. 10–20 units per kg factor VIII were then adequate for the control of bleeding. Altogether he was treated on 33 occasions before the age of 2 years. At 25 months gingival haemorrhage started and this time it did not respond to 'conventional' treatment. A factor VIII inhibitor was detected in his plasma with a concentration of 10 Bethesda units per ml. The bleeding was eventually controlled by