Hyperhomocysteinaemia is a risk factor for thrombosis and recurrent pregnancy loss (1–2). Similar mechanisms appear to mediate thrombosis and pregnancy loss associated with hyperhomocysteinaemia and with antiphospholipid antibodies (3). We report the case of a female patient with an unusual association of hyperhomocysteinaemia, normocalcemic hyperparathyroidism, growth hormone deficiency and antiphospholipid syndrome.

Case report

A 41-year-old woman had a previous history of smoking, migraine, placental abruption, bronchial hyperreactivity, arterial hypertension, unstable angina and multinodular goitre. She was admitted to the Department of Immunology because of two consecutive transient ischaemic attacks with one month interval between the ischaemic episodes. The patient complained of left hemi-sensory loss affecting face and upper extremity, inability to comprehend spoken and written language, facial weakness and nasolabial flattening accompanied by superior quadrantanopsia. Otherwise, the examination was unrevealing. Symptoms cleared within six hours. Ischaemic foci were seen on magnetic resonance imaging (MRI). In the second episode, a right parietal posterior ischaemic lesion with mild subarachnoid bleeding was observed. Complete investigations were performed for other risk factors of thrombosis. Echocardiography showed mitral valve prolapse and insufficiency. Cerebral angiography, magnetic resonance renal angiography with a fast 3D gradient echo and ultrasonography of the supraaortic vessels were normal. Laboratory investigations revealed the presence of elevated titres of antiphospholipid antibodies (66 GPL-units/ml) and significant hyperhomocysteinaemia [total homocysteine concentration = 36 μM (normal range: 1.6–11 μM)]. Lupus anticoagulant was negative. Plasma folate (5.08 ng/ml) and vitamin B12 (347 pg/ml) concentrations were normal. Screening for factor V Leiden and prothrombin G20210A mutations was negative. Normal functional protein S and protein C activity were observed. The genotype of the thermolabile C677T allele of 5,10 methylene tetrahydrofolate reductase was studied by PCR-RFLP. The patient had the C677T homozygous genotype. An extended immunological study performed three months after the latest transient ischemic attack confirmed high levels of anticardiolipin antibodies (95 GPL-units/ml). Serum immunglobulin G (858 mg/dl), A (265 mg/dl), M (154 mg/dl), complement factors C3 (103 mg/dl), C4 (17 mg/dl) and complement activity were within normal values. Antinuclear, anti-DNA, anti-ENA and anti-thyroid antibodies were negative. Elevated levels of the parathyroid hormone (PTH) were observed. Studies performed to rule out apparent causes of secondary hyperparathyroidism including creatinine clearance, phosphorus, alkaline phosphatase and vitamin D serum levels, low bone mineral density and urine calcium levels were normal. Serum calcium levels were normal. Interestingly enough, the patient was found to have low levels of growth hormone (<0.3 ng/ml). L-Dopa stimulation test showed peak growth hormone of 3.7 ng/ml. She was treated with acenocoumarol to maintain INR of 3–4. During a follow-up of three years there was no recurrence of the ischaemic attacks, and ischaemic foci disappeared on MRI. The patient started treatment with folic acid and vitamin B6. Hyperhomocysteinaemia was normalised.

The complex of hyperhomocysteinemia, normocalcemic hyperparathyroidism and adult growth hormone deficiency observed in this case is unusual and not previously described in association with antiphospholipid syndrome. Benekli et al. reported on another case with primary hyperparathyroidism and antiphospholipid syndrome in a patient with impending renal failure due to systemic lupus erythematosus (4). In the case presented here, renal function was normal, and the clinical and laboratory assessment yielded no evidence of lupus erythematosus. Recently, normocalcemic primary hyperparathyroidism has been characterised (5). A proportion of patients with normocalcemic primary hyperparathyroidism have hypertension. Interestingly enough, the endothelium is a recognised target organ of PTH and may contribute to its effects on vascular tone and blood pressure regulation. Endothelium-dependent vasodilation is impaired in patients with primary hyperparathyroidism (6). Antiphospholipid antibodies and plasma homocysteine levels independently predict intima media thickness of carotid arteries (7). In addition, it has been suggested that growth hormone deficiency is associated with known cardiovascular risk factors such as body shape, lipid profile, insulin resistance, blood pressure, vessel wall morphology and haemostatic factors (8).
We suggest that the cardiovascular morbidity in this patient was likely to be facilitated by the coexistence of antiphospholipid syndrome, hyperhomocysteinaemia, normocalcemic primary hyperparathyroidism, and growth hormone deficiency. Since these factors can affect the coronary and cerebral vasculature, we speculate a role for vasculature damage as a common pathway to cardiovascular morbidity in this patient.

References