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Tuberous sclerosis and parathyroid adenoma

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Abstract

Very little is known about the pathogenesis of tuberous sclerosis. Over the past 10 years, however, increasing numbers of reports on adenomatous diseases in association with tuberous sclerosis have been published. A case of hypercalcaemia and parathyroid adenoma in association with tuberous sclerosis is presented, of which there has been one such report published previously.

This association might be another manifestation of this complex disease: it is therefore recommended that plasma calcium concentrations should be measured in such patients.

Tuberous sclerosis (also known as Bourneville's disease and epiloia) is a syndrome that is characterised by a triad of epilepsy, mental retardation, and cutaneous sebaceous adenomas. A variety of other clinical symptoms and subclinical abnormalities have also been described over the past decade. It is an autosomal dominant inheritance disease, not fully penetrant, with a high incidence of fresh mutations.¹⁻⁵

In most populations the prevalence of tuberous sclerosis has been estimated to be about one in 100 000, but there are considerable regional differences (one in 20 000 to one in 300 000).⁶⁻⁸ The basic metabolic mechanism underlying the disease remains unknown. Diagnosis can be made in utero.

Epilepsy, the most common clinical manifestation, is often present from early childhood, but not always. Mental retardation is found in about half the patients.

Sebaceous adenomas or cutaneous fibroangiomas are diagnostic and are found in up to 90% of the cases. The appearance varies and the most frequently affected areas are the nose, the chin, and the forehead. Hypopigmented areas are often a concomitant feature.

The central nervous system abnormalities in tuberous sclerosis are characterised by calcified subependymal and cortical nodules (tubers). Intracranial gliomas and retinal or optical phacomias are also often found. The skeleton is often affected. Characteristically, sclerotic areas in the calvarium, pelvic bone,

and columna are present. The metacarpals and metatarsals display periosteal thickening and cysts. Other organs have been reported as being affected: renal angiomyolipomas or cysts are not uncommon, as are cardiac rhabdomyomas. Pulmonary cysts may also be evident.¹⁻¹⁰

Although apparently rare, glands have also been affected in some cases: hepatic angiomyolipomas, islet-cell adenomas of the pancreas, adrenal adenomas, pituitary adenomas, a few reports of precocious puberty, and disease of the testes, ovaries, and thyroid gland.¹³⁸⁹

We are aware of only one previous description of parathyroid disease in a patient with tuberous sclerosis.¹⁰ We report the second published case of primary hyperparathyroidism associated with tuberous sclerosis.

Case report

A 15 year old boy was admitted to hospital with abdominal pains. He had no history of endocrine disease. One of his sisters had confirmed tuberous sclerosis comprising epilepsy, mental retardation, and cutaneous adenomas. Our patient also had cutaneous sebaceous adenomas, and tuberous sclerosis was suspected; the family history was then obtained. The mother was subsequently found to have tuberous sclerosis; she had typical cutaneous signs but no other symptoms, and she was normocalcaemic.

Acute pancreatitis and hypercalcaemia was diagnosed in our patient. Further examination showed biochemical hyperparathyroidism, with an eight-fold increase in parathyroid hormone activity (intact PTH) (using an immunoreactive PTH assay measuring the intact PTH molecule, normal range 10-65 ng/l.) Combined thallium-technetium scintigrams and subsequent ultrasonography indicated a parathyroid adenoma located on the right side of the neck, just above the clavicle. A parathyroid adenoma was removed and the diagnosis was verified microscopically. After surgery calcium metabolism returned to normal along with intact plasma PTH. Tuberous sclerosis was diagnosed because of dermatological changes, sebaceous adenomas of the face, and hypopigmented areas on both

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thighs. Furthermore, a computed tomogram verified subependymal calcifications. He had no central nervous system symptoms. The following clinical investigations were normal: ophthalmic examination, roentgenograms of the skeleton and chest, and ultrasonographic examination of upper abdomen, including kidneys and heart. Biochemically, no abnormalities apart from those associated with hyperparathyroidism were found, including thyroid hormone and androgen activities.

Discussion

The coexistence of tuberous sclerosis (prevalence one in 100 000) and primary hyperparathyroidism (population prevalence in adults about one in 1000, much lower in juveniles), was unexpected. Only one previous case of tuberous sclerosis and parathyroid adenoma has been described. Over the past 10 years different symptoms, mostly adenomas, have been included in the syndrome. Parathyroid adenoma might be another adenomatous abnormality that is associated with tuberous sclerosis.

In hyperparathyroidism decalcification of bones with defects in metacarpal bones occur. The calvarium is thickened with lacunar

changes and cysts. In secondary hyperparathyroidism osteosclerosis is a feature.

In tuberous sclerosis intracranial calcification, cortical thickening of bones, osteosclerosis and bone cysts are common. The association between skeletal changes in tuberous sclerosis and hyperparathyroidism is not obvious, but, on the other hand, cannot be excluded. We therefore suggest that disturbances of calcium metabolism may occur in patients with tuberous sclerosis, and suggest that plasma calcium should be measured in these patients.

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Distinction between antinuclear antibody and P-ANCA

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Abstract

To differentiate between perinuclear immunofluorescence staining of antinuclear antibody (ANA) and the perinuclear form of anti-neutrophil cytoplasmic antibody (P-ANCA), the pattern after formaldehyde vapour fixation of normal human neutrophils was compared with that of standard ethanol fixation. Fifteen out of 17 myeloperoxidase antibody positive sera showed cytoplasmic staining on formaldehyde vapour fixed cells; 30 of the 32 ANA positive samples became negative or gave weak nuclear staining on the same substrate.

Formaldehyde vapour fixation is a simple, useful technique for differentiating between ANA and P-ANCA.

Anti-neutrophil cytoplasmic antibody (ANCA) is emerging as an important class of autoantibody, useful in the diagnosis of vasculitic diseases. The correlation between the cytoplasmic form (c-ANCA) and Wegener's granulomatosis is well established.¹ Perinuclear staining on neutrophils fixed in eth-

anol is gradually receiving more attention due to its reported association with myeloperoxidase antibody and necrotising and crescentic glomerulonephritis.² This artefactual perinuclear immunofluorescence, however, can closely resemble the perinuclear staining pattern of antinuclear antibody (ANA). In other cases P-ANCA may be masked by strong homogeneous staining due to the presence of associated ANA. The differentiation between P-ANCA and perinuclear ANA is of clinical importance, especially in populations with a high incidence of systemic lupus erythematosus (SLE). We describe a simple method of distinguishing between the two entities in routine clinical laboratory practice.

Methods

Two groups of serum samples were analysed. Group 1 comprised 32 patients with SLE with positive ANA demonstrable on Hep-2 cells but who were negative for myeloperoxidase antibodies. Group 2 comprised 17 serum samples from 11 patients with the antibodies. The presence of myeloperoxidase antibodies was determined by enzyme linked immunosorbent

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