Hyperparathyroidism in a Patient with Wilson’s Disease

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We describe hyperparathyroidism in an 18-year-old man with Wilson’s disease—the first report in the English literature of the simultaneous occurrence of these two conditions.

Additional Keyphrase: heritable disorders

Most cases of Wilson’s disease present with hepatic, neurological, or psychiatric disturbance. However, many other systems may be involved. Patients may present with an acute hemolytic anemia (1). Bone and joint disorders are common (2) and include osteoporosis, spontaneous fractures, osteomalacia, osteoarthritis, osteochondritis dissecans, and renal rickets (Fanconi syndrome) (3). Proximal renal tubular absorption is often impaired. The resulting phosphaturia may cause hypophosphatemia and eventual bone disease (3). Endocrine abnormalities reported include abnormal thyrotropin response to thyrocalcitonin, decreased thyroid-binding globulin, amenorrhea, recurrent miscarriages, and glucose intolerance (4). Hypoparathyroidism has also been described, probably related to the deposition of copper in the parathyroid glands (4).

Here we document the occurrence of primary hyperparathyroidism in an 18-year-old man with Wilson’s disease. Although an association between these disorders is unlikely, the probability of both conditions occurring in the same patient is small. The patient also had significant osteoporosis, most probably attributable to liver cirrhosis. However, hyperparathyroidism may have been a contributing factor.

Case Report

The patient was the 13th child in a sibship of 15. Two older brothers had been diagnosed with Wilson’s disease in 1971 and 1972. Another sibling was diagnosed with this condition in 1988. (This very large sibship will be the subject of a separate report.) In 1972, when most of the sibship was screened for Wilson’s disease by measuring the ceruloplasmin concentration in serum, this patient, who was then two years old, had a result of 0.27 g/L (normal reference interval = 0.20–0.35 g/L) and was not further tested.

In 1981, at age 11 years, the subject presented with a gradual onset of lethargy and inability to keep up with other children on the sporting field. There was a two-week history of abdominal distension and swollen ankles. Examination revealed mild hepatomegaly with a hard, irregular liver edge. There was moderate splenomegaly, moderate ascites, and bilateral pitting edema at the ankle.

The serum ceruloplasmin was 0.20 g/L. The 24-h urinary copper excretion was 5.5 μmol (reference interval = 0.16–0.94 μmol). The value for plasma albumin was 31 g/L (reference interval = 39–48 g/L), for plasma globulins 38 g/L (reference interval = 22–34 g/L). The aspartate aminotransferase activity in plasma was 58 U/L (reference interval = 10–45 U/L). Slit-lamp examination of the cornea revealed Kayser–Fleischer rings. The patient’s prothrombin ratio was 1.7 (reference interval = 0.8–1.2) and the platelet count was 122 × 10^4 (reference interval = 150–350 × 10^4). Liver biopsy was not performed because of the increased risk of bleeding. However, the diagnosis of Wilson’s disease was considered secure and has subsequently (1988) been confirmed with radiocopper studies (5). Treatment with penicillamine, 250 mg three times daily, was begun in addition to therapy with a diuretic. At this time the total calcium concentration in plasma was 2.16 mmol/L (reference interval = 2.20–2.55 mmol/L), a result falling within the normal reference interval when corrected for plasma albumin.

The patient continued at school until age 16 years, then worked for two years as a spray painter in a car factory. In August 1988, he resigned because of increasing fatigue and exertional dyspnea. He had a large ascites and severe peripheral edema that partly responded to diuretic therapy.

In 1986, measurement of his total calcium in plasma yielded a result of 3.25 mmol/L; the plasma albumin was 35 g/L (plasma calcium had not been measured during the previous four years). In July 1988, his total calcium was 2.87 mmol/L and his albumin was 28 g/L. With normal renal function and a markedly increased calcium, the serum parathyroid hormone (INCSTAR mid-region PTH assay) of 87 pmol/L (reference interval <75 pmol/L) supported a diagnosis of primary hyperparathyroidism. The concentration of alpha-fetoprotein in serum was normal. A thallium–technetium subtraction scan of the parathyroid (6) showed a focus of residual activity in the right lower pole of the thyroid, consistent with an adenoma (Figure 1). No hypercalcemia has been documented in the six first-degree relatives in whom plasma calcium was measured.

The forearm bone mineral density was 324 g/L. Although reference intervals are not well established for 18-year-old males, this result is well below the tenth percentile for 30-year-old males (unpublished data). Roentgenograms of the hands and skull suggested generalized osteopenia, but there were no changes consistent with hyperparathyroidism. The patient had fractured a tarsal bone in 1987 after only a mild trauma.

Urinalysis revealed a normal amino acid profile and a glucose concentration of 1.1 mmol/L, excluding Fanconi’s syndrome. The 24-h urinary calcium excretion was 2.6
mmol (reference interval = 3.0–8.0 mmol).

In March 1989, a liver transplant was done because of gradual worsening of indices of hepatic synthetic function and because of recurrent episodes of spontaneous ascitic infection. Three weeks later he underwent parathyroidectomy and the right superior parathyroid gland was removed. It consisted of a well-circumscribed portion of tissue measuring 28 × 18 × 10 mm and weighing 3.585 g. The cut surface revealed a soft, ovoid red-brown nodule with blood-stained cystic areas. On microscopic examination there was the typical appearance of a parathyroid adenoma with complete absence of adipose tissue, moderate cytological pleomorphism of tumor cells including spindle-cell areas, and a thin rim of residual compressed “normal” parathyroid gland separated from the adenomatous component by a connective tissue capsule (Figure 2). The total calcium concentration (corrected for albumin) in plasma returned to normal after the parathyroidectomy.

The patient developed a severe cytomegalovirus infection in mid-April 1989 and died several weeks later.

Discussion

The association of hypoparathyroidism and Wilson’s disease may be explained by deposition of copper in the parathyroid glands (4), but it is much more difficult to postulate a pathophysiological basis for any proposed association between Wilson’s disease and hyperparathyroidism. Moderate to marked hypercalcemia occurs in Wilson’s disease (7), and theoretically it may result in an increase in parathyrin secretion, eventually leading to autonomous parathyroid function. However, this hypothesis is unlikely for three reasons. First, in vitamin D deficiency there is hypocalcemia, which stimulates parathyrin release, but there is no reported increase in the prevalence of hyperparathyroidism. Second, the above postulate is not consistent with the current proposed etiology of parathyroid adenomas, which suggests a monoclonal origin (8). Third, the 24-h urinary calcium excretion was slightly low, rather than high, although interpretive comment is difficult because the patient was not on a standard diet.

The prevalence of primary hyperparathyroidism is quoted as five to 30 per 10 000 in the general population (9, 10), but among male teenagers the prevalence would be expected to be much lower. In a series of 326 surgically proven cases of primary hyperparathyroidism from the Middlesex Hospital, there were 13 patients in the age range 10–20 years (11), making a prevalence in teenagers of around two to 12 per 100 000. The absence of hypercalcemia in other members of the patient’s family makes familial hyperparathyroidism unlikely.

The prevalence of Wilson’s disease in the general population is estimated at around 30 per million (12). Despite the very low probability of these two conditions occurring in the same patient, one can but ascribe this to chance until further similar cases are described.

This case demonstrates that when one is screening for a potentially lethal disease in a high-risk population (the sibs of a patient with Wilson’s disease have a 25% chance of being similarly affected) the diagnostic sensitivity should be 100%. Measurement of ceruloplasmin in serum is known to have 95% sensitivity in diagnosis of homozygous Wilson’s disease if one uses a cutoff value of 0.20 g/L (13). The specificity becomes unacceptably low if the cutoff value is further increased. Other causes of a low serum ceruloplasmin include 20% of cases of heterozygous Wilson’s disease, Menke’s disease, protein-losing states, severe liver disease, and familial hypoceruloplasminemia.

For certainty of diagnosis of homozygous Wilson’s disease, other testing is required (13). This will involve, in addition to serum ceruloplasmin, aminotransferase assays and slit-lamp examination of the eyes for Kayser–Fleischer rings. If the ceruloplasmin concentration is low, but the eyes do not show Kayser–Fleischer rings, hepatic biopsy with measurement of hepatic copper concentration is indicated (13). The 24-h urinary excretion of copper is usually increased (>1.25 µmol/24 h) in untreated Wilson’s disease, but may also be increased in chronic liver disease with cholestasis and in severe proteinuria (13). This measurement is frequently made in addition to the above-mentioned tests, but is probably of most value in monitoring response to treatment with penicillamine. Hepatic copper concentration usually exceeds 250 µg per gram of dried tissue in Wilson’s disease. However, this may also occur in primary biliary cirrhosis. The definitive test for homozygous Wilson’s disease is a study involving radioactive
copper (5). This will rarely be necessary in routine clinical practice.

The gene for Wilson’s disease is on chromosome 13 (14). Linkage with the esterase D locus and several restriction fragment length polymorphisms has been demonstrated. Possibly these techniques soon will be applied to presymptomatic diagnosis of siblings of affected patients (15).

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References