Penicillamine treatment of Wilson's disease and optic neuropathy

We report a case of optic neuropathy associated with penicillamine treatment of Wilson's disease.

A twenty-six year old woman presented with a one year history of progressive shaking of her hands and a four months of shaking of her head. As a result she had to give up her job on the line. There was no personal or family history of neurological or liver disease. She had a history of tachycardia and had taken disopyramide 100 mg three times a day for three years. A mitral regurgitation murmur had been noted in the past.

On examination her pulse was 80/min and regular, and blood pressure was 115/60. There was a mild and late systolic murmur loudest at the left sternal edge. Higher functions were intact, but her manner was disinhibited. Visual acuity was 6/9 on the right and 6/6 on the left. Fundus examination showed normal optic discs. Slit lamp examination showed Kayser-Fleischer rings. The other cranial nerves were normal. She had titubation, tremor of the upper limbs, worse on the right and severe to and fro movement of the lower limbs. The arm and leg reflexes were normal.

Semen copper was 7-0 micromol/l (Normal: 12-26 micromol/l) and ceruloplasmin 70 mg/l (Normal: 190-450 mg/l) and 24 hour urinary copper was 5-1 micromol/l (24 hours, Normal <0.8 micromol/l). Biochemical screen, plasma glucose, and chest and skull radiographs were all normal. Haemoglobin was 119 to 136 g/l, white blood count 2-2 to 3-9 x 10^9/l with polymorphs 1-0 to 2-3 x 10^9/l and platelets 85 to 116 x 10^9/l. The bone marrow was mildly hypocellular, with reduced numbers of erythroid and myeloid cells and megakaryocytes. A CT brain scan showed low densities in the thalami and cerebral peduncles. Echocardiography showed there was a severe left ventricular systolic dysfunction. A diagnosis of Wilson's disease was made and penicillamine 50 mg thrice a day was started.

Three weeks after starting penicillamine the patient presented with failing vision. On examination the right pupil reacted sluggishly to light. Corrected visual acuity was 6/24 on the right and 6/18 on the left. Near vision was N18 bilaterally. Visual evoked potentials (VEP) were bilaterally delayed. On examination both optic discs were pale and both pupils reacted sluggishly to light. Corrected visual acuity was 6/24 on the right and 112 ms on the left (Normal <115 ms). Brainstem auditory (BAEP) and somatosensory evoked potentials (SSEP) were bilaterally delayed. The wave form of the BAEPs was small. Electroretinogram and autoinmune profile were normal.

Penicillamine was stopped and pyridoxine 50 mg twice a day was started. Nine days later near vision was N9/6 (right) and N9/6 (left). Trientine dihydrochloride 600 mg three times a day was started. Three weeks after stopping penicillamine colour vision had returned to normal. A week later pupillary reactions were improved and near vision was N6 (right) and N4 (left). The VEPs showed improved amplitude, but the latencies were unchanged. Three months after stopping penicillamine the VEP latency on the left had improved to 99 ms and on the right was 106 ms. The BAEPs and SSEPs were unchanged. After seven months the visual acuity was 6/12 on the right and 6/9 on the left. After a year of trientine the patient had greatly improved. She has since returned to work and her manner appears normal.

No case of untreated Wilson's disease with optic neuropathy has been described. BAEPs are commonly delayed in Wilson's disease, but delayed VEPs have been found in only a minority of cases with neurologological involvement. Recovery of VEP latency with treatment has been described.1 The abnormal BAEPs may be related to cerebral hemisphere involvement.

Optic neuropathy in Wilson's disease treated with trientine and D-penicillamine has been associated with penicillamine induction pyridoxine deficiency: in two cases the optic neuropathy developed only after months at higher doses of penicillamine and improved with pyridoxine. Against this theory is a third case, which developed while on prophylactic pyridoxine. In all cases there was an improvement in the Wilson's disease index with penicillamine treatment, making the Wilson's disease itself unlikely to be the cause of the optic neuropathy.

Optic neuropathy has been described in association with D-penicillamine treatment of chronic active hepatitis for two months and rheumatoid arthritis for six months and for a year. The last was associated with development of a single level titter of 1520 and improved with steroids.2

This case differs from the others described as the duration of treatment before the development of optic neuropathy is much shorter. Pyridoxine deficiency is unlikely, because of the low dose and short duration of treatment. The short history and negative autoinmune profile make autoimmune disease unlikely. Neurological deterioration in the first month of penicillamine treatment of Wilson's disease has been recognised recently and the time course in this case would be consistent although optic neuropathy has not been described in this situation. A blurred vision of one eye, the presence of eyeglass-signs is seen in this syndrome, but was absent in this case. The neurological deterioration may be due to redistribution of copper. Trientine therapy has not been associated with neurological deterioration. Neuro-ophthalmic complications of desferrioxamine, including one case with optic neuropathy, have been associated with raised cerebrospinal fluid copper levels and attributed to redistribution of copper.3

Another explanation of the optic neuropathy in this case consistent with the short history would be an idiiosyncratic hypersensitivity reaction to penicillamine. Given the severe complication, physicians should regularly assess the visual acuity of their patients on penicillamine, particularly when starting treatment or increasing the dose.

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Serum erythroproteins levels in von Hippel-Lindau syndrome

No serum marker exists in von Hippel-Lindau syndrome (HLS), an autosomal-dominant inherited cancer-prone disorder
associated predominantly with hemangioblastomas of the central nervous system (Hbl), angiomas in retina (AR), renal cysts, renal cancer, pancreatic cysts, pheochromocytoma and epididymal cystadenoma.

Since paraneoplastics production of erythropoietin (EPO) or of erythropoiesis stimulating factors has been described in cerebellar Hbl, renal cancer, renal cysts, and pheochromocytoma, we investigated whether the serum EPO concentration is an indicator of HLS, which might facilitate an early diagnosis of affected individuals.

Our study included 44 patients (23 females, 21 males) with positive gene carrier status of HLS. Their mean age was 38.7 (16-79) years. Five of the patients had Hbl, 25 had AR, two had renal cancer, three had renal cysts, seven had pheochromocytomas; four had a history of surgical treatment for Hbl, and 11 for pheochromocytoma. Fifteen subjects presented with multiple lesions. Three asymptomatic individuals were identified as gene carriers by pedigree analysis.

Semen for EPO radioimmunoassay was prepared from venous blood samples without anticoagulant. The assay was carried out in duplicate using human urinary EPO standard, $^{125}$I-labelled recombinant human EPO (specific activity 11-33 TBq/mmol; Amer sham Buchler, Braunschweig, Germany) and antisierum (1:5000) from a rabbit immunised with human urinary EPO. The antibody-bound $^{125}$I-EPO was precipitated with polyethylene glycol 6000 (160 g/l). The mean within and between assay coefficients of variation were 7% and 19% in the EPO range 40-50 mU/ml. The detection limit was 5 mU/ml.

Comparative measurements of immuno reactive EPO were performed on serum samples from 14 normal subjects (five females, nine males; ages 40-38 years). Their EPO values were essentially normally distributed with a mean (1 SD) of 18.1 (7.5) mU/ml. Thus with the assay described, 95.5% of all normal values are in the range 3.1-33.1 mU/ml, mean (2 SD).

Serum EPO was elevated (> 33.1 mU/ml) in two of five (40%) patients with Hbl, in two of five (8%) with AR, in one of seven (14%) with pheochromocytoma, but in none of the patients with renal and pancreatic lesions. No significant correlation was found between elevated EPO values and serum haemoglobin concentrations. One patient with AR and one patient with a history of pheochromocytoma surgery presented with erythrocytosis (haemoglobin > 180 g/l), but serum EPO was normal in both cases.

We conclude that EPO is not a suitable marker for identifying patients affected with HLS, either in asymptomatic or in symptomatic individuals, and subsequently does not support our recently published clinical screening programme.

Application of gadolinium-DTPA magnetic resonance imaging for detection of a filum terminale myxopapillary ependymoma allowing successful surgical resection

Myxopapillary ependymomas of the spinal cord are histologically distinct low-grade gliomas which arise almost exclusively in the regions of the conus medullaris and filum terminale. Radiographic confirmation of these tumours has traditionally relied upon myelography and, more recently MRI. We report a further case that demonstrates the diagnostic value of Gadolinium-DTPA enhanced MRI.

A 41 year old male teacher of gymnastics presented with a one and a half year history of low back pain which radiated intermittently and alternatingly to the right and left buttocks and thighs, and was exacerbated by valsalva manoeuvres. He did not complain of focal motor weakness, sensory or sphincteric disturbances.

Physical examination of the patient's lumbosacral region as well as his neurological examination were unremarkable. He had normal strength, sensation and rectal tone, as well as active and equal deep tendon reflexes throughout, with downgoing plantar reflexes and a normal gait. Leseuge's test was negative bilaterally.

Plain radiographs and unenhanced CT scans of the entire lumbosacral spine were repeated at our institution and were unremarkable. Intravenous enhanced lumbosacral (L1-S1) CT also failed to show any intraspinal enhancing mass. Spin-echo


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