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 four months of shaking of her head. As a result she had to give up her academic line. There was no 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/minute and regular, and blood pressure was 115/60. There was a mid and late systolic murmur.

Penicillamine was stopped and pyridoxine 50 mg twice a day was started. Nine days later near vision was reduced to 6/60. Foveal responses were normal. Temporal 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 VEP's 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 SSEP's were unchanged. After seven months the visual acuity was 6/12 on the right and 6/9 on the left. After a year of treatment the vision 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. BAEP's are commonly delayed in Wilson's disease, but delayed VEP's have been found in only a minority of cases with neurological involvement. Recovery of VEP latency with treatment has been reported. The abnormal VEP's may be related to cerebral hemisphere involvement.

Optic neuropathy in Wilson's disease treated with D-penicillamine and D-penicillamine has been attributed to penicillamine induced 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 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 macular plaque titre of 1/320 and improved with steroids. 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 autoimmune 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 reported in this situation. The development of extrapyramidal signs is often 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. Another explanation of the optic neuropathy in this case consistent with the short history would be an idiosyncratic hypersensitivity reaction. Treatment of this unusual 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 erythropoietin 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 heman-
gioblastomas of the central nervous system
(Hbl), angiomatosis retinae (AR), renal cysts,
renal cancer, pancreatic cysts, phe-
chochromocytoma and epididymal cystadenoma.
Since paraneoplastic production of eryth-
ropoietin (EPO) or of erythropoiesis
stimulating factors has been described in
cerebellar Hbl,2 renal cancer,3 renal cysts,4
and pheochromocytoma,5 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 present-
ied with multiple lesions. Three asymptom-
tomatic individuals were identified as gene
 carriers by pedigree analysis.

Serum for EPO radioimmunoassay was
prepared from venous blood sampled with
out anticoagulant. The assay was carried out in
duplicate using human urinary EPO stan-
dard,101-labelled recombinant human EPO
(specific activity 11-33 TBq/mmol; Amer-
sham Buchler, Braunschweig, Germany) and
antiserum (1:5000) from a rabbit immunised
with human urinary EPO. The antibody-
bound125I-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
40-90 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 30-38 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 3-33-1
mU/ml, mean (2 SD).

Serum EPO was elevated (> 33-1 mU/ml)
in two of five (40%) patients with Hbl, in two
of 25 (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

We conclude that EPO is not a suitable
marker for identifying patients affected with
HLS, either in asymptomatic or in symp-
tomatic individuals, and subsequently does
not support our recently published clinical
screening programme.5

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Application of gadolinium-DTPA
magnetic resonance imaging for detec-
tion of a filum terminale myxopapillary
ependymoma allowing successful sur-
gical 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.1,2 Radiographic confirmation of
these tumours has traditionally relied upon
myelography and, more recently MRI.3,4

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

Figure (a) Spin echo pulse sequence, T1 (TR/TE = 600/20) and (b) T2 (TR/TE = 2500/ 80) weighted sagittal MRIs of the lumbar spine: the tumour was not apparent on T1, however,

on T2 weighted image an intradural tumour extending from approximately mid L2 to the superior
border of L3 could be seen. (c) Post Gad-DTPA injection T1-weighted sagittal MRI of the lumbar spine: the location, margin and extent of the intradural tumour was readily
identifiable due to the striking enhancement of the tumour. (d) Light microscopy of the tumour
revealing papillary low columnar cells surrounding a central core of hyaline containing small
vessels (Haematoxylin and Eosin × 40).