report of an unusual relapsing rhombencephali-
tis associated with seroconversion to
L monocytogenes.[5] Until recently serological
diagnosis has been unreliable because of cross
reacting antibodies, but the present assay, only
available at the Public Health Laboratory Service
(PHLS) in Colindale in the UK, is more
accurate and seroconversion is suggestive of
disease.

Our patient had severe brain stem involve-
ment but differed from the above descriptions
in having myelitis as well. Acute demyelinating
encephalomyelitis has not to our knowledge
been associated with listerial infection and
would be difficult to distinguish from micro-
abscesses by imaging or evoked potentials.
Partially treated meningitis and the brain stem
encephalitis described in children by Bickerstaff
have different clinical features.[6] Other causes
of a lymphocytic encephalitis were excluded.

We recommend that any child with focal
brain stem and/or spinal cord signs and a
cerebrospinal fluid lymphocytosis, with or with-
out encephalitis, should be treated with high
dose intravenous ampicillin and gentamicin
until listerial infection has been excluded.

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No sensory neuropathy during pyridoxine treatment in homocystinuria

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Abstract
**Seventeen patients with cystathionine synthase
deficiency homocystinuria were examined
clinically and neurophysiologically for
evidence of sensory neuropathy. All had
received high dose pyridoxine (vitamin B–6)
for many years. Absence of neurological
disturbance in all cases suggests long term
treatment with pyridoxine in the dosages used
in homocystinuric patients is not harmful.**

Homcystinuria due to cystathionine synthase
deficiency, an autosomal recessive disorder of
methionine metabolism, results in mental,
ocular, skeletal, and vascular disease if untreated.
About half of the patients respond to treatment
with pharmacological doses of pyridoxine
(vitamin B–6).[1] In our experience unresponsive
patients can be managed effectively with a diet
low in methionine. We have also given pyridoxine
to patients with no clear response to the vitamin
on the basis that the exact mechanism of
pyridoxine responsiveness is unknown and the
assessment of partial responsiveness is difficult.
High dose pyridoxine is reported to be associated
with sensory neuropathy.[2] Reports of toxicity in
humans on relatively low pharmacological
dosages (200 mg/day)[3] have alerted us to the
possibility of pyridoxine toxicity in patients
with homocystinuria.

Seventeen patients with homocystinuria
(eight clearly pyridoxine responsive) who had
been treated with large doses (200–600 mg/day)
of pyridoxine over many years (10–24 years)
were examined clinically and neurophysio-
logically for evidence of neuropathy.

Patients and methods
All patients were under the care of the Willink
Biochemical Genetics Unit. Sex, age at diagnosis,
pyridoxine responsiveness, daily dosage, and
duration of treatment are shown in the table.

Inquiry was made about sensory symptoms,
including difficulty handling objects, absence of
sensation leading to unnoticed injury, weakness,
and problems with balance and walking.
Physical examination looked specifically at
touch (cotton wool), pain (pin prick), pro-
prioception, Romberg's sign, tendon reflexes,
and observation of gait.

Plasma concentrations of pyridoxal phosphate
were measured by high performance liquid
chromatography.[4]

Electrophysiological studies were performed
to look for possible subclinical effects of
pyridoxine on the peripheral nerves. A supra-
maximal stimulation of 0·1 ms duration was
delivered at 1 second intervals, using surface
electrodes (ring electrodes for finger stimu-
lation). The median (index finger to wrist) and
sural (calf to lateral malleolus) sensory potentials
were recorded using surface electrodes. Onset
to latency (ms), peak to peak amplitudes (uV),
and sensory conduction velocity (m/s) were
measured. The median and lateral popliteal
motor responses were recorded over abductor

Details of 17 patients studied

Patient No	Sex	Age at diagnosis	Response to pyridoxine	Daily dose of pyridoxine (mg)	Duration of treatment (years)	Plasma concentration pyridoxal phosphate (nmol/l)	Motor conduction velocity (N1) (m/s)	Sensory nerve conduction (N2) μV)*
1	M	13 years	Yes	200	7	1337	39	10
2	F	18 years	Yes	200	9	1014	47	15
3	F	10 years	Yes	200	10	882	44	10
4	F	19 days	None	300†	11	166	49	12
5	F	14 days	None	300	14	1123	50	20
6	M	17 days	Part	400	14	636	52	10
7	F	12 days	None	300†	15	29	48	15
8	M	14 days	Part	400	16	585	58	10
9	F	20 days	None	300	16	1451	51	10
10	M	30 days	None	450	18	402	49	20
11	M	10 days	None	400	18	618	49	15
12	M	7 years	None	300	19	1352	39	10
13	F	10 years	Yes	500	20	1390	53	10
14	F	14 years	Yes	500	21	1347	50	13
15	F	10 years	Yes	200	22	781	51	15
16	M	7 years	None	400	22	478	44	10
17	F	3 years	Yes	200	24	1582	41	10

*Nerve conduction was also performed in the upper limbs, all results were normal. In this table the results from left lateral popliteal nerve (motor conduction, N1) and the left sural nerve (sensory amplitude, N2) are shown.
†Non-compliance.
Normal ranges: pyridoxal phosphate 20–50 nmol/l, motor conduction velocity (NI) 40–56 m/s, and sensory nerve conduction (N2) >5 μV.

pollicus brevis and extensor digitorum brevis respectively after stimulation of the median nerve at wrist and elbow and the lateral popliteal nerve at ankle and fibular head. Distal and proximal latency (ms), compound muscle potential amplitude (negative component, mV), and motor conduction velocity (m/s) were recorded.

Results

Inquiry indicated no symptoms suggestive of neuropathy in any of the patients and physical examination was normal in all cases. Plasma concentrations of pyridoxine metabolites and the results of electrophysiological studies are shown in the table.

Very high plasma concentrations of pyridoxine and pyridoxal phosphate in most patients confirmed compliance with treatment, at least at the time of study. This indicates adequate uptake of pyridoxine, conversion to pyridoxal phosphate, and maintenance of high concentrations of these compounds. In two patients with much lower concentrations of vitamers poor compliance was confirmed after direct questioning.

Nerve conduction was completely within the normal range for each of the four nerves studied.

Discussion

Evidence of peripheral neuropathy was first reported in seven adults aged 20–43 years receiving 2–6 g/day of oral pyridoxine for periods of two to 40 months.[2] In a less detailed study in which some subjects were not clinically examined evidence of neuropathy was reported in 16 subjects receiving 0·2–5·0 g of pyridoxine daily, notably in three subjects receiving 200, 500, and 500 mg/day respectively, for eight months to three years.[3] In a review based on a literature survey it was concluded that pyridoxine administration below 500 mg/day appears to be safe,[5] although this was based on treatment periods of only up to six years and takes no account of intake related to body weight.

In our study daily doses are less than those

reported to cause neuropathy. However these doses related to body weight ranged from 10–90 mg/kg/day during the the first 10 years of life, which is closer to the 25–120 mg/kg/day (based on assumed body weights) in adults reported by Schaumburg et al.[2] Also our homocystinuric patients received pyridoxine for 7–24 years (mean 16 years), which is far longer than in previous reports. Therefore the finding of no evidence of neuropathy by extensive clinical and neurophysiological studies is reassuring. This suggests that long term treatment of homocystinuria with doses up to 800 mg of pyridoxine per day is not harmful.

Differences in handling and storage of pyridoxine vitamers between adults and children or in cystathionine synthase deficiency are unlikely. In fact pyridoxal phosphate concentrations in our compliant patients ranged from 8–32 (average 20) fold higher than the upper limit of the control range. This is higher than the 6–7 fold increase of pyridoxal phosphate reported in six healthy adults receiving 100 mg oral pyridoxine/day.[6] Despite these reassuring results careful thought should be given to the class of homocystinuric patient treated with pyridoxine and the amount prescribed. The justification for giving patients who are unresponsive to pyridoxine large amounts of the vitamin must be questioned. In patients who are responsive to pyridoxine the smallest dosage compatible with good biochemical control (absence of homocystine from plasma) should be recommended.

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