

Neurophysiological results

	Day 3	Day 19	Day 90	Normal
Motor:				
Right cubital nerve				
MAP (wrist/elbow) (mV)*	9.6/8.6	2/3	3.8/4.5	6-16
Distal latency (ms)	3.4	3.5	2.9	1.8-3.5
Conduction velocity (m/s)	57.2	56	58.8	49-71
F wave	34.7	NR	33.6	<31
Right posterior tibial nerve				
MAP (ankle/popliteal fossa) (mV)†	8.2/7.9	1.8/2	6.1/6.3	6-37
Distal latency (ms)	5	5.1	5	3.9-5.1
Conduction velocity (m/s)	50.3	50.2	50	45-60
F wave	58.1	49.1	47.2	<55
Sensory:				
Right sural nerve				
SAP (µV)		5	5.2	2-19
Conduction velocity (m/s)		52.9	52.1	48-62

*Muscle action potential recorded from the hypothenar eminence. †Muscle action potential recorded from the abductor hallucis. SAP = sensory action potential; NR = no response.

eight hours for six weeks). This treatment did not improve the neurological damage but resulted in sterile CSF and bronchial cultures. We also used intravenous immunoglobulin and dexamethasone before laboratory data showed features of respiratory syncytial virus infection. Spine MRI was normal. Six months later serum immunoglobulins, IgG subclasses, C3, C4, CH₅₀, B, T, and NK lymphocyte subsets, CD4/CD8 ratio, lymphocyte blastogenic responses to both B and T mitogens, NBT test, chemotaxis, serum opsonisation capability, and neutrophil and monocyte phagocytosis were normal. The patient began a slow recovery in the fifth week and artificial ventilation was discontinued on day 44. He started to walk unaided on day 70. After 10 months the patient was transferred to a rehabilitation centre. Motor examination at that time still showed grade 2-3 strength and there was considerable atrophy in the shoulder girdle muscles.

Neurophysiological studies were performed on the third, 19th, and 90th days after the onset of neuropathic symptoms (table). The nerve conduction velocities, distal motor latencies, H reflexes, and sensory nerve action potentials were always normal. The first electrophysiological examination showed slightly prolonged F wave latencies as a principal feature. Ulnar F response was absent on the next examination. The second and third studies showed a reduction in the size of the compound muscle action potentials. Electromyography showed mild to moderate denervation in the lower limbs and considerable denervation in the upper limbs, affecting mainly the C3-C6 innervated muscles. Values of somatosensory evoked potentials were in the normal range after median and posterior tibial stimulation.

Respiratory syncytial virus infection has rarely been associated with neurological abnormalities. In a few old reports respiratory syncytial virus infection could be serologically established in cases with polyradiculitis, meningitis or myelitis.^{2,3} More recently it has been documented in patients with Guillain-Barré syndrome⁵ and a case of Guillain-Barré syndrome preceded by a cold with serological evidence of respiratory syncytial virus infection has been described.⁴ As far as we know, our case is unique in reports of respiratory syncytial virus associated neurological disorders for two reasons: the infectious agent could be cultured from CSF and the development of purely lower motor neuron damage in a pattern similar to generalised poliomyelitis. The major findings in this case were an acute

generalised weakness and amyotrophy without appreciable sensory change, sphincter disturbance, or clinical involvement of the corticospinal tract, and signs of meningeal infection. The EMG features place the likely site of the lesion at the anterior horn cell. The slowing of F waves in the first examination could be related to primary demyelination in the motor root but this feature can occur in motor neuron disease.⁶ The most effective chemotherapeutic management of respiratory syncytial virus infection is ribavirin.¹ Our patient was treated with this antiviral agent after the tetraparesis was complete, but ribavirin treatment was effective in sterilising the CSF.

In conclusion, respiratory syncytial virus infection should be incorporated in the differential diagnosis of the clinical syndrome of acute flaccid paralysis with meningitis. Because respiratory syncytial virus infection can be clearly diagnosed and is a treatable disorder, its recognition is important.

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Hereditary defect of cobalamin metabolism (homocystinuria and methylmalonic aciduria) of juvenile onset

Disorders of cobalamin (Cbl) are caused by inadequate intake, malabsorption, impairment of the extracellular transport, or inborn errors of intracellular Cbl metabolism.¹

Two Cbl-dependent enzymes are known: the adenosylcobalamin (AdoCbl)-dependent methylmalonyl-CoA mutase (MCM; EC 5.4.99.2) and the methylcobalamin (MeCbl)-dependent methionine synthase (5-methyltetrahydrofolate homocysteine methyltransferase; EC 2.1.1.13). Nine complementation classes of defects of intracellular Cbl metabolism or of the apoenzymes have been described.² A combined defect of intracellular synthesis of AdoCbl and MeCbl is a rare autosomal recessive disorder reported in about 20 patients to date. Complementation analysis has disclosed two genetically distinct groups designated cblC and cblD. Most patients present in early infancy with failure to thrive, developmental retardation, and megaloblastic anaemia.¹ Manifestation later in life is rare. In one female patient the disorder manifested at the age of 14 years as subacute myelopathy and dementia.³ After systemic OH-Cbl treatment cognition improved rapidly whereas the myelopathy responded slowly. In another patient a disorder of the CNS occurred at 21 years of age and a diagnosis of multiple sclerosis was first made.⁴ After a six year relapsing and remitting disease course an isolated defect of methionine synthase (cblG) was detected.

Here a 30 year old woman (patient 1) with a 13 year disease course of relapsing and remitting myelopathy and neuropathy due to the cblC defect and her 34 year old sister (patient 2) are reported.

At the age of 12, patient 1 complained of unsteadiness of gait and urinary incontinence for a few weeks. Her motor and mental development had been normal. There was no family history of neurological disorders. She showed signs of a spinal cord disorder with pyramidal signs, and an impaired position sense. All ancillary tests, including vitamin B12 absorption and CSF studies, were normal. She had a complete remittance with prednisolone treatment. Two years later she developed similar signs, but more severe, which lasted several weeks until almost complete remission.

At the age of 19 another relapse occurred with first signs of a neuropathy with bilateral foot drop and absent ankle reflexes. Nerve conduction testing showed a reduction in amplitude and a low normal conduction velocity. A needle EMG showed chronic denervation. Treatment with high dose corticosteroids resulted in partial improvement.

In the next two years four additional relapses occurred with progressive residual deficits and mild neuropsychiatric abnormalities. Cranial and spinal MRI and CSF studies were normal. A sural nerve biopsy showed a predominantly axonal neuropathy. During the next five months there was a progressive deterioration, with inability to walk, bladder incontinence, ascending sensory loss, severe respiratory alkalosis (pH 7.51, bicarbonate 34 mmol/l, base excess 10.9) with a severe disturbance of electrolytes (hypokalaemia (2 mmol/l, normal 3.5-5.0 mmol/l), hypophosphataemia (0.55 mmol/l, normal 0.8-1.5 mmol/l)), and respiratory insufficiency. Serum Cbl was in the

Enzyme activities in cell sonicates grown in normal or OH-Cbl supplemented medium

	OH-Cbl in medium ($\mu\text{g/l}$)	Methionine synthase (pmol/min/mg)		MCM (pmol/min/mg)	
		No added MeCbl	+50 $\mu\text{mol/l}$ MeCbl	No added AdoCbl	+50 $\mu\text{mol/l}$ AdoCbl
Patient	0	—†	49	57	1604
Patient	1000	206	348	162	727
Controls	0	24–109	65–244 (n = 14)*	29–201	440–837 (n = 20)*
Controls	1000	646‡	810‡	192–347	448–802 (n = 6)*

*n refers also to the assay without added coenzyme.

†Not detected; detection limit of the assay < 5 pmol/min/mg.

‡Simultaneously assayed control.

MCM activity was assayed in fibroblast homogenates as described.⁶ Methionine synthase activity was determined by measuring the formation of labelled methionine from [¹⁴C] methyl tetrahydrofolate and homocysteine. All of these activities were related to the protein content determined by the Lowry method.

lower normal range. Screening for more common metabolic white matter diseases was inconclusive.

Quantitative analysis of organic acids by gas chromatography—mass spectrometry showed an increase in urinary methylmalonic acid (MMA) (2900 mmol/mol creatinine; normal < 2 mmol/mol creatinine). Total plasma homocysteine was raised (174 $\mu\text{mol/l}$; normal < 15 $\mu\text{mol/l}$) and methionine was abnormally low (7 $\mu\text{mol/l}$, normal 13–28 $\mu\text{mol/l}$). A disorder of Cbl metabolism was suggested and treatment with intravenous OH-Cbl was started at 500 $\mu\text{g/day}$ at the age of 25. Weaning from the respirator was possible. The patient gradually improved but remained confined to a wheelchair with mild ataxia of the arms. She had to continue on intramuscular OH-Cbl (10 mg weekly) because oral OH-Cbl failed to maintain metabolic control.

Metabolism of Cbl and Cbl related enzymes were investigated in skin fibroblasts. The principal findings were reduced MCM and methionine synthase activities, which were restored in the presence of the coenzymes (table). The incorporation of [¹⁴C]-propionate and the formation of labelled methionine and serine from formate were much reduced in cells grown in normal medium and returned to almost normal with OH-Cbl supplementation (data not shown). Complementation studies in fibroblasts were performed with previously characterised cell lines displaying a cblC or a cblG mutation. Methionine synthesis increased ninefold over baseline values with the cblG mutant cell line and remained unchanged with the cblC cell line. These results confirmed the cblC defect.

In a sural nerve biopsy obtained before B12 treatment odd numbered long chain fatty acid concentrations were increased (4.13% of the total 14- to 22-carbon fatty acids in the samples; controls 0.82 (SD 0.42%)) but not in muscle whereas the content in erythrocyte membrane lipids was moderately increased after six months of OH-Cbl treatment (1.3%, controls 0.7 (0.12%)) and returned to normal (0.84%) after prolonged OH-Cbl treatment.

The sister of patient 1, who is 4 years older, was first examined at the age of 23. Electrophysiological studies disclosed normal motor conduction velocity of the peroneal nerve (58 m/s; normal > 43 m/s). Neurological examination was normal. At the age of 31 tibial nerve conduction velocity was at the lower limit of normal (41 m/s) and the deep tendon reflexes of the legs were hypoactive indicating a subclinical neuropathy. Metabolic screening performed at the age of 29 showed increased excretion of MMA (1550 mmol/mol creatinine). A single intramuscular dose of 2 mg OH-Cbl led to a 60% reduction of MMA excretion. The

patient refused further investigations and did not accept treatment.

A thorough laboratory screening of the parents of the sisters including analysis of urinary MMA excretion and plasma methionine and homocysteine concentrations was normal.

Our patients illustrate the extremely variable presentation of inherited disorders of Cbl metabolism. During the 18 year disease course patient 1 presented with neurological symptoms and signs of the CNS and PNS that developed gradually in a relapsing and remitting fashion over many years and seemed to respond to glucocorticosteroid treatment. Neither the variability of disease expression, as exemplified by the finding in our patient 2, nor the surprising initial response to steroids can be explained at present.

All previously described patients with the cblC/D defect have responded biochemically to a varying degree when treated with pharmacological doses of OH-Cbl. Adequate long term control of MMA and homocysteinemia was obtained only by systemic treatment. There was a good correlation between the clinical response and the results of fibroblast studies in which normalisation of activities was shown when cells were grown in OH-Cbl supplemented medium (table). The response to OH-Cbl was greater than that seen in fibroblasts of most patients with this defect (B Fowler, E R Baumgartner, unpublished data). The clinical benefit from OH-Cbl treatment was evident by full restoration of arm function although improvement in walking was limited. Moreover, no further relapses occurred over six years and the disease did not progress. The lack of complete recovery is not unexpected in view of other reports.⁵

Our cases add a new variant to the clinical range of inherited Cbl disorders. Disturbance of Cbl metabolism including the cblC/D defect should be taken into consideration in patients with relapsing and remitting disorders of the CNS and PNS, regardless of the age of the patient. Screening must be performed by measurement of total homocysteine and methylmalonic acid as normal concentrations of Cbl measured in a routine assay do not rule out inherited disorders of Cbl metabolism.

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Detection of dilated subarachnoid space around the optic nerve in patients with papilloedema using T2 weighted fast spin echo imaging

Magnetic resonance imaging is often used to detect lesions of optic nerves.^{1,2} However, MRI using conventional T2 weighted spin echo sequence and short inversion time inversion recovery sequences take about 10 minutes for imaging. The use of time consuming methods causes image artifacts due to patient's movements because of discomfort or positioning in a routine clinical setting; the above mentioned MRI methods hardly discriminate between the optic nerve and the surrounding subarachnoid space. Improvement of sensitivity of MRI and shortening of imaging time is required to image optic nerve lesions as routine. This problem can be achieved by the use of the T2 weighted fast spin echo sequence with fat suppression. Recently, Gass and associates applied this technique for the description of optic nerves in various optic neuropathies.³ Imaging by fast spin echo is based on recent modifications of the rapid acquisition with relaxation enhancement sequence pioneered by Hennig and associates.⁴

We scanned 10 normal subjects and three