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

T2 weighted fast spin echo imaging of the optic nerve complex. The high-intensity ring shaped area around the optic nerve represents CSF in the subarachnoid space in a 25 year old normal subject (upper) and a 17 year old patient with papilloedema due to congenital hydrocephalus (lower). The lower MRI shows the dilated subarachnoid spaces.

patients with papilloedema resulting from congenital hydrocephalus (17 year old boy) or secondary hydrocephalus due to brain tumours (45 year old woman and 46 year old man) using the fast spin echo sequence with a frequency selective fat suppression technique. We used a 1.5-Tesla magnet (Signa, GE Medical Systems, Milwaukee, WI, USA) with a 5 inch circular coil for genetic surface imaging. Coronal images were obtained of 3 mm thick sections (a 256×192 matrix, 14 cm field of view) at a repetition time of 4000 ms and an echo time of 104 ms using two excitations. Coronal, axial, or sagittal images were obtained in one patient in about two minutes for each type. Ring shaped high intensity areas were seen around the optic nerves in nine of 10 normal subjects (upper figure). Very dilated ring shaped high intensity areas were seen in six eyes of the three patients with papilloedema, having the same high intensity as the CSF in dilated ventricles (lower figure; ventricles not shown). These findings confirm that the high intensity ring surrounding the optic nerve represents CSF in the subarachnoid space.

The volume of subarachnoid space within the optic nerve sheath was increased in patients with papilloedema, possibly associated with increased subarachnoid pressure on the optic nerve and intracranial pressure. A postmortem study of a patient with hydrocephalus showed distension of the subarachnoid space.⁵ We measured the longitudinal diameters of the optic nerve and the outer circle of subarachnoid space (3 mm to 6 mm posterior to the globe), and then calculated the ratio of these diameters. The mean ratio in nine normal subjects (18 eyes) was 0.58

(SD 0.02). The mean ratio in three patients (six eyes) with papilloedema was 0.40 (SD 0.03). Brain MRI for three patients one month after the decompression surgery also showed ring shaped areas, the mean diameter ratio of which was 0.48 (SD 0.04).

Brain MRI with a T2 weighted fast spin echo sequence successfully showed the CSF within the sheath around the optic nerve in living humans as a non-invasive technique. A T2 weighted fast spin echo sequence with a surface coil and a fat suppression technique provides high enough resolution and speed to allow measurement of the optic nerve complex in the orbital portion.

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Alzheimer's disease in a case of cortical basal ganglionic degeneration with severe dementia

Cortical basal ganglionic degeneration (CBGD) is a neurodegenerative disease with core features of both basal ganglionic and cortical dysfunction.¹⁻⁴ CBGD typically presents as an akinetic rigid syndrome poorly responsive to levodopa, often with asymmetric limb dystonia. Signs of cortical dysfunction include limb apraxia, astereognosis, and language disturbance. Cognitive function is characteristically well preserved, even in the advanced stage of the illness. Dementia is so unusual as an early sign in pure CBGD that presentation with cognitive impairment has been proposed as an exclusionary criterion for the diagnosis.³ We describe a patient with clinical features of CBGD who presented with prominent, early dementia. Neuropathological examination confirmed the diagnoses of both CBGD and Alzheimer's disease.

A 72 year old woman presented with a six month history of gait disturbance, falls, and confusion. Examination showed cognitive impairment, pronounced rigidity in all four limbs, and left limb apraxia. Examination at

the age of 74 disclosed that she was alert and cooperative, but unable to give any meaningful history. She was not oriented to day or year. Speech was slow but she could name objects, repeat, and follow a two step command. There was left/right confusion. Facial dystonia was apparent. All four limbs were very rigid, left more than right. Although strength was good in both arms, she was unable to voluntarily raise her left arm or to use her left hand for any skilled movement. Her left hand spontaneously assumed unusual postures suggestive of an alien limb phenomenon. She could not manipulate a coin with her left hand but could pick up and identify a coin with her right hand. Her dementia precluded further assessment of cortical sensory deficits. There was no resting or postural tremor. Muscle stretch reflexes were brisk at the left biceps but otherwise unremarkable. Plantar responses were equivocal. There were pronounced suck, snout, and bilateral grasp reflexes. With assistance she could rise from a chair and stand independently. She walked with a small stepped shuffling gait, with the trunk flexed and the left arm held in a flexed, dystonic posture. Laboratory studies were normal. Cranial CT showed evidence of generalised cerebral atrophy, mild periventricular white matter hypodensity, and asymmetrically enlarged frontal horns of the lateral ventricles, more pronounced on the left. The patient deteriorated steadily with progressive motor impairment and inability to speak. She died aged 76, four and a half years after the onset of her disorder.

At necropsy, the brain (weight 1010 g) displayed moderate diffuse, symmetric frontoparietal atrophy and mild temporal atrophy. The lentiform nuclei were shrunken and discoloured and the thalamus was decreased in mass. The substantia nigra had a rusty hue. The pons, medulla, and cerebellum were grossly normal.

Microscopic examination of the cerebral cortex showed neuronal loss, most evident in layer 3, with spongiosis in layer 2, most pronounced in the parietal and frontal regions. Swollen, achromatic neurons or "balloon cells" (figure A) were seen in the deeper layers of the parietal cortex, particularly around the central sulcus, but not in other cortical areas. Neuronal degeneration with achromasia was pronounced in the globus pallidus and lateral thalamus, moderate in the putamen. There was pronounced degeneration of pigmented neurons in the substantia nigra, particularly the lateral portions. Some of the remaining nigral neurons contained lightly basophilic fibrillar inclusions (figure B), typical of "corticobasal inclusions,"² whereas others contained homogeneous pale eosinophilic cytoplasm. Corticobasal inclusions were also present in the red nucleus and locus ceruleus. Swollen achromatic neurons were also seen in the red nucleus, periaqueductal grey, pontomedullary tegmentum, basis pontis, olivary nuclei, and cerebellar dentate nucleus. Reactive gliosis paralleled the severity of neuronal loss.

Bielschovsky silver staining showed neurofibrillary tangles and neuritic plaques in the cerebral neocortex and hippocampi (figure C). Maximum plaque densities were: frontal cortex 30-40/mm²; parietal cortex 15-20/mm²; temporal neocortex 20-30/mm²; occipital cortex 15/mm². Neuritic plaques were common in the amygdala and medial nucleus basalis of Meynert, but rare in other subcortical regions.