cortical vascular pathology in two patients in whom CT images were reported as normal. It is reasonable to assume that comparable changes would have been found in other patients with clinical features of subcortical vascular disease, had MRI been performed.⁸

This study provides support for the assumption that treatment resistance in elderly depressed patients might, at least in part, reflect the presence of subcortical vascular pathology. This finding has important implications with regard to the clinical management and prognosis of elderly patients with treatment resistant depression. It is important to note, however, that study patients were a highly selected group in whom underlying cerebral pathology had already been suspected by the referring psychiatrist. It is not possible, therefore, to draw conclusions with regard to the prevalence of subcortical vascular pathology in other groups of elderly depressed patients. Nevertheless, this study serves to highlight those clinical features that might indicate the presence of underlying subcortical vascular disease, and the importance of MRI in the investigation of patients in whom subcortical pathology is suspected, but in whom CT imaging fails to show abnormality. Furthermore, ^{99m}Tc-HMPAO SPECT imaging seems sensitive to the presence of subcortical vascular disease, and might therefore provide a useful contribution to the investigation of such patients. A prospective study of an unselected population of elderly depressed patients is required to consider these issues, and in particular to determine the prevalence of subcortical vascular pathology in this population, and the contribution such changes make to treatment resistance.

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Hereditary transcobalamin II deficiency: a 22 year follow up

Transcobalamin II (TCII) is the main plasma transport protein for vitamin B12. Its gene has been localised to chromosome 22.¹

Genomic structure suggests that it, the two other cobalamin transporters TCI and TCIII, and gastric intrinsic factor originated by duplication of an ancestral gene.² Inherited deficiency of TCII leads to reduced delivery of vitamin B12 to the tissues and to its impaired absorption from the ileum. We reported a patient with hereditary TCII deficiency with neurological involvement in 1982³ and have recently re-examined him. He was born in 1974 to healthy unrelated parents. A brother had died aged 6 months with peripheral pancytopenia and a megaloblastic bone marrow. The patient developed feeding difficulties in the neonatal period and was found to have a megaloblastic anaemia. He was diagnosed as having dihydrofolate reductase deficiency⁴ and was started on parenteral treatment with folinic (5-formyl tetrahydrofolic) acid. When aged 6 months he was stated to have had normal mental and physical development. He continued to receive daily injections of folinic acid but from the age of 12 months his mental and motor development regressed. When examined in London at the age of 2 years he was unable to sit or stand unsupported and there was jerky ataxia of the upper limbs. His tendon reflexes were generally depressed and both plantar responses were extensor. Frequent spontaneous attacks occurred in which he became transiently rigid and unresponsive. Reinvestigation showed normal hepatic dihydrofolate reductase activity but absent vitamin B12 binding to serum TCII. Folinic acid treatment was discontinued and he was started on thrice weekly injections of 1000 mg hydroxocobalamin. His mental and neurological state gradually improved.

When reviewed in 1980 his intellectual development was still severely reduced. He walked unsteadily with assistance with both feet in an equinus position. Neurological examination showed microcephaly and bilateral pyramidal signs with extensor plantar responses. All his tendon reflexes were obtainable apart from the ankle jerks. He was reviewed again in June 1996 when, after further improvement, his condition had stabilised. His peripheral blood count was normal. He had been experiencing grand mal seizures at about three-monthly intervals but these had ceased after an increase in the dosage of sodium valproate. Speech utterance was limited and restricted to single words. Speech comprehension was reasonable. Tongue movements were sluggish. Upper limb muscle strength was good but discrete finger movements were sluggish. There was no upper limb ataxia. There was increased tone in both legs with moderate weakness of upper motor neuron distribution. He walked with a spastic "scissors" gait with his feet in equinus. His tendon reflexes were generally brisk and both plantar responses were extensor. Adequate sensory testing was not possible.

An ECG was of low medium voltage with somewhat discontinuous 10-12 Hz central and postcentral rhythmic activity and low voltage beta activity. A single burst of bilateral but predominantly right sided 2.5 Hz waves was recorded. Brain MRI with T2 weighted axial sequences showed reduced volume of the cerebral white matter, particularly of the corpus callosum which was diffusely thinned. There was hyperintensity of the FLAIR sequence in the immediate periventricular white matter and in the subcortical white matter in the higher frontal images. Imaging of the brainstem and cerebellum was normal.

Except for two possible instances, neurological dysfunction has not been present at the time of haematological presentation of hereditary TCII deficiency in the cases reported to date but has appeared later.⁵ The clinical features resulting from vitamin B12 deficiency in infancy seem to differ from those that occur when deficiency develops in later life. In the present case, in a child reported by Burman *et al*,⁶ and in a further case documented by Mane *et al*⁷ and Gimferrer *et al*⁸ the neurological syndrome was dominated by CNS changes that included microcephaly, generalised epilepsy, impaired cognitive development, and gait disturbance because of ataxia and spastic lower limb weakness. Sensory neuropathy was not a feature. Motor and sensory nerve conduction studies were normal in our case in 1980 and were not repeated at the recent review.

It is vital that hereditary TCII deficiency should be recognised promptly so that treatment with vitamin B12 can be initiated to avoid irreversible cerebral changes. In the present case diagnosis and appropriate treatment were unfortunately delayed. Comparison of the patient's present state with that in 1976 and 1980 indicates that further neurological improvement has occurred but he remains with severe cognitive impairment, controlled epilepsy, poor manual function, and a spastic gait. The possible mechanisms for neural dysfunction related to B12 deficiency have recently been reviewed.⁹ The mechanism of B12 uptake into the CNS is not established but cobalamin receptors could be present on brain capillary and choroid plexus endothelial cells. TCII is known to be present in the CSF and it has been shown that TCII is synthesised by astrocytes.¹⁰ Astrocytes may possibly be involved in cobalamin recycling and transport in the CNS.

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