Genomic structure suggests that it, the two other cobalamin transporters TCI and TCIII, and gastric intrinsic factor originated by duplication of an ancestral gene. Inherited deficiency of TCII leads to reduced delivery of cobalamin B12 to the tissues and to its impaired absorption from the ileum. We reported a patient with hereditary TCII deficiency with neurological involvement in 1974 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 had developed signs of the neurological syndrome in his neonatal period and was found to have a megaloblastic anemia. He was diagnosed as having dihydrofolate reductase deficiency 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 but from the age of 12 months his mental and motor development slowed. 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 gait was more pronounced 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 methyltetrahydrofolate and neurological and developmental 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 equinovarus 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 this time and had been managed with carbamazepine for 10 years 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 reasonably good. Tongue fasciculations 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 ECQ 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 occipital lobes, 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 occipital frontal images. Imaging of the brainstem and cerebellum was normal.

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. 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., it and in a further case documented by Ball et al. and Gimferrer et al. the neurological syndrome was dominated by CNS changes that included microcephaly, generalised epilepsy, impaired cognitive function, and chronic ataxia. In our patient the disturbance due to 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 be recognised promptly so that treatment with vitamin B12 can be initiated to avoid further central nervous system damage. The present case diagnosis and appropriate treatment were unfortunately delayed. Comparison of the patient's present state with that in 1974 and 1980 indicates that his 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. The mechanism of B12 uptake into the CNS is not established but cobalamin receptors could be present on brain capillaries and choroid plexus epithelial cells. TCII is known to be present in the CSF and it has been shown that TCII is synthesised by astrocytes. Astrocytes may possibly be involved in cobalamin recycling and transport in the CNS.

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