We report on a child in whom severe nutritional vitamin B₁₂ deficiency was exacerbated by a genetic impairment of the folate cycle, causing reduced CSF concentrations of the methyl group donor 5-methyltetrahydrofolate. Some patients with vitamin B₁₂ deficiency may benefit from high dose folic acid supplementation, even if plasma concentrations are high.

DISCUSSION
The severe and prolonged neurological disease in our patient may be explained by the combined effect of vitamin B₁₂ (cobalamin) depletion and folate cycle disruption. Nutritional vitamin B₁₂ deficiency has long been recognised as a cause of severe encephalopathy in breast fed infants of mothers on a vegetarian diet.¹ The vitamin is exclusively obtained from animal sources, and hepatic stores in infancy may fall rapidly with insufficient supply. Vitamin B₁₂ may be low in breast milk of vegetarian mothers, and this may have been exacerbated in our patient (who was comparatively old at the time of presentation) by the new pregnancy of the mother; maternal vitamin B₁₂ concentrations are known to decrease during pregnancy.³

Children with nutritional vitamin B₁₂ deficiency develop normally in the first months of life but subsequently show progressive lethargy, muscular hypotonia, loss of acquired skills, and coma. Neurological damage is thought to be a result of insufficient availability of S-adenosylmethionine, the principal methyl group donor in cellular metabolism (fig 1). Typical laboratory findings include macrocytic anaemia, hyperhomocysteinaemia caused by reduced activity of vitamin B₁₂ dependent methionine synthase, and methylmalonic aciduria caused by reduced activity of vitamin B₁₂ dependent methylmalonyl-CoA mutase. Most children improve rapidly after vitamin B₁₂ supplementation.¹

The slow neurological recovery in our patient is unusual and appears to be caused by concomitant mild MTHFR deficiency that exacerbated the disruption of the folate cycle. It is well established that vitamin B₁₂ deficiency causes folate to become trapped as MTHF, as has also been reported in methionine synthetase deficiency.¹ We expected, therefore, to find an increased CSF concentration of MTHF in our patient. Instead, MTHF was notably reduced, indicating an independent second pathogenetic factor.

The MTHFR polymorphism A222V (allele frequency 0.32 in whites) causes reduced enzyme activity and MTHF availability and is associated with hyperhomocysteinaemia, vascular disease, and neural tube defects in homozygous individuals. Approximately 10% of the general population are homozygous for A222V and thus at risk for adverse effects under certain conditions. It is important to note that plasma folic acid in our patient (as well as previously described children with nutritional vitamin B₁₂ deficiency) was increased. Cerebral folate cycle disruption was evident only in reduced MTHF concentration in CSF, a result which became available only weeks after the start of treatment. In retrospect we believe that high dose folic acid supplementation (in addition to cobalamin) may have benefited our patient by increasing the intracellular availability of MTHF as methyl group donor, although this will need to be confirmed in future patients.

In conclusion, detailed characterisation of cerebral folate status should be considered in patients with nutritional vitamin B₁₂ deficiency and severe neurological symptoms, even if
plasma concentrations of folic acid are high. Mutation analysis for the common MTHFR polymorphism A222V, which is rapid, relatively inexpensive, and now widely available, may be helpful in cases in which CSF investigations are not possible. Further study of paediatric and adult patients with nutritive vitamin B12 deficiency is required to confirm a correlation between severity of neurological symptoms and genetic variants of the folate cycle.

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