3. Progressive Neonatal Leukoencephalomyopathy Due to Absent Methylene tetrahydrofolate Reductase, Responsive to Treatment
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A first-born infant girl developed a deteriorating encephalopathy-myopathy at age 1 month. Progressive flaccid tetraparesis accompanied macrocephaly, increased intracranial pressure, abnormal electroencephalograms, and decreased white matter density, with ventricular dilatation on CT scans. Studies revealed homocystinuria (1.6 μmol/mg creatinine) and homocystinemia (3.1 μmol/L), hypomethioninemia (1.0 μmol/L), reduced serum free carnitine (21.6 nmol/ml), reduced cerebrospinal fluid (CSF) folate (6.4 nmol/ml), and altered CSF catecholamines. Muscle biopsy (including electron microscopy) showed lipid storage and reduced muscle free carnitine (3.04 nmol/mg noncollagen protein). White cell and fibroblast assays demonstrated absent methylenetetrahydrofolate reductase (MTHFR) (0.34 nmol formaldehyde produced/hr/mg protein) with flavin adenine dinucleotide, 0.53 nmol without but normal cystathionine synthase and 5-methyltetrahydrofolate-homocysteine methyltransferase. On neurological examination at 6 months, with folate/methionine/carnitine therapy, the infant was near normal. White matter density was normal on CT scans, and repeat muscle biopsy showed a reduction in lipid and increased tissue carnitine. CSF folate levels had increased, homocystinuria had disappeared, and plasma methionine was increased.

Previously reported infants have died even with folic acid therapy. Since absence of MTHFR activity interferes with the methionine cycle, the response to treatment suggests that this is a substrate deficiency syndrome with secondary reductions in plasma and tissue carnitine rather than a toxic effect from accumulated homocysteine. Carnitine depends on the methyl donor role of S-adenosylmethionine (SAM) in formation from lysine. The role of SAM in phosphatidylcholine formation may account for phosphoglyceride defects in myelin and the secondary leukodystrophy. An underlying lipid myopathy has not previously been recognized in this disease, nor has a role for carnitine been reported. Treatment appears to reverse both effects.