Short report

Dystonia in homocystinuria

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SUMMARY Three patients with homocystinuria due to cystathionine beta-synthase deficiency who developed progressive generalised dystonia are described. Although cerebrovascular thrombosis is usually thought to be responsible for neurological dysfunction in homocystinuric patients, neuropathological studies in one case and clinical and radiological evidence in the other two suggested that dystonia was not caused by brain infarction. Movement disorder associated with homocystinuria may result from the neurochemical changes in the basal ganglia related to the inherited defect in sulphur amino acid metabolism.

Several inherited defects of sulphur amino acid metabolism may result in homocystinuria (HCU). The commonest is a recessively inherited deficiency of the enzyme cystathionine beta-synthase leading to impaired transformation of homocysteine to cystathionine and elevated levels of plasma homocysteine and methionine.¹ (fig 1). The biochemical abnormalities in some patients are responsive to administration of pyridoxine.² Clinical features of HCU include skeletal abnormality, lens dislocation and spontaneous arterial and venous thromboses. Neurological involvement may occur in the form of cerebral thrombotic episodes, seizures and mental retardation.³⁻⁶

The majority of patients with juvenile or adult onset dystonia do not have associated neurological disorders and pathological or neurochemical abnormalities are seldom demonstrated. However, symptomatic dystonia may be seen in association with a variety of inherited and acquired neurological conditions.⁷ Dystonia due to HCU has been described in two previous cases^{8,9} and was attributed to multiple basal ganglia infarcts although pathological and neuroradiological data were not available. We describe an additional three patients with HCU complicated by progressive dystonia. Pathological findings in one

case and clinical and radiological features in the others suggested that thrombo-occlusive disease was not the cause of the extrapyramidal disturbance.

Case reports

Case 1 An 11 year old boy with intellectual impairment (IQ = 60), Marfanoid skeletal deformity, osteoporosis and bilateral lens dislocation was found to have HCU. The biochemical changes were not improved by treatment with pyridoxine. At the age of 18 years he developed spasmodic torticollis followed by truncal and upper limb dystonia. He had prominent retrocollis and truncal hyperextension which were exacerbated by walking. Tetraabenazine and anticholinergic agents had no effect on the dystonia although bromocriptine produced a modest improvement. He died at the age of 22 from bronchopneumonia secondary to severe neurological disability.

Neuropathological examination The brain weighed 1520g and showed no macroscopic abnormalities on external and cut surfaces. The vessels of the circle of Willis were of normal configuration and serial sections of the main cerebral vessels revealed no sign of organised thrombus. Histological examination with haematoxylin and eosin staining showed no evidence of thrombosis affecting small intraparenchymal vessels. Sections through areas of frontal lobe convexity and orbital cerebral cortex and temporal lobe cerebral cortex were normal with respect to thickness of the cortical ribbon, and cell numbers, type and layering; there was no sign of gliosis. Sections of caudate nucleus, putamen, globus pallidus, subthalamic nucleus, red nucleus and substantia nigra were also completely normal and cells of the substantia nigra were normally pigmented. Cell populations in all of these areas were assessed semi-quantitatively in

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Fig 1 Sulphur amino acid metabolic pathways.

luxol fast blue/cresyl violet sections; standard areas were examined using eyepiece graticule and stage micrometer to check magnification and compared with an age and sex matched control. This did not indicate any significant loss of neurons.

Case 2 This girl presented at the age of 7 years with mental retardation (IQ = 60) and bilateral lens dislocation. At that time a diagnosis of pyridoxine resistant HCU was made. At age nine, right upper limb tremor and hypertonia associated with abnormal posture of the right shoulder were observed and over the subsequent years she developed progressive dystonia affecting limbs, neck, trunk and tongue associated with dysarthria, generalised hypertonia, hyperreflexia and a shuffling gait (figures 2 a, b). A cranial computed tomographic scan at the age of 20 was normal apart from a small cortical area of low density in the right temporal region. Now aged 26, she has persistent generalised dystonia which has proved resistant to treatment with haloperidol, lioresal, bromocriptine and clonazepam.

Case 3 This boy presented at the age of 4 years with marked developmental delay and bilateral lens dislocation. Pyridoxine resistant HCU was diagnosed. At age 9 years he began to have tonic-clonic and akinetic seizures, which were treated with phenytoin and sodium valproate. He developed a Marfanoid body habitus and was severely intellectually impaired (IQ less than 50). At age 5 years he first showed a tendency to walk on his toes and by the age of 10 his gait was unsteady, he was dysarthric and there was generalised hyperreflexia. Thereafter gradual evolution of involuntary movements affecting neck, trunk and lower limbs occurred. At the present time, aged 19, he has dystonic posturing of the neck and feet with superimposed rapid torsional neck movements and choreiform lower limb movements. A cranial CT scan at the age of 13 was normal: electroencephalography

showed bilaterally synchronous paroxysms of polyspike and wave activity. Haloperidol and clonazepam were ineffective in controlling the movement disorder.

Discussion

These three patients show clinical similarities to the previously reported cases of extrapyramidal disturbance in HCU^{8,9} with progressive dystonic movements affecting limb and axial musculature commencing between 9 and 18 years of age. In each of the present cases, HCU was due to cystathionine synthase deficiency and the biochemical deficit was resistant to pyridoxine. Abnormal movements developed prior to any exposure to neuroleptic drugs in each case and none had acute neurological episodes suggestive of cerebral thromboses. Intellectual impairment was present in all the patients, pyramidal tract signs in two and one had a seizure disorder. However, there was no radiological evidence to suggest that dystonia was due to vascular changes in the basal ganglia and neuropathological findings in Case 1 were completely normal. Although all patients received pyridoxine, movements preceded this treatment in one of our patients and in both of the previously reported cases.^{8,9}

Many neuropathological studies of patients with HCU have shown evidence of arterial or venous thrombosis and infarction affecting cerebral cortex and deep grey matter structures.³⁻⁶ However, widespread white matter vacuolar degeneration in the absence of vascular pathology has been reported,¹⁰ as has hippocampal neuronal loss and gliosis not associated with local vascular changes.⁶ Pathological correlation with dystonic clinical features has not been previously described but our findings suggest that dystonia in HCU may relate to functional disturbance in neurotransmission rather than to detectable neuronal damage.

Several of the metabolic alterations which occur in HCU might disturb normal neurotransmitter function. Homocysteine is epileptogenic in animals¹¹ and homocysteic acid, an oxidation product of homocysteine, is known to have excitotoxic activity *in vitro*.¹² The importance of this oxidative pathway for homocysteine is uncertain but homocysteic acid is detectable in normal rat brain slices and may act as an endogenous neurotransmitter.¹³ Increased production of homocysteic acid would be expected in HCU. Homocysteic acid shows a similar glutamate displacing pattern to N-methyl-D-aspartate in neural tissue and its excitotoxic effects are likely to be mediated at this N-methyl-D-aspartate binding subgroup of glutamate receptors.¹⁴ Glutamate is considered to be an important central nervous system excitatory transmitter and glutamate receptors mediate cerebral

Fig 2 (a) Hand and (b) foot dystonic postures in Case 2.

cortical input to the striatum.¹⁵ Dystonia in HCU may therefore result from an imbalance of neurotransmission in the basal ganglia as a consequence of abnormal glutamate receptor stimulation. As stimulation of glutamate receptors can potentiate hypoxic cerebral damage,¹⁶ this hypothesis would also be consistent with previous pathological reports of neuronal and white matter degenerative changes disproportionate to vascular occlusive pathology.^{6,10}

The production of taurine from methionine is likely to be reduced by cystathionine synthase deficiency, although brain taurine levels in HCU have not been measured. Taurine has an inhibitory action in the central nervous system¹⁷ and may modulate neurotransmitter release, including that of dopamine.¹⁸ Reduction in basal ganglia taurine levels is therefore a possible cause for dystonia in HCU.

One further possible mechanism for basal ganglia neurochemical derangement in cystathionine synthase deficient HCU involves the excessive consumption of folate that occurs owing to increased folate dependant reconversion of homocysteine to methionine. Tyrosine hydroxylase, which catalyses the rate limiting step for catecholamine synthesis, uses tetrahydrobiopterin as a cofactor.¹⁹ There is some evidence to suggest a link between central nervous system metabolism of folate, biopterins and amine neurotransmitters. In a rarer form of HCU due to 5,10-methylenetetrahydrofolate reductase deficiency, Parkinsonian extrapyramidal disturbance has been reported in association with folate deficiency and reduced cerebrospinal fluid levels of biopterins and

amine metabolites.²⁰ It is possible that folate deficiency leads to a similar abnormality of dopaminergic neurotransmission in cystathionine synthase deficient HCU and that this may cause dystonia.

Our clinico-pathological findings suggest that extrapyramidal and possibly other neurological features of HCU may occur independent of cerebrovascular thrombo-occlusion. Although the relative importance of several possible mechanisms remains speculative, an abnormality of brain neurochemistry related to disordered sulphur amino acid metabolism is a likely explanation.

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