The intellectual abilities of early-treated individuals with pyridoxine-nonresponsive homocystinuria due to cystathionine β-synthase deficiency

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Summary: The pathological sequelae of untreated homocystinuria due to cystathionine β-synthase deficiency include ectopia lentis, osteoporosis, thromboembolic events and mental retardation. They occur at a significantly higher rate with poorer mental capabilities (mean IQ = 57) in the untreated pyridoxine-nonresponsive individuals. The mental capabilities of 23 pyridoxine-nonresponsive individuals with 339 patient-years of treatment were assessed using age-appropriate psychometric tests and were compared to those of 10 unaffected siblings (controls). Of the 23 individuals, 19 were diagnosed through newborn screening with early treatment, two were late-detected and two were untreated at the time of assessment. Thirteen of the newborn, screened group who were compliant with treatment had no complications, while the remaining 6, who had poor compliance, developed complications. Good compliance was defined by a lifetime plasma free homocysteine median < 11 μmol/L. The newborn screened, good compliance group (n = 13) with a mean age of 14.4 years (range 4.4–24.9) had mean full-scale IQ (FIQ) of 105.8 (range 84–120), while the poorly compliant group (n = 6) with a mean age of 19.9 years (range 13.8–25.5) had a mean FIQ of 80.8 (range 40–103). The control group (n = 10) with mean age of 19.4 years (range 9.7–32.9) years had a mean FIQ of 102 (range 76–116). The two late-detected patients aged 18.9 and 18.8 years had FIQ of 80 and 102, while the two untreated patients aged 22.4 and 11.7 years had FIQ of 52 and 53, respectively. There was no statistical evidence of significant differences between the compliant, early-treated individuals and their unaffected siblings (controls) except for the FIQ, which was significantly higher than that of the unaffected siblings ($p = 0.0397$). These data, despite the relatively small numbers,
suggest that early treatment with good biochemical control (lifetime plasma free homocystine median < 11 μmol/L) seems to prevent mental retardation.

Homocystinuria (HCU; McKusick 236200) due to cystathionine β-synthase (CβS; EC 4.2.1.22) deficiency is an inherited disorder of methionine metabolism. In Ireland, newborn screening for HCU was started in 1971 (Naughten et al 1998) and, based on newborn screening and clinically detected cases, the incidence of 1 in 50 000 is among the highest in the world. Individuals with CβS deficiency are clinically normal at birth. Its natural history was first documented by Mudd and colleagues in 1985. The clinical features of untreated CβS deficiency include ectopia lentis, dolichostenomelia, osteoporosis, thromboembolic events and mental retardation (Mudd et al 1995).

Mental retardation remains the most frequent abnormality of the central nervous system and is often the first recognized sign of CβS deficiency, presenting as developmental delay during the first and second years of life (Mudd et al 1995). It is, however, not at all a consistent finding, particularly among pyridoxine responders. The natural history (n = 629) of the condition, as described by Mudd and colleagues in 1985, showed a very wide range of patients’ IQ (n = 284) from 10 to 138 with a median of 64. The study also documented that pyridoxine (B₆)-responsive patients had significantly better (p ≤ 0.0001) mental capabilities (n = 107; mean IQ = 79) than did pyridoxine-nonresponsive patients (n = 115; mean IQ = 57) (Mudd et al 1985). Only about 22% of B₆-responders had IQ of 90 or above compared to 4% of pyridoxine-nonresponders with IQs in this range (Mudd et al 1985). When compared to unaffected siblings, 34% of pyridoxine-responders had IQs comparable with their siblings and a further 63% had lower IQ levels. Among pyridoxine-nonresponders, 94% had IQs below and only 6% were comparable to their unaffected siblings (Mudd et al 1985). These data excluded patients who were detected through newborn screening (Mudd et al 1985). Another series by Abbott and colleagues also documented a wide IQ range of 23–144 with a median of 83 in 63 patients (Abbott et al 1987). The findings of a Dutch study on 20 late-detected, pyridoxine-responsive patients were also consistent with a wide range of IQs (Boers 1986).

There are few reports of early treatment on the mental capabilities of patients with CβS deficiency. This paper documents the intellectual abilities of a group of long-term, early-treated pyridoxine-nonresponsive patients and their unaffected siblings.

PATIENTS AND METHODS

Subjects: A total of 23 pyridoxine-nonresponsive patients with CβS deficiency from 18 families attending the National Centre for Inherited Metabolic Disorders were included in the study. The mean age at assessment was 16.5 years (range 4.4–24.9). These patients were divided into three groups depending on the time of commencement of treatment. The newborn screened patients were further divided...