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Homocystinuria in New South Wales

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SUMMARY Homocystinuria was studied in 27 patients from 15 families in New South Wales. All 27 had biochemical findings consistent with cystathionine synthetase deficiency. One patient was ascertained by newborn screening, but the remaining index cases were detected because of symptoms: poor eyesight 6, mental retardation 3, thromboses 2, skeletal abnormalities 2, and urinary infection 1. 9 patients, one-third of all cases, were mildly affected: either they had no features of the disease, or these did not occur until the late teens. Pyridoxine responsiveness was found in 8 sibships, and clinically there were two distinct kinds of response.

For patients born in the decade 1960–69 the ascertainment rate for the total population was 1:58 000. The true incidence must be much higher. Our series indicates that homocystinuria occurs more frequently than has heretofore been thought, and that mild cases are common. It is likely that cases are often missed in current newborn screening programmes.

Homocystinuria due to cystathionine synthetase deficiency was first reported in 1962 by Carson and Neill, and the basic defect was explained in 1964 by Mudd and colleagues. Well over 100 cases have been reported and the clinical syndrome of dislocation of the ocular lenses, marfanoid habitus, osteoporosis, arterial and venous thromboses, and mental retardation in moderately to severely affected cases is well known. McKusick (1972) described a large series of 83 cases in 45 kindreds, largely ascertained through screening of patients with nontraumatic dislocation of the lenses of marfanoid skeletal features.

This paper describes the mode of presentation of 27 cases seen in New South Wales between 1967 and 1976, and emphasizes the considerable variation in clinical presentation and within families so that some biochemically affected individuals may be asymptomatic until adult life. Our results indicate a greater frequency of homocystinuria than newborn screening has suggested, and a higher incidence of mild cases than was previously supposed.

Patients and methods

Twenty-seven patients (17 males, 10 females) from 15 families were ascertained when referred for investigation of possible homocystinuria (10), when referred for other investigations and a screening test was positive (4), from the newborn screening programme (1), and during family studies of ascertained cases (12).

Diagnosis was made initially by screening for urinary homocystine by paper chromatography and by high voltage electrophoresis, followed by demonstration of increased levels of methionine, presence of homocystine, absent cystathionine, and very low or absent cystine in plasma by ion exchange chromatography. Plasma was deproteinised within 10 minutes of venepuncture, and amino acids quantitated on a Beckman Unichrome Aminoacid Analyzer using standard methods. Plasma amino acid studies also were carried out on all sibs and both parents. No enzyme studies were performed. All patients had general medical and ophthalmological examinations and skeletal *x*-rays. IQ assessment was completed for most patients.

When the diagnosis was confirmed, patients were treated with pyridoxine (200–500 mg/day) in divided doses, and serial measurements were made of plasma amino acids and serum and red cell folate concentrations. Folate was estimated by a microbiological method using *Lactobacillus casei*. Patients were judged to be pyridoxine responsive if homocystine disappeared from the plasma, methionine was reduced to normal or near normal levels, and cystine was present at normal concentrations in fasting plasma.

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Results

The age of diagnosis, sex, clinical features, and biochemical response to pyridoxine of the 27 patients and the presenting problem for each index case are given in Table 1.

Eyes. 5 patients were referred for diagnostic testing because of poor eyesight and 1 because of apparent traumatic dislocation of the lenses (see Table 1). 2 others were aphakic following surgery. A further 7 patients who had dislocated lenses when first seen had been investigated for other reasons. The youngest age at which lens dislocation was seen was 18 months, occurring after a fall from a high chair (Case 16). 6 patients, now aged 14–28 years, do not have dislocated lenses. In 4 treatment was started at 8, 11, 14, and 21 years respectively. The remaining 2, Cases 10 and 21, are on no treatment.

Mental retardation. 14 of the 27 patients had overt mental retardation, with IQs of less than 70 (Table 1). Many of the rest, including some of above average intelligence, were considered by their families and teachers to be less clever than their unaffected sibs, even before homocystinuria was diagnosed (Cases 13, 14, 19, 21, 22, 24–27). In three families this was confirmed by school reports. 3 of these patients had poor eyesight during school years, but in the rest vision was unaffected.

Thrombotic episodes. These occurred in 7 patients, 4 severely affected (Cases 4–7) and 3 of the mildly affected (Cases 11, 15, 19). Deaths in the series were probably all related to thrombosis (Table 2).

Table 2 *Deaths in the series*

Case no.	*Age (yr)*	*Cause*
4	2	Sudden
6	5	Cerebral thrombosis
1	7	Cerebral thrombosis
5	9	'Stroke'
8	10	Cerebral thrombosis
15	30	Pulmonary embolism

Skeletal abnormalities. A marfanoid habitus was noted at diagnosis in 6 patients, ages ranging from 6–12 years. Other clinically obvious skeletal abnormalities, mainly sternal deformities or genu valgum, were common, but 6 of the 15 patients aged 8 or over at diagnosis had none.

Pyridoxine responsiveness and folic acid requirements. 13 patients from eight of the 15 families responded to pyridoxine therapy (responsiveness or nonresponsiveness was always consistent in sibships). In one patient (Case 9) folic acid was also required to maintain full biochemical response, and in 4 of the remaining 'responsive' families pyridoxine alone was needed, though plasma and red cell folate concentrations fell to low levels without supplementation.

Table 1 *Clinical features of the patients*

Case no.	*Age (yr)*	*Sex*	*Ectopia lentis*	*Mental retardation*	*Marfanoid habitus*	*B6 response*	*Presenting problem (index cases)*
1	6	M	+	+	+	−	Mental retardation
2	11	M	+	+	+	−	
3	4	M	+	+	−	−	
4	2	F	?	+	−	−	
5	7	F	+	+	+	−	Mental retardation
6	5	F	+	+	−	−	
7	1·8	M	−	+	−	−	
8	5	M	+	+	−	t−	Eyesight
9	8	F	+	+	+	+	Eyesight
*10	8	M	−	+†	−	+	Urinary infection
*11	11	F	−	−	+	+	
*12	8	M	−	−	−	+	
*13	14	M	−	−	−	+	Mild pectus carinatum
*14	17	M	+	−	−	+	
*15	27	F	+	−	−	+	Venous thrombosis
16	1·9	F	+	+	−	−	Traumatic dislocation of lenses
17	0·1	F	−	−	−	t−	Newborn screening
18	2	M	+	+	−	t−	
*19	41	M	+A	−	−	+	Venous thrombosis
20	7	M	+	+	−	−	Eyesight
*21	24	M	−	−	−	−	
22	29	M	+A	−	−	+	Severe osteoporosis
23	3	M	+	+	−	−	Mental retardation
24	12	F	+	−	+	+	Eyesight
*25	14	M	−	−	−	+	
26	7	M	+	−	−	+	Eyesight
27	4·5	F	−	−	−	+	

*Mild cases (see text). †Mental retardation apparently due to birth trauma. A = aphakia—surgical; t = temporary response. Brackets indicate sibships.

There were insufficient data on folic acid requirements in Cases 15, 19, and 22.

Among the families not responsive to pyridoxine, there was a definite but temporary biochemical response with near normalisation of methionine and homocystine levels in plasma, and normal plasma cystine, lasting for 1 to 3 months in two families, and none at all in the remaining five (see Table 1).

Incidence. In the decade 1960–69 there was a total of 820 797 births in New South Wales; 14 cases of homocystinuria have so far been diagnosed, an ascertainment rate of 1:58 000.

Mild cases

Nine cases from six families were considered to be very mildly affected (Table 1) in that either they have few if any of the features commonly associated with homocystinuria, or these have occurred relatively late in life. All but one of the mild cases were in the pyridoxine-responsive group. One of these sibships (Cases 10–12), including a boy and girl of superior intelligence, has been described by McKusick (1972). We report 5 further cases.

Cases 13 and 14. A boy presented at the age of 14 with a mild sternal deformity. A urine test suggested homocystinuria, but further investigations were refused until he was 21 years old. Then he was 187 cm tall, well built, with normal bodily proportions, apart from large hands and feet, and very mild pectus carinatum. Eyesight was normal; no ectopia lentis. He appeared intelligent, completed year 10 at school, and had an excellent work record. His brother, then aged 19, was ascertained by family screening. He was 190 cm tall, heavily built, and recently subluxation of the lenses had been noted. He had been considered slow at school. 3 unaffected brothers were all very tall.

Case 19. An intelligent man of 41 presented with deep venous thrombosis of the calf after myocardial infarction. He was 186 cm tall, ruddy faced, and had had grey hair for years—the only prematurely grey person in his family. He had had thrombosis of the left calf aged 15 years, overt dislocation of the ocular lenses aged 18 years after a severe blow to the head, and a stroke aged 37 with good recovery.

Case 21. A tall (186 cm) man of 24 years with very dark hair was ascertained during family screening. (His brother, Case 20, aged 8, was moderately severely affected clinically.) He was well built, with large hands and wrists and large ankles, but no other bony abnormality; *x*-rays showed slight osteoporosis. No ocular abnormalities. He completed year 10 at school but did less well than other nonaffected members of the family. He was B6 nonresponsive. His parents' plasma amino acid levels were normal.

Case 25. Brother of Case 24, a small brown-haired boy of 14, of stocky build. Height was between 25th and 50th centiles, and the upper-to-lower segment ratio was 0·90, normal for age. Vision and eye examination normal; no skeletal deformities. He did well in year 9 (the appropriate year for age) at high school. Plasma amino acid levels in his parents were normal.

Discussion

In this series of 27 cases, ascertained with one exception by clinical presentation and subsequent family screening, one-third of the patients were very mildly affected by their disease—indeed a boy aged 14 years and a man aged 24 years, both untreated, had no clinical features suggesting homocystinuria. There were some intrafamily differences in severity, but it is reasonably certain that all these patients were indeed homozygotes for the defective gene. In no case did their parents exhibit any biochemical abnormality, and only one case has been reported with raised levels of plasma homocystine and methionine who may have been a heterozygote, but her genetic status remains uncertain (Finkelstein *et al.*, 1964).

There is clearly a group of patients who remain relatively asymptomatic until adult life, and physicians need to be alerted to the possibility of homocystinuria in adult patients presenting with thromboses. In addition, the diagnosis must be considered in otherwise normal girls presenting with tallness for evaluation at the time of puberty. In one of our patients this was the first untoward symptom, although she had in fact been ascertained earlier during family screening (Case 11). Although McKusick (1972) described cases of mild homocystinuria, others have suggested that they are particularly rare (Wappner and Brandt, 1973).

McKusick suggested that ectopia lentis is an almost constant feature of homocystinuria in patients over age 10 years; and only 2 of his 83 patients over 10 had intact eyes, sisters aged 12 and 17 years. Certainly poor eyesight was the most common feature leading to diagnosis in our series, but 6 of our 27 patients now over the age of 10 have no ectopia lentis, and no visual disturbance of any kind (see Results). The oldest of these is now 28, is not responsive to pyridoxine, and receives no treatment. Only one of the rest was treated before the age of 10 years. 7 patients who had dislocated lenses were ascertained when

being investigated for problems not related to eyesight. 4 of these were mentally retarded, and 2 were under 4 years.

Although mental retardation, with an IQ below 70, was present in only half our patients, and was quite mild in several of these, it is probable that almost all patients had suffered some loss of intelligence. It is notable that several patients with minimal or no clinical signs were considered by the family, before diagnosis, to be slower than unaffected family members, and school reports often confirmed this (see Results).

The ascertainment of homocystinuria in New South Wales from this series is 1:58 000 for the decade 1960–69. As only one case was identified by newborn screening, the true incidence is probably much higher. Newborn screening using the Guthrie bacterial inhibition assay has generally shown an apparent incidence of from $<1:500\,000$ to about 1:100 000. Two centres, Manchester, England (using plasma chromatography at 6+ days), and Dublin, Ireland, have found 1:80 000 and 1:56 000 respectively (Thalhammer, 1975). The gene for homocystinuria may indeed be more frequent in the Irish population (both Manchester and N.S.W. have many people of Irish extraction) but it also seems very likely that an appreciable number of cases of homocystinuria are missed in other centres when the test is carried out on the fourth day of life. Levy, for example, found an incidence of 1:179 000 in Massachusetts where there is a large Irish population (Thalhammer, 1975).

The N.S.W. neonatal screening programme includes a urine chromatography test at 6 weeks of age. This has been specially modified to detect homocystinuria (Wilcken *et al.*, 1972), but nevertheless only one case has been detected in 400 000 tests (Case 17) and one case is known to have been missed (Case 27). It is very probable that other missed cases will come to light. 8 of the 9 mild cases in this series were responsive to pyridoxine therapy, and diagnosis of these cases by infant screening tests would be particularly beneficial. Perhaps these cases cannot be detected by a Guthrie bacterial inhibition assay at 4 days of life, and a further test at, say, 4 weeks should be carried out. A second test for phenylketonuria is already being done in many centres.

Response to pyridoxine occurred in eight of the 15 families. Clinically there were two types of pyridoxine responders: those in whom folic acid was also required continuously to maintain biochemical control, and those who remained stable and controlled on pyridoxine alone, even though red cell and serum folic acid concentrations fell to low levels. An example of the first response (Case 9 in this series) has been reported by Wilcken and Turner (1973) and another by Morrow and Barness (1972). In the absence of enzyme studies it is impossible to say whether these differences are related to differences in enzyme activity response noted by Seashore *et al.* (1972), or whether this represents a further variant of 'classical' homocystinuria.

Many patients in this series were originally patients of the late Dr Brian Turner, who was the first in New South Wales to investigate cases of homocystinuria.

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