9. Thompson DP, Moore TC. Acute thoracic distress in childhood due to spontaneous rupture of a large mediastinal teratoma. J Pediatr Surg 1969, 4: 416-423.

10. Berry CL, Keeling J, Hilton C. Teratomata in infancy and childhood: A review of 91 cases. J Pathol 1969, 98: 241-252.

Wilson's Disease: Initial Worsening of Neurologic Syndrome with Penicillamine Therapy

A. Kher
B.A. Bharucha
N.B. Kumta

Wilson's disease was described in 1912(1). It results from expression of a locus on chromosome 13(2). Interpretation of diagnostic tests often pose problems especially in heterozygote detection. D-penicillamine, the gold standard of therapy was introduced by Walshe in 1956(1). This was proved quite dangerous at times as exemplified by this report.

Case Report

A 10-year-old girl presented with neurologic deterioration in the form of unsteady gait, worsening of handwriting and speech over two years. She had no prior history of jaundice or neurological disorder. On nervous system examination, she had dysarthria, slurred speech, inco-ordination, unsteady gait and brisk tendon jerks. There were no involuntary movements, focal deficits or cranial nerve palsies. There was no hepatosplenomegaly. A Kayser Fleischer ring was detected unilaterally and confirmed on slit lamp. Serum copper (Cu), ceruloplasmin, and urine copper values were 50 μg/dl (n 70-160 μg/dl), 0.032 OD (n 0.25-0.49 OD) and 401.85 μg/dl (n 40 u/day) respectively. Liver functions and tests for renal tubular involvement were normal. The patient was put on 250 mg six hourly of D-penicillamine (40 mg/kg/day) with a diet restricted in copper.

The child had an acute neurologic worsening in the form of loss of sensorium, speech and all higher functions and frequent vomiting within 15 days of instituting the above therapy. Biochemical parameters, cerebrospinal fluid examination and CT scan of the brain failed to reveal any abnormality. She slowly recovered with mannitol, dexamethasone and oral glycerol therapy given to treat cerebral edema. D-penicillamine was omitted during this time and restarted after 15 days in a low dose of 125 mg 12 hourly (10 mg/kg/day) with a daily dose of 100 mg pyridoxine. A similar episode occurred again within 12 days of restarting D-penicillamine and the child improved with similar treatment. D-penicillamine was reintroduced in the dose of 25 mg only (1 mg/kg/day). It was gradually increased to 250 mg 12 hourly (20 mg/kg/day). Urine copper was closely monitored and this dose was tolerated well.

Discussion

D-penicillamine acts by promoting

From the Department of Pediatrics, Seth G.S. Medical College and K.E.M. Hospital, Parel, Bombay 400 012.

Received for publication: August 16, 1991; Accepted: February 5, 1992

urinary excretion copper; 250 mg of the drug is given 6 hourly along with 25 mg of pyridoxine per day. The urine copper rises to 1-2 mg/day and then decreases to 0.05 mg, and therefore, has to be monitored weekly initially. The patient should be assessed once a month for the first year of therapy(1).

About 20% cases develop early side effects in the first month of therapy(1). Fever, rash, lymphadenopathy and rarely bone marrow suppression and thrombocytopenia may evolve. Late reactions like dermatopathy, proteinuria, systemic lupus erythematosis, Good Pasteur's syndrome and myasthenia gravis may develop after a year of therapy. The major drawbacks with penicillamine are continued hepatic or neurological deterioration despite biochemical evidence of decoppering during the initial months.

Brewer and Carol(3) have reported neurological worsening in a 19-year-old male within two weeks of chelating treatment. His magnetic resonance imaging of the brain showed appearance of low lesions even after eleven months of therapy. Of the 25 cases (aged 13-60 years) who received D-penicillamine, 13 cases worsened in 2 weeks and 10 cases within 4 weeks. Longhi *et al.*(4) have noticed similar deterioration of symptoms within 5 months of therapy in a 13-year-old boy. It was attributed to excessive mobilization of Cu^{++} from tissue deposits. Walsh also reports rapidly progressive neurological deterioration despite all modes of treatment (Personal communication, 1989). It is difficult to predict which patients will follow this course and the same reaction can occur with other chelating agents.

Trientene in the dose of 400-800 mg three times a day may serve as an alternative drug(1). It mobilises Cu^{++} and increases the urinary excretion of Cu^{++}. It can pose similar problems and is unsafe for prolonged use. Oral zinc sulphate produces a negative Cu^{++} balance of 1 mg/day by blocking the gut uptake and reabsorption of secreted copper in salivary, gastric and intestinal juices(3). It is mainly used for maintenance therapy but 50 mg of the drug given 5 times a day can be used for initial therapy. Neurological deterioration does not occur, but gastro-intestinal intolerance may limit the use of this simple remedy(1).

Ammonium tetrathimolybdate has a genuine decoppering mode of action unlike the detoxifying effect of D-penicillamine which releases free, highly reactive copper(5). Walshe has also suggested its use in the dose of 30 mg 12 hourly (personal communication, 1989). It may now prove to be an ideal agent since it blocks adsorption of Cu^{++} and renders it unavailable for cellular uptake and reduces toxic blood levels by forming complexes(6). Brewer has used 2-3 mg/kg of this drug in 6 cases (1/3 dose with meals and 2/3 between meals). No reaction was observed with over 8 weeks of treatment(7).

The current recommendation is thus to begin 250 mg per day of D-penicillamine and increase it by 250 mg every 4 days till a urine Cu^{++} excretion of 2 mg is reached. A prompt reduction of the dose to 250 mg per day is required in case of neurologic worsening with 1-2 g of the drug(3). These obstacles will be bypassed soon, once a breakthrough with an ideal decoppering agent is achieved.

Acknowledgement

The authors wish to thank Dr. (Mrs.) P.M. Pai, Dean, Seth G.S. Medical College and K.E.M. Hospital for allowing them to publish this article.

REFERENCES

1. Marsden CD. Wilson's Disease. Q J Med 1987, 65: 959-966.
2. Strarosta R, Anne B, Kaven K, *et al.* Clinical assessment of 31 patients with Wilson's disease. Arch Neurol 1987, 44: 365-370.
3. Brewer GJ, Carol A, *et al.* Worsening of neurologic syndrome in patients with Wilson's disease with initial D-penicillamine therapy. Arch Neurol 1987, 44: 490-493.
4. Longhi R, Riva A, Rottoli R, *et al.* Nuclear magnetic resonance–Brain study in a case of Wilson's disease. J Infern Metab Dis 1989, 12 (Suppl 2): 386-388.
5. Manson J, McQuaed Amm, Pheiffer H. Can Wilson's disease patients be decoppered. Lancet 1989, 24: 1455.
6. Pall HS, Williams AC, Blake DR. Deterioration of Wilson's disease following the start of Penicillamine therapy. Arch Neurol 1989, 4: 359-361.
7. Brewer GJ, Robert D. Initial therapy of patients of Wilson's disease with tetrathiomolybdate. Arch Neurol 1991, 48: 42-48.

Inherited Deletion of Chromosome (21p-) in a Child with Congenital Malformation and Psychomotor Retardation

B. Kar
K. Prabhakara
S.K. Murthy

Polymorphic variants of chromosome 21 short arms ($21p^+$, p^-, s^+, s^-, dNOR, secondary constriction, *etc.*) are common and are inherited as simple Mendelian traits. Deletion resulting in loss of genetic material leads to varying degree of malformations and mental retardation. Advances in banding techniques have enabled in detecting minor regions of chromosomes in delineating several deletion syndromes. Abnormalities of chromosome 21 (numerical and structural) are relatively more frequently associated with congenital malformation, mental retardation, fetal loss and infertility. Lejeune *et al.* reported the first case of partial monosomy of chromosome 21 resulting from ring 21(1). Later on deletion of shot arm of a G-group chromosome was reported by many workers(2-8). In this report a case of familial 21p- associated with congenital malformation and psychomotor retardation is described.

Case Report

The index patient, 8-month-old male child was the product of normal full term 3rd pregnancy, born to nonconsanguinous parents through breech delivery. His weight was 5 kg, height 67 cm and head circumference 40 cm. Other two siblings of ages 6 years (III–1) and 4 years (III–2) were female children (*Fig. 1*). The father and mother were 30 and 29 years, respectively at the time of proband's birth. The pregnancy and neonatal history were unremarkable. The child was referred for investigations with history of poor weight gain, severe hypotonia, delayed milestones, receding chin, low set ears, genu valgum (knock knees), bilateral edema, undes-

Reprint requests: Dr. Sabita K. Murthy, Department of Zoology, University School of Sciences, Gujarat University, Ahmedabad 380 009.

Received for publication: September 10 1991; Accepted: February 13, 1992