Short reports

Organic aciduria

Treatable cause of floppy infant syndrome

The floppy infant syndrome has several causes ranging from disorders of the lower motor neurone and muscle, such as infantile spinal muscular atrophy and congenital myopathy, to various endocrine and metabolic disturbances. These have been fully reviewed by Dubowitz (1969). This report describes a floppy infant in whom hypotonia was due to a rare disorder of organic acid metabolism which responded to treatment with pharmacological doses of the vitamin biotin.

Case report

A girl was the first child of healthy Irish parents, who are second cousins. There have been 3 unexplained childhood deaths in the family. She was born by normal delivery at term after a normal pregnancy, birthweight 3300 g, and was in good condition at birth. There was some initial feeding difficulty and vomiting but by the end of the first week she was feeding well. Development was thought to be normal; by 5 months she was able to sit supported with cushions, roll from supine to prone, make crawling movements, support some weight on her legs and reach out for toys.

When she was 5 months old she developed an upper respiratory tract infection and was treated with ampicillin. She seemed to recover from this infection but the parents noticed that her respirations had become more rapid than before. The mother recalls that at about this time she changed the milk from Cow and Gate 'V' formula to Babymilk 2, representing an increase in protein intake from 1·8 to 3·3 g/100 ml reconstituted milk.

From the age of 8 months there was a gradual onset of floppiness and weakness. She stopped sitting and lost her good head control. She no longer reached out for toys and eventually most of her spontaneous movements ceased so that she lay in her cot, limp and uninterested. She continued to have deep and rapid respirations with inspiratory stridor. Numerous investigations directed mainly toward the respiratory system, including laryngoscopy, bronchoscopy, and tests for avian precipitins, failed to show the cause of her tachypnoea and hypotonia. She was given a trial of steroids for one month on suspicion that she had some form of pulmonary fibrosis, but this had no effect. She was referred to the Hammersmith Hospital at the age of 10 months for further assessment of what was still thought to be primarily a respiratory problem.

Examination showed a profoundly hypotonic, cushion-oid female child. She was relatively uninterested in her surroundings, seeming to have difficulty focusing on objects and exhibiting rolling eye movements. She lay in a frog-like posture, the hips being easily abducted to 90° with no resistance. She had a very weak grasp of objects placed in her hand. On arm traction there was gross head lag (Fig. 1a) and on ventral suspen-
There were generalized weakness with little spontaneous activity and few antigravity movements. Cranial nerves and fundi were normal. Reflexes were easily elicited and there was a poorly sustained ankle clonus. Plantar responses were extensor. Respiratory rate was 48/min, the respirations deep and acidotic in character with inspiratory stridor, but there were no adventitious sounds on auscultation of the chest.

**Investigations.** Arterial blood gases in air showed pH 7·43, P\textsubscript{a}O\textsubscript{2} 97 mmHg, P\textsubscript{a}CO\textsubscript{2} 25 mmHg, standard bicarbonate 19 mmol/l (19 mEq/l), bases excess −6 mmol/l (−6 mEq/l). These results were not consistent with lung pathology and suggested some underlying metabolic abnormality. Motor nerve conduction velocity in the ulnar and posterior tibial nerves was normal for her age (55 and 39 m/s respectively). Electromyography of deltoid muscle was normal.

Plasma amino acids showed slightly raised branched chain amino acids and alanine. Blood lactate was raised at 4·4 mmol/l (39 mg/100 ml) (normal up to 2·0 mmol/l; 18 mg/100 ml), as was blood pyruvate 240 μmol/l (2·1 mg/100 ml) (normal up to 200 μmol/l; 1·4 mg/100 ml). Urine gas chromatography for organic acids (Dr. D. Gompertz) showed grossly abnormal amounts of β-methylcrotonic and β-hydroxyisovaleric acids. This was confirmed by mass spectrometry. Trace amounts of β-methylcrotonylglycine were also detected.

The following investigations were normal: chest x-ray, blood count, blood urea, sodium, potassium, creatinine, creatine phosphokinase, serum glutamic oxaloacetic transaminase, total protein, albumin, calcium, phosphate, alkaline phosphatase, bilirubin, urine amino acid chromatography, urinary ketones, thyroid function tests, bone age, immunoglobulins.

**Diagnosis.** The excess of the two abnormal metabolites, β-methylcrotonic acid and β-hydroxyisovaleric acid, in the urine indicates a block in the degradative metabolic pathway of the branched chain amino acid leucine due to impaired activity of the enzyme β-methylcrotonyl coenzyme A carboxylase (Fig. 2).

**Treatment and progress**

As a result of previous experience with this condition (Gompertz, 1974), the child was treated with massive doses of d-biotin, the coenzyme of β-methylcrotonyl coenzyme A carboxylase, in a dose of 10 mg daily (i.e. approximately 300 times the average adult daily requirement). Within 12 hours the hyperventilation was reduced, the stridor had disappeared, and the child seemed more alert and responsive. Within 6 days there was marked improvement in the hypotonia (Fig. 1b). The metabolites disappeared from the urine and the gas chromatogram returned to normal. She was discharged home after 14 days. At a recent follow-up at the age of 11½ months she was smiling,

![Fig. 1.—(a) Child on presentation showing gross head lag when pulled up by the arms. (b) 6 days after starting therapy with biotin, showing improvement in head lag.](image-url)

**Fig. 2.—Synthesis of β-hydroxyisovaleric acid and β-methylcrotonic acid associated with an impaired β-methylcrotonyl coenzyme A carboxylase.**
alert, and sat unsupported. She plays with toys and has two clearly recognizable words. Muscle tone is normal and there is no weakness. She continues on biotin 5 mg twice daily.

Discussion

Hypotonia was a striking clinical feature in our patient and has been noted before in one of the three published reports of this condition. Eldjarn et al. (1970) described a 41-month-old infant whose muscular hypotonia and retarded motor development was severe enough to consider the diagnosis of Werdnig-Hoffmann disease. The other two reports (Gompertz et al., 1971, 1973) do not mention hypotonia but both patients had metabolic acidosis associated with a variable neurological picture ranging from abnormal behaviour and irritability to coma and delayed motor development. However, the patient described by Gompertz in 1971 is now thought to have had a defect in \( \beta \)-methylcrotonyl CoA carboxylase activity secondary to a more generalized defect in biotin metabolism (Gompertz, 1974).

The mechanism of the hypotonia in our child is not known. Organic acids have been shown to be encephalopathic in rabbits when infused intravenously, causing sleep and excess of slow wave activity on the electroencephalogram (White and Samson, 1956). A similar peripheral effect at the level of the spinal cord, neuromuscular junction, or within the muscle itself cannot be excluded. Hypotonia is also a feature of some other inborn errors of organic acid metabolism—methylmalonic aciduria (Gompertz, 1974) and propionic acidemia (Hommès et al., 1968, Gompertz et al., 1970). It is interesting that glycine, an inhibitory neurotransmitter, is often raised in the plasma of patients with propionic and methylmalonic acidemia and it is tempting to speculate that glycine may be responsible for the hypotonia in these conditions. This, however, seems unlikely in our patient since the plasma glycine was normal.

Although symptoms became apparent in our patient at the time of an intercurrent infection and coincided with the dietary protein increase, we have not imposed any protein restriction because of the excellent clinical and biochemical response to biotin therapy.

Metabolic disease, especially the organic acidemias, must be considered in the differential diagnosis of the floppy infant syndrome. The responsiveness of several of the organic acidemias to protein restriction, and/or massive doses of the appropriate vitamin, shows that though these inborn errors probably account for only a very small proportion of the floppy infants, these children are treatable if the diagnosis is made.

Summary

A floppy infant is described who has an inborn error of organic acid metabolism due to defective activity of the enzyme \( \beta \)-methylcrotonyl CoA carboxylase. She presented with hyperventilation, hypotonia, and regression of motor and intellectual development. She responded to treatment with biotin.

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References


B. R. Keeton and A. Moosa

Department of Paediatrics and Neonatal Medicine, Hammersmith Hospital, London.

*Correspondence to Dr. B. R. Keeton, Brompton Hospital, Fulham Road, London SW3 6HP.*

Balanced translocation, impaired sperm motility, and offspring anomaly

This communication reports an example of a father with a balanced translocation who produced an abnormal child with a similar translocation after treatment for a low sperm motility.

Case report

A 27-year-old Pakistani woman had 5 spontaneous, unexplained, first trimester abortions. Her husband showed no physical abnormality, but had a sperm motility of only 5% in a total count of 110 million. During