

Baby of a phenylketonuric mother

Inferences drawn from a single case

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Farquhar, J. W. (1974). *Archives of Disease in Childhood*, 49, 205. **Baby of a phenylketonuric mother: inferences drawn from a single case.** Reports on pregnancy in phenylketonuric women are rare, but fetal brain damage has been well documented and attributed to the mother's biochemical disturbance. Reports on fetal health after the treatment of phenylketonuria (PKU) in pregnancy are even rarer. Since the treatment of PKU girls is often stopped or relaxed at various prepubertal ages, pregnancy may occur soon in apparently normal girls who have high phenylalanine levels and PKU. In view of the scarcity of information, implications are cautiously suggested from the experience gained of one case. More information is needed urgently, not about the effects of PKU alone, but also of hyperphenylalaninaemia. The present case suggests that it is possible for a fetus to escape malformation, brain damage, and growth failure if maternal dietary treatment is good from about the 20th week of gestation. It would be unwise, however, to accept this finding as holding true for all cases.

Very few successful pregnancies in treated phenylketonuric women have been recorded (Allan and Brown, 1968; Farquhar, Miller, and Lindsay, 1971) and little has been said about the later development of the offspring. The subject is obviously important since, with increasing neonatal screening for PKU and with better methodology, growing numbers of intellectually normal cases are reaching or nearing adolescence and marriage. Since some and perhaps all of the girls may have returned to normal diet and PKU before puberty, the fate of their children commands attention now.

Case report

The mother was 24 years old and about 20 weeks pregnant when her condition was recognized. She had been a difficult child and her classical PKU was recognized on routine urine testing at a school clinic for retarded children when she was 12. Her age, behaviour, and social circumstances were such that she received no dietary treatment. Her IQ of 55, however, enabled her to undertake simple paid employment at times, and it was suggested by relatives that she had been sexually promiscuous since adolescence without contraception or previous pregnancy. She was sterilized after delivery.

Since the age of 12 her serum phenylalanine had ranged from 20 to 30 mg/100 ml and her urine had always

been strongly positive for phenylketones. On strict dietary control in hospital from mid-pregnancy, weekly serum phenylalanine levels ranged from 3 to 8 mg/100 ml, but rose to 12 mg/100 ml in labour. The amniotic fluid level at delivery was 2.33 mg/100 ml (controls 0.11–0.38 mg/100 ml). Her baby boy weighed 2380 g at a reputed 40 weeks and seemed relatively mature, but there was inevitably some doubt about the mother's dates. At least it is certain that she had been untreated and phenylketonuric for at least half of the baby's prenatal life. He was shown not to have either phenylketonuria or hyperphenylalaninaemia (Farquhar *et al.*, 1971) and made encouraging normal progress during the first year of postnatal life without any treatment. This was remarkable in that the father was believed to be a mentally retarded patient at the same hospital, and that the parents absconded with the baby after a few weeks. He was later found neglected and starved. At the age of 2 years 2 months, in the care of a relative, he was a happy normal baby (Fig. 1) whose developmental progress was judged to be average by a very experienced psychologist. His length was then 83.4 cm, skull circumference 49.2 cm, weight 12.25 kg, bone age 2 years, and he had presented no behavioural difficulty or suffered any significant illness. The mother herself was better behaved during treatment and relapsed soon afterwards.

Discussion

Absence of placental protection. Phenylalanine levels are known to be higher in fetal arterial



FIG. 1.—At 2 years 2 months this child of a phenylketonuric mother is developmentally normal.

plasma than in maternal venous plasma between 15 and 20 weeks' gestation in normal pregnancy, and in both normal and phenylketonuric pregnancy at term the fetal phenylalanine varies with the maternal, i.e. the human placenta does not 'protect' the fetus from hyperphenylalaninaemia (Cockburn, Robins and Forfar, 1970; Cockburn *et al.*, 1972; Emery, Farquhar, and Timson, 1972). It can therefore be assumed that this woman's fetus was exposed to high phenylalanine levels until about 20 weeks' gestation.

Intellectual preservation of fetus. Since it seems inconceivable that the genetically determined intelligence of this baby could have exceeded average, his healthy normal development suggests that during the first half of pregnancy the fetal brain is relatively unharmed by hyperphenylalaninaemia or phenylketonuria.

Good dietary control of the mother's serum phenylalanine level during the second half of pregnancy seems to have been enough to protect the brain during a period of greater vulnerability.

Physical preservation of fetus. Fetal development progressed normally without threatened miscarriage and without malformation. Follow-up has shown none of the postnatal growth retardation described in such cases by Frankenburg *et al.* (1968). The baby has had no convulsions and no other minor or major illness.

Future relevance.

Treated PKU. Girls who have been adequately treated and are indistinguishable from normal must now be reaching sexual maturity, and possibly marriage, in increasing numbers. They may have had no dietary restriction in recent years.

The introduction or reintroduction of diet to a pregnant phenylketonuric patient in the first trimester is very nauseating and another case of the author's persistently vomited and soon afterward miscarried. It is therefore heartening to find a case in which the imposition of diet was delayed until mid-pregnancy without obvious harm to the baby. Should this prove to be the experience of others, it may make unnecessary the reintroduction of diet to previously treated patients before a planned conception.

Unrecognized PKU. Illustrative cases. Fig. 2 and 3 provide examples of unsuspected PKU in the community. Some such as these, along with an unknown number of hyperphenylalaninaemics without phenylketonuria, may give birth to brain-damaged infants unless treated. The 5-year-old girl on the right in Fig. 2 has classical PKU, has been treated from the first month of life, and has an IQ of 116. Her sister is unaffected, but the 7-year-old boy in the centre has classical PKU with phenylketones in his urine at all times and shows

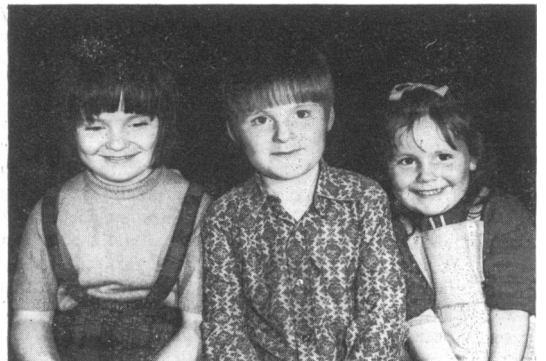


FIG. 2.—Sibs who, from left to right, are nonphenylketonuric, phenylketonuric, and successfully-treated phenylketonuric.

TABLE

Results of phenylalanine loading tests on serum phenylalanine and tyrosine levels in untreated phenylketonuric children with well-preserved intelligence who had been regarded previously as normal

Patient	Amino acid (mg/100 ml)	Time of specimen (hr)				
		Fasting	1	2	3	4
Male (Fig. 2)	Phenylalanine	20·4	39·3	37·8	36·7	33·7
	Tyrosine	1·8	0·6	1·7	1·5	<0·5
Female (Fig. 3)	Phenylalanine	17·7	31·7	34·7	33·0	32·4
	Tyrosine	2·0	2·2	2·4	2·6	2·5



FIG. 3.—Sibs of whom the girl has phenylketonuria and the boy is being successfully treated for phenylketonuria.

a sustained rise in serum phenylalanine after an oral dose as well as failure to convert to tyrosine (Table). He has had no treatment at any time and has an IQ of 102. He might equally well have been an unrecognized female.

The 3-year-old boy in Fig. 3 has classical PKU, has been treated from the first month of life, and has an IQ of about 89. His 12-year-old sister has classical PKU with phenylketones in the urine at all times and shows a sustained rise in serum phenylalanine after an oral dose as well as failure to convert to tyrosine (Table). She tries hard at school, is about average in her peer group, and has an IQ of 93, though she has never been treated. In a few years she may be pregnant. Might her child suffer prenatal brain damage were she to be untreated?

Screening clinically normal pregnant women. Doubt still surrounds the importance of

hyperphenylalaninaemia (levels up to 20 mg/100 ml in the newborn period). It is short-lived and apparently harmless in many babies but it may persist in others, while in yet others it may appear late or be intermittent. Unaccompanied by phenylketones in the urine it escapes detection when urine alone is tested and could be missed by the Guthrie test depending on its timing. How often does it persist into adult life and how harmful might it be to the developing fetus? How many asymptomatic PKU patients, such as those described, were unrecognized until neonatal screening became routine, and will marry and bear children? It is claimed (Hansen, 1970) that where the hyperphenylalaninaemic mother is intellectually normal or near normal, the fetus is less likely to be adversely affected.

Pregnant women attending the antenatal clinic of the Simpson Memorial Maternity Pavilion in Edinburgh during the past 3 years have been screened routinely by the blood Guthrie test (about 5000 deliveries per annum) without detecting a single abnormal result. This is part of a much wider national study being conducted by Dr. John Stevenson in Glasgow, the results of which should provide information as to the justification of such a programme.

Thanks are due to Dr. John Stevenson and his staff who maintain the Guthrie test service for Scotland at Stobhill Hospital, Glasgow; and to Mrs. Sheena Maxwell, principal psychologist, Royal Hospital for Sick Children, Edinburgh.

REFERENCES

- Allan, J. D., and Brown, J. K. (1968). Maternal phenylketonuria and foetal brain damage—an attempt at prevention by dietary control. In *Some Recent Advances in Inborn Errors of Metabolism*, p. 14. Ed. by K. S. Holt and V. P. Coffey. Livingstone, Edinburgh.
- Cockburn, F., Farquhar, J. W., Forfar, J. O., Giles, M., and Robins, S. P. (1972). Maternal hyperphenylalaninaemia in the normal and phenylketonuric mother and its influence on maternal plasma and fetal fluid amino acid concentrations. *Journal of Obstetrics and Gynaecology of the British Commonwealth*, **79**, 689.

- Cockburn, F., Robins, S. P., and Forfar, J. O. (1970). Free amino-acid concentrations in fetal fluids. *British Medical Journal*, **3**, 747.
- Emery, A. E. H., Farquhar, J. W., and Timson, J. (1972). Amniotic fluid amino acids in maternal phenylketonuria. *Clinica Chimica Acta*, **37**, 544.
- Farquhar, J. W., Miller, M. C., and Lindsay, G. (1971). Maternal phenylketonuria. *British Medical Journal*, **1**, 46.
- Frankenburg, W. K., Duncan, B. R., Coffelt, R. W., Koch, R., Coldwell, J. G., and Son, C. D. (1968). Maternal phenylketonuria: implications for growth and development. *Journal of Pediatrics*, **73**, 560.
- Hansen, H. (1970). Epidemiological considerations on maternal hyperphenylalaninaemia. *American Journal of Mental Deficiency*, **75**, 22.

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