

# Atypical Phenylketonuria

## An Approach to Diagnosis and Management

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**Yu, J. S., Stuckey, S. J., and O'Halloran, M. T. (1970.)** *Archives of Disease in Childhood*, 45, 561. **Atypical phenylketonuria: an approach to diagnosis and management.** Nine children with atypical phenylketonuria are described from a Phenylketonuric Clinic of 56 children. The diagnostic criteria are (i) raised serum phenylalanine level, 4–20 mg./100 ml.; (ii) phenylalanine intolerance indistinguishable from classical phenylketonuria on loading; (iii) abnormal urinary metabolites after loading. They differ from classical phenylketonuria in their greater tolerance to dietary phenylalanine and better prognosis for future intelligence.

The arguments for dietary restrictions in these infants are discussed and their dietary management outlined. Their greater tolerance to phenylalanine results in an increased danger of phenylalanine deficiency. This requires closer supervision in the first months of treatment. It is speculated that dietary restrictions will be eased by pre-school age, but that females with atypical phenylketonuria will again require dietary restrictions when pregnant.

Routine screening of infants for phenylketonuria has revealed a group of infants with persistently but mildly raised serum phenylalanine levels. This condition is called hyperphenylalaninaemia in the United States (Hsia, 1967), while in the United Kingdom it is generally known as atypical phenylketonuria (Woolf *et al.* 1961). In 1967, Justice, O'Flynn, and Hsia reported that infants with atypical phenylketonuria had only a partial lack of the liver enzyme, phenylalanine hydroxylase, as compared to a total deficiency in classical phenylketonuria (Jervis, 1953; Mitoma, Auld, and Udenfriend, 1957; Wallace, Moldave, and Meister, 1957; Kaufman, 1958). Such a direct approach to diagnosis is not possible in routine clinical medicine, and other criteria must be determined for the diagnosis.

The pathogenesis of mental retardation in classical phenylketonuria is not known. Phenylketonurics with normal intelligence have been described, but they are few in number (Knox, 1966). These facts and the recent questioning of dietary restrictions in classical phenylketonuria (Birch and Tizard, 1967) make a decision on treatment

difficult in atypical phenylketonuria where the fasting serum phenylalanine level is generally below the safe limits of 20 mg./100 ml. In this paper our experience in the diagnosis and treatment of atypical phenylketonuria is described.

### Material and Methods

From April 1964, 56 infants were seen with a positive screening test for phenylketonuria. In New South Wales, both Guthrie testing and urine chromatography are used in the screening programme. In 6 infants the abnormality was no longer present at the time of retesting, while 42 had classical phenylketonuria and 8 showed an atypical phenylketonuric pattern. Subsequent family studies revealed 5 other phenylketonuric children, all of whom were retarded, and one other atypical phenylketonuric boy. The present report concerns the investigations and management of these 9 atypical phenylketonuric children.

All the infants were examined by one of us (J.S.Y.). Oral phenylalanine loading tests were performed on the index case, on all sibs, and on both parents. 100 mg. l-phenylalanine/kg. body weight was given in aqueous solution after an overnight fast, and urine and blood were collected at 0, 1, 2, and 4 hours.

Phenylalanine was estimated by the fluorometric method of McCaman and Robins (1962) and tyrosine by the method of Udenfriend and Cooper (1952).

TABLE I  
*Clinical Details of Atypical Phenylketonuric Children*

Case No.	Sex	Age at Diagnosis (wk.)	Ascertainment	Initial Serum Phenylalanine (mg./100 ml.)	Treatment with Diet	Comments
1	M	3	Guthrie test	3·8*	No	Mother has PKU; microcephalic
2	M	6 yr.	Sib of Case 1	6·3	No	Microcephalic and retarded
3	M	34	Urine test	3·5*	No	Normal development
4	M	6	Guthrie test	7·6	Yes	Normal development
5	M	4	Guthrie test	15·0	Yes	Normal development
6	F	7	Guthrie test	5·8	Yes	Normal development
7	M	8	Guthrie test	8·8	Yes	Normal development
8	M	20	Urine test	20·0	Yes	Normal development
9	M	3	Guthrie test	9·1	Yes	Normal development

\*2 further estimations on both these infants were greater than 6 mg./100 ml.

Urinary phenolic acids were estimated qualitatively by one-way paper chromatography.

Atypical phenylketonuria was diagnosed if the serum phenylalanine level was raised (4–20 mg./100 ml.), but not as high as one would expect in classical phenylketonuria, if loading showed phenylalanine intolerance with a poor tyrosine conversion response, and when phenylpyruvic and orthohydroxyphenylacetic acids were present in the urine after loading but absent on a normal diet.

Heterozygosity was diagnosed when the one-hour phenylalanine: tyrosine ratio was greater than 5·0 (Hsia, 1958) and the initial fasting serum phenylalanine was normal.

#### Dietary Management

The indications for dietary restrictions of phenylalanine in infants with atypical phenylketonuria were: (i) a fasting serum phenylalanine level of 15 mg./100 ml. or higher; or (ii) phenylalanine intolerance as shown by serum levels of 15 mg./100 ml. persisting at 4 hours after an oral load of 100 mg. l-phenylalanine/kg. body weight.

All infants diagnosed in the first 6 months of life were treated with a low phenylalanine milk 'Lofenalac' (Mead Johnson). This milk is fortified with fat, carbohydrate, and vitamins, so presenting a balanced and complete feeding. Its milk-like appearance and consistency help family acceptance of the change in diet. 'Lofenalac', however, contains 60–100 mg. phenylalanine/100 g. dry powdered milk, and if the older infant and child is to receive most of his growth and maintenance protein from 'Lofenalac', the quantity of phenylalanine in the milk will reduce the daily phenylalanine allowance remaining to be taken in other foods. From 6–9 months of age infants were slowly weaned on to another milk hydrolysate, 'Cymogran' (Allan and Hanbury), or a beef serum hydrolysate 'Albumaid XP' (Scientific Hospital Supplies), which contains negligible amounts of phenylalanine. The last two feedings are not balanced and so present some additional problems when used in the first months of life. All infants received a full vitamin supplement as detailed in the Medical Research Council Report (1963).

The aim of treatment is to keep the fasting serum phenylalanine level between 5–7·5 mg./100 ml. and, to achieve this, the phenylalanine intake is titrated against regular serum estimations. Infants were initially seen weekly, then monthly.

#### Results of Investigations

Clinical details of the 9 children are given in Table I. Six infants were diagnosed by the Guthrie technique, 2 by urine chromatography, and 1 was the sib of a positive Guthrie test baby. Urine testing is usually performed at about 4–6 weeks at Well Baby Centres. 2 infants (Cases 3 and 8) failed to attend the centres until later in life, which explains the delay in diagnosis. These 2 infants were born in maternity hospitals where Guthrie testing was not available.

Two infants (Cases 1 and 3) had low initial serum phenylalanine levels of 3·8 and 3·5 mg./100 ml., respectively, when the oral loading test was performed, but both infants subsequently had fasting levels greater than 6 mg./100 ml. on more than one occasion.

Tolerance tests on the infants are listed in Table II. Tolerance tests were also performed on the sibs and the parents, and, on the basis of these tests, the family trees in Fig. 1 were constructed.

Case 8 was the only infant with phenylpyruvic acid in his urine on a normal diet. Phenylpyruvic acid and orthohydroxyphenylacetic acid appeared in the urines of all the other children 2–4 hours after phenylalanine loading. There was a total of 20 children in the families studied, 9 were atypical phenylketonurics, 5 were heterozygotes, and 5 were normal<sup>1</sup>. 15 of the parents were heterozygotes, and 1 was homozygous for the phenylketonuric gene: this homozygous mother has been reported elsewhere (Yu and O'Halloran, 1970). Only 2 of the 20

TABLE II  
Phenylalanine Loading Test

Case No.	Age at Testing (wk.)		Serum Levels (mg./100 ml.)			
			0 hr.	1 hr.	2 hr.	4 hr.
1	3	Phenylalanine	3.8	18.6	21.0	22.6
		Tyrosine	1.5	1.3	1.2	1.1
2	6 yr.	Phenylalanine	6.3	22.1	18.9	18.2
		Tyrosine	1.2	1.1	1.1	1.1
3	34	Phenylalanine	3.5	13.8	14.6	10.2
		Tyrosine	1.0	1.0	0.8	0.7
4	3	Phenylalanine	7.6	19.5	19.2	16.2
		Tyrosine	3.5	2.9	2.2	1.6
5	4	Phenylalanine	15.0	29.2	35.0	38.4
		Tyrosine	1.9	1.6	1.3	1.1
6	6	Phenylalanine	5.8	28.1	26.1	28.8
		Tyrosine	1.2	1.1	1.1	1.1
7	6	Phenylalanine	8.8	25.0	20.1	19.0
		Tyrosine	1.5	1.3	1.2	1.0
	40	Phenylalanine	7.1	21.2	21.9	20.0
		Tyrosine	2.3	1.8	1.5	1.2
8	16	Phenylalanine	20.0	32.8	30.4	29.8
		Tyrosine	3.6	2.4	1.7	1.6
9	3	Phenylalanine	9.1	22.2	23.2	23.0
		Tyrosine	1.4	1.3	1.0	0.9

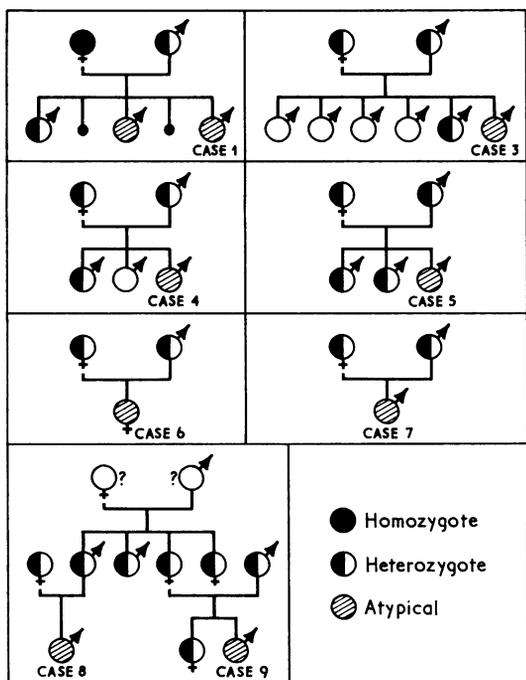


FIG. 1.—Family pedigrees.

children were female. One of these had atypical phenylketonuria.

**Dietary experience.** 6 of the 9 children were placed on restricted diets; the remaining 3 infants were not treated. Case 3 did not fulfil the indica-

tions for treatment, while the 2 sibs, Cases 1 and 2, were both microcephalic. As their mother had classical phenylketonuria and was intellectually dull, it was felt that the benefits of treatment in these 2 boys did not justify the immense problems that the diet would entail.

It seemed likely that because of the incomplete nature of the enzyme block, children with atypical phenylketonuria should be more tolerant of phenylalanine than children with the classical disease. This view has been confirmed by the larger amounts of phenylalanine tolerated by children with atypical phenylketonuria compared to those with classical phenylketonuria (Fig. 2). The

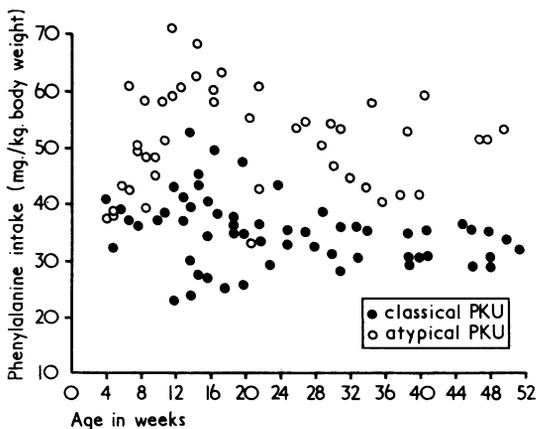


FIG. 2.—Dietary phenylalanine intake in atypical and classical phenylketonuria.

atypical children will tolerate more than 45 mg. phenylalanine per kg. body weight, while classical phenylketonuric children rarely tolerate this amount. When phenylalanine intake is plotted against age, then the trends in any one child show a maximum phenylalanine tolerance in the first 6 months of life. This trend correlates well with growth velocities. During these first months, frequent adjustments to phenylalanine intake were required to maintain the serum level above 3 mg./100 ml.

The oldest of the treated infants is 15 months, and so it is too early to be sure of developmental progress. All of the children except the microcephalic sibs, Cases 1 and 2, appear normal to clinical and EEG examination.

### Discussion

Routine screening of well babies has established that many varieties or grades of phenylketonuria exist (Hsia, 1967). All degrees of hyperphenylalaninaemia have been described. This varied chemistry is matched by an equally wide scatter in the mental development of untreated patients, though the prognosis for atypical phenylketonuria is much more optimistic than in other types (Hsia, O'Flynn, and Berman, 1963).

The number of phenylketonurics discovered who have a normal intelligence and a serum phenylalanine level greater than 20 mg./100 ml. is small (Knox, 1966). Clinical experience has shown that the empirical serum phenylalanine level of 20 mg./100 ml. is a useful upper limit of safety in phenylketonuria. The level of 20 mg./100 ml. has been used in this clinic as the arbitrary demarcation between classical and atypical phenylketonuria. There is no common agreement on the level. Hsia *et al.* (1963) use 30 mg./100 ml. as the lower limit for the diagnosis of classical phenylketonuria. However, our experience suggests that after adolescence many classical phenylketonurics with the full clinical picture have serum phenylalanine levels of 25–30 mg./100 ml.

The genetics of atypical phenylketonuria remains obscure. The major problem is our inability to distinguish between heterozygotes for the classical and atypical types. It is not possible at the present to determine whether the atypical form of phenylketonuria results from a third allele at the phenylalanine hydroxylase locus, or whether it results from the effects of one or more modifying genes.

While the numbers are small, there is a striking predominance of males to females (18 to 2) in our families with atypical phenylketonuric children.

The dietary treatment of classical phenylketonuria has been challenged in recent years (Bessman, 1966;

Birch and Tizard, 1967), but the evidence in support of dietary treatment is strong (Brown and Waisman, 1967; McBean and Stephenson, 1968; Dobson *et al.*, 1968). The management of atypical cases is equally controversial. For while high-grade phenylketonurics and atypical cases with normal intelligence undoubtedly exist in the population (Hsia *et al.*, 1963), mentally retarded persons with the atypical form of the disease have been described (Justice *et al.*, 1967; Bickel and Grüter, 1957).

Berry *et al.* (1967) treat children whose serum phenylalanine exceeds 15 mg./100 ml., while Kennedy *et al.* (1967) treat all infants with levels greater than 12 mg./100 ml. Auerbach, Di George, and Carpenter (1967) take a more conservative approach and only treat atypical patients who excrete phenylpyruvic acid in excess of 15 mg./100 ml. or who maintain serum phenylalanine levels around 30 mg./100 ml. Many workers would regard children with these levels as classical phenylketonurics.

Atypical phenylketonuria in this clinic is treated with a low phenylalanine diet if the initial fasting serum phenylalanine level is over 15 mg./100 ml. or, if after an oral load, the 4-hour phenylalanine level is still over 15 mg./100 ml. The loading test, on an average, is equivalent to 2–3 times the phenylalanine load in a half strength cow's milk feeding of 100 ml., and so does not represent an unrealistic stress. There is no evidence that dietary restrictions are necessary in these atypical infants with fasting serum levels less than 20 mg./100 ml., but while on such a diet there will be no marked variation in serum phenylalanine levels through the day and certainly no transient peaks over 20 mg./100 ml., as is seen during loading tests. It is our policy to keep the fasting serum levels of phenylalanine at 5–7.5 mg./100 ml. in the atypical infants. In early infancy, they tolerate 45 mg. phenylalanine/kg. body weight per day and upwards, while the infant with classical phenylketonuria rarely tolerates an intake as high as 45 mg./kg. This greater tolerance to phenylalanine continues throughout infancy, and requires more intense dietary supervision than the classical case to prevent the development of phenylalanine deficiency. The increasing phenylalanine tolerance with age suggests that the dietary restrictions will be self-limiting if we titrate intake against serum levels. It is anticipated that by pre-school age, when the diet will probably be abandoned, the atypical phenylketonuric will be taking unlimited amounts of low phenylalanine foods and will be receiving his protein maintenance in the form of a milk hydrolysate.

The next major problem in the management of

atypical phenylketonuria will be when affected girls reach child-bearing age. The effects of maternal phenylketonuria on the offspring have been recently reviewed (Yu and O'Halloran, 1970). It is very likely that pregnant women with atypical phenylketonuria will also require some dietary restrictions again when they become pregnant.

Early diagnosis and careful dietary management make the outlook for atypical phenylketonuric children excellent. Their greater phenylalanine tolerance and more liberal diet seem unlikely to provoke some of the emotional problems seen in children with classical phenylketonuria, who require much more rigid dietary control.

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