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CLINICAL AND GENETIC STUDIES IN CASES OF PHENYLKETONURIA (PKU) AND A REPORT OF FOLLOW UP AFTER DIETARY THERAPY

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SUMMARY

A report is made of cases of phenylketonuria detected at Bangalore along with experiences in the dietary therapy and management of the cases. The need for early detection and early dietary intervention is indicated.

Garrod (1909) recognised the relationship between hereditary factors, biochemical defects and clinical abnormality. Folling (1934) described mentally retarded patients excreting Phenylpyruvic acid later designated as Phenylketonuria (PKU). Jervis (1939, 1940) noted that the condition is due to autosomal recessive inheritance and reported that large amounts of phenylalanine accumulated in these patients. Jervis (1953) demonstrated that the liver enzyme viz. phenylalanine hydroxylase was absent or deficient in patients with PKU.

Armstrong and Tyler (1955) described an effective method of prevention giving the PKU infants a low phenylalanine diet. PKU is a recessively inherited metabolic disorder in which knowledge regarding the enzymatic defect has helped in devising a dietary therapy. The present study was undertaken to study the long term follow up of cases detected at Bangalore and the problems encountered during the dietary regimen.

Material and Methods

The material consisted of cases of Mental retardation attending the M.R. Clinic at NIMHANS. There were 4000 children available for the study. They were all below the age of 14 years. In all the cases detailed clinical, genetic, psychological and biochemical investigations were carried out. During this study twenty cases of PKU were detected. All the sibs and family members were interviewed. Wherever necessary home visits were made to examine and followup, the cases. In co operative patients the EEG was also done.

Results

Twenty cases of PKU were detected. The detailed genetic family history and follow up of 20 index cases revealed another 15 cases of phenylketonuria in the sibs out of which 4 patients, who gave a similar history, were dead. The remaining 11 PKU cases were examined in detail (Clinical, Psychological and Biochemical). All these 15 cases of PKU detected

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were from 9 families. In 5 other families there were 9 relatives probably suffering from PKU. Only 3 cases were alive and could be examined. Since a detailed examination was not possible they were excluded for the detailed study.

It was noted that there were eleven cases from Bangalore district, three each from Mandya and Kolar districts and three from Tumkur District. It was noted that many of the cases were not able to mix with the other children or able to move about freely. Many of them also had difficulty in toilet control and some of them were often crying with no reason.

The family history of these 20 index cases revealed that there was consanguinity in two or more generations in 19 families and in one family consanguinity was present among the parents only. In 19 out of 20 families consanguinity was present among the grand parents also.

In phenylketonuria, in the present study consanguinity was noted in parents and in grand parents of cases with PKU.

Tables 1 & 2 indicate the age and sex of the index cases and other sibs who were having a similar illness.

Table 1
Age and Sex of the index cases

Age Group (yrs)	Male	Female	Total
0–11/12	0	3	3
12–23/12	3	3	6
2–3	2	1	3
4–6	2	1	3
7–9	2	0	2
10–14	2	1	3
Total	11	9	20

Table 3 indicates the present complaints as reported by the parents. Table 4 gives the distribution of all cases available for the study.

Table 2
Others sibs who were found to be suffering from PKU

Age Group (yrs)	Male	Female	Total
0–11/12	1	–	1
12–23/12	2	2	4
2–3	3	3	6
4–6	4	–	4
7–9	–	–	–
10–11	–	–	–
Total	10	5	15

5 cases were already dead before the index cases were brought and the rest 10 cases were detected by screening in other centres from which PKU had been referred to the M.R. Clinic.

Table 3
Presenting complaints on different age group (7 to 23 months) of index cases (n=10)

Does not recognise the parents	10
No social smile	10
Unable to sit, stand & walk	10
Unable to talk even a word	7
Peculiar continous movement of hands or fingers	6
Shaking of head repeatedly	5
Shaking the body for loud sound	1
Skin problem	1
Grinding the teeth very frequently	1

Table 4
Age and Sex distribution of both index and affected sib available for detailed clinical and biochemical examination*

Age Group (yrs)	Male	Female	Total
0–11/12	1	3	4
12–23/12	5	5	10
2–3	5	4	9
4–6	2	1	3
7–9	2	0	2
10–14	2	1	3

* The mojority of cases (both index and affected) were below the age of 3 years. The IQ level of the 8 cases above 4 years were severely retarded and 4 were profoundly retarded. In the rest of 23 PKU children the IQ was between 3 months to 12 months.

In about 93% of cases the parents on questioning reported that urine of the PKU children had a fishy odour. In about 80% of the cases the circumference of the head was less than normal and in many cases the skull circumference was less by 2 cms.

Discussion

Paine (1957) reported 64% blue eyes and 17% brown eyes. He also reported 60% of them had bland hair and the remainder had light brown or brown eyes. In the present series, all the PKU patients had fair or light coloured skin compared to their healthy sib and parents. Knox (1972) found that 34% of PKU patients had eczema. In the present study only 12.9% of cases had periodic eczema in infancy and childhood but which did not persist till adolesence (Tables 5 & 6).

Table 5
The Presenting Symptoms (N=31)

Inability to walk	24(70.6%)
Cannot walk properly	4(12.9%)
Cannot talk even a few words	28(90.3%)
Can comminicate with a few words	3(9.7%)
No toilet control	24(70.6%)

EEG could be done only in 12 cases. In 8 cases EEG was abnormal with spike and wave complexes-high voltage fast and slow waves occuring more irregularly (Table 7).

Table 6
Clinical features of 31 cases of PKU

Musty odour	.. 29(98.5%)	
Hyperhydrosis	.. 6(19.4%)	
Microcephaly	.. 25(80.6%)	(Includes head 2 cm small than the age)
Brownish hair or light coloured	.. 31(100%)	
compared to healthy sibs	.. 25(80.6%)	
Sparse hair or partial alopecia	.. 16(51.6%)	
Blue eyes or light coloured iris	.. 31(100%)	
Fundus pale or light colour	.. 24(80.6%)	
Skin:		
a) Fair or light coloured skin compared to parents and healthy sib	.. 31(100%)	6 of them after the age of 5 years became darker.
b) Dry or rough skin	.. 3(9.7%)	
c) Eczema	.. 4(12.9%)	
d) Loose or lax skin	.. 4(12.9%)	Rural area, below the age of 3 years
Prominent maxillae	.. 7(22.6%)	
Face ape like loose due to prominence of jaw	.. 2(6.6%)	
Widening of the inter dental space	.. 7(22.6%)	
Delayed dental eruption	.. 29(93.5%)	
Appearing shorter than their age	.. 6(19.4%)	Between the age of 4 and 14 and one is rather taller than his sib.
Flat foot	.. 12(38.7%)	
Interventricular septal defect cardiac, cong. anomalies	.. 4(12.9%)	

Table 7
Clinical features of 31 PKU cases

Neurological Signs		
Seizures:		
a) GM Fits ..	8	25.8%
b) Myoclonic jerks ..	4	12.4%
Squint ..	6	19.4%
Nystagmus ..	4	12.9%
Hypotonia ..	9	41.9%
Hypertonia ..	13	41.9%
Reflexes increased ..	13	41.9%
Stopping walk, short steping gait pithe cold stance ..	4	12.9%
Tremors of outstretched hand ..	5	16.1%

Table 8
Behavour Disorder
The most common symptoms seen in these cases (n=31)

I. **Autistic Behaviour:**		
Peculiar movements of hands or fingers (fiddling of fingers) ..	23	(74.2%)
Shaking the head repeteadly side to side ..	14	(45.1%)
Rocking movements and swinging ..	20	(64.5%)
Shy, Restless, Agitated ..	26	(83.9%)
Odd rocking movements of the body ..	20	(64.5%)
Laughing to himself and withdrawn ..	6	(19.4%)
II. **Hyperactivity** ..	6	(19.4%)
III. **Shouting, continuosly** ..	1	(3.3%)

Most of the studies (Jervis 1954, Paine 1957) reported the frequency of seizures to be 26% which was noted in the present study also.

Knox (1972) reported hypertonia of muscles in 75% of his cases but in the present study it was noted only in about 42% of the cases.

Knox (1972) reported hyperkinesia in 50% of the cases but in the present study it was seen in 19% of the cases. This may be probably due to the fact that many of the PKU children (nearly 70%) were unable to walk. The commonest behaviour noted in the present series was autism (Table 8).

Thirtyone cases of PKU were followed and of these 17 cases died before the age of 6 years. The cause for death being: Two developed quadriplegia and were bedridden (with bed sores). Other 15 cases died of intercurrent infections like pneumonia, diarrohea, etc. Out of 17 cases, 15 cases who died were from different rural areas and who could not get any medical aid.

Out of PKU children below the age of 2 years, only in 5 cases the low phenylalanine diet could be started after six months. Due to non availability and high cost of the diet only in two cases the diet could be continued.

After starting the diet and maintaining the serum phenylalanine level at 5mg/100ml, one of the cases showed improvement in autistic behaviour, and communicated with parents with a smile. Improvement was noted in milestones of development like sitting, standing etc. The two cases who were continuing on diet (aged 3 & 4 years) had shown significant improvement in the milestones of development.

There was evidence of PKU in all these cases as indicated by qualitative and quantative biochemical tests.

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