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Inborn errors of Metabolism (IEM) - A Review of Cases of IEM Reported from India

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Abstract

Genetic disorders with detectable biochemical anomalies which impair normal metabolism are referred to as Inborn Errors of Metabolism (IEM). These includes conditions with defects in the metabolism of amino acids, lipids, carbohydrates, mucopolysaccharidoes, among others. In some of these, early detection and early intervention are found to avert the otherwise ensuing harmful effects. This paper reviews reports published from different centres in India regarding cases with inborn errors of metabolism.

Key words -
Inborn errors of metabolism,
Metabolic defects,
Genetic anomalies

Uptil now, about 2000 human disorders are found to have a genetic etiology and of these at least 200 are known to be regulated by recessive gene defects [1]. Out of these 200, many are due to autosomal defects with detectable biochemical anomalies where early detection and early intervention have a considerable role to play in diagnosis and management [2]. Such conditions where biochemical (metabolic) anomalies arise as a result of genetic defects are referred to as 'Inborn Errors of Metabolism' (IEM). The present paper reviews work done in different centres in India in the detection and management of IEM. These are discussed under different headings based on the nature of biochemical defect predominantly seen and these include: amino acid imbalances; mucopolysaccharidoses; lipidoses; carbohydrate imbalances and a few others.

Amino acid imbalances

Several centres have reported cases with a variety of amino acids imbalances such as phenylketonuria; homocystinuria; histidinemia; maple syrup urine disease; proline disorders; disorders of urea cycle and a few others.

Phenylketonuria (PKU)

Cases of PKU have been reported from six centres in India and they are indicated in Table I.

Table 1 - PKU cases reported from India

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All the cases of PKU reported from India were mentally retarded, had light coloured skin and hair and some of them had history of seizures during early infancy. All of them had elevated levels of phenylalanine in blood and urine. Cases reported from Bangalore showed excretion of orthohydroxy phenyl acetic acid (OHPAA) in urine which is a characteristic feature of classical PKU.

One case reported from Vellore and another reported from Delhi originate from Karnataka state. Thus, the total number of cases reported from this state comes to 72 which represents 74% of the total number of PKU cases reported from India. It is interesting that, out of the four cases of PKU reported from Pakistan, one is a migrant from Karnataka state. Whether the large number of PKU cases reported from Bangalore is due to the screening being carried out in a high risk population (i.e., cases with mental retardation) seen at the hospital or whether there is any possible heterozygote advantage for the PKU gene is not clear. The latter could be elicited only when extensive screening programmes are undertaken and attempts in this direction are being made at the Indian Institute of Science, Bangalore [12].

Homocystinuria (HCU)

HCU is characterized by Marfan-like features with dislocated lenses. Homocystine is elevated in blood and urine of these cases. Table II indicates the number of HCU cases reported from India.

Table II - HCU cases reported from India

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All the cases were mentally retarded and had Marfan-like features. All of them had dislocated lenses, except in three cases reported from Bangalore, which is not considered highly obligaory for confirming the diagnosis if other features (clinical and biochemical) are present. All the HCU cases showed increased levels of homocystine in blood and urine.

Histidinemia

This condition is characterized by mental retardation invariably associated with speech problems. The blood and urine levels of histidine are elevated.

A total of 4 cases of histidinemia have been reported from India, out of which 2 are from Bangalore [3] and one each from Madras [16] and Hyderabad [17]. In the case reported from Madras, besides the other features there was associated craniostenosis [18]. Three cases have been detected during neonatal screening by Appaji Rao et al [12].

Maple syrup urine disease(MSUD)

Cases of MSUD have neurological problems, failure to thrive and have elevated levels of branched chain amino acids in blood and urine

Five cases of MSUD have been reported from India which include 2 from Bangalore [3] and one each from Hyderabad [13], Bombay [19] and Madras [20]. Eleven cases have been reported during neonatal screening by Appaji Rao et al [12].

Proline disorders

Two cases of hydroxyprolinemia and one of hyperprolinemia have been reported from Bangalore [3]. All the 3 were mentally retarded. Cases with Hydroxyprolinemia had increased levels of the amino acid in blood and urine while the cases with hyperprolinemia had abnormally high levels of proline in the body fluids.

Urea cycle disorders

One case each of arginosuccinicaciduria, cystathioninuria and ornithenemia have been reported in mentally retarded subjects from Bangalore [3]. A case of neonatal arginosuccinicaciduria has been reported from Vellore [21].

Some rare aminoacidurias

Two cases of hypervalinemia and one case of threoninemia have been reported by Reddi et al [22] from Hyderabad. A case of hydroxykynureninuria has been reported by Jyothy and Reddy [23] from Hyderabad.

Generalised aminoaciduria associated with indicanuria is noted in cases with Hartnup's disease. These cases also have periodic episodes of cerebellar ataxia and photosensitive dermatitis. Eleven cases of Hartnup's disease have been reported from India which include 6 from Bangalore [3], 3 from Madras [24] and one each from Hyderabad [25] and Trichur [26]. All these cases had characteristic clinical and biochemical features.

Mucopolysaccharidoses (MPSes)

Based on the excretion of different types of mucopolysaccharides (MPS) the cases of MPSes are differentiated taking into account the clinical features as well. The number of different types of MPSes reported from India are indicated in Table III.

Table III - Number of cases of MPSes reported from India

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Cases of Hurler and Hunter have the same type of MPS excreted in the urine, viz., dermantan and heparan sulfate but, however, the differential diagnosis is based on clinical features in that cases of Hunter's have clouding of cornea and X-linked inheritance and differ from Hurler's in that they have no clouding of cornea and there is autosomal recessive inheritance of the defect.

Skeletal anomalies are seen in both Morquio and Maroteaux-Lamy syndromes but the type of MPSes excreted varies in that the former has keratosulfate in the urine while the latter has dermatan and heparan sulfate in the urine (however, the clinical features vary from Hurler's and Hunter's where these two MPS are excreted.) Skeletal anomalies are also seen in Sanfilippo syndrome but here heparan sulfate is excreted in the urine.

Lipidoses

Cases of Niemann-Pick disease, Gaucher's disease and Tay-sach's disease have been reported. Table IV gives the number of cases detected in India.

Cases with Tay-sach's disease had progressive neurological deterioration, cherry red spot in the macula and serum hexasaminidase-A deficiency. Sandhoff's disease is a variant of this condition.

Niemann-Pick disease cases had visceromegaly and hepatosplenomegaly. Cases of Gaucher's disease had massively enlarged spleen.

Table IV - Cases of lipidoses detected in India

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Galactosemia

Cases with a history of feeding problems, failure to thrive, vomiting and hepatosplenomegaly with positive Benedict's test in urine have been subsequently diagnosed as galactosemia by detecting elevated galactose levels in blood and urine.

From India, 22 cases of galactosemia have been reported which include the following:

Two cases each from Agra [4], Aurangabad [42], Bombay [43], [44] and Hyderabad [25].

One case each from Amritsar [45], Bangalore [32], Bombay [47], Delhi [48], Guntur [49], Jammu [50], Lucknow [51], Mysore [52], Pondicherry [53], and Pune [54].

The case of galactosemia reported from Pondicheery is unique in that it is a combination of both classical and Duarte variant of galactosemia [53].

Other inborn errors of metabolism

Some of the rare types of IEM reported from India are reported here:

Cases of alkaptonuria have been reported from Delhi [55], Hyderabad [56], Bangalore [32] and Vellore [57]. All of them were clinically asymptomatic and excretion of homogentisic acid in urine was detected during screening of urine for other purposes.

Clinically asymptomatic cases of tyrosinemia have been reported from Hyderabad [32] and Nagpur [58] and during neonatal screening by Appaji Rao et al [12]. Cases of kinky-hair disease (Menke's disease) have been reported from Bangalore [59], Bombay [60] and Delhi [61]. All cases had characteristic appearance of hair on the scalp.

Cases of cretinism have been reported from Bangalore [59] and from Hyderabad [45].

The first and most extensive survey of cases of Wilson's disease from India have been reported by workers from Bombay [62a], [62b]. Cases have also been reported from Bangalore [59] and Pune [63].

A report has been made of three sibs with xylosuria in a family with six other normal sibs. The cases of xylosuria were clinically asymptomatic [64].

Cases of glycogen storage disease have been reported from Tamil Nadu, Maharastra and Delhi. These include one case of Type I (Von Gierke's) from Tamil Nadu [65] and 4 from Delhi [66]. One case of Type IV has been reported from Delhi [67] and another from Bombay [68].

Forty-one cases of glucose-6-Phosphate dehydrogenase deficiency have been reported from India which includes 34 cases reported from Hyderabad [69] and 7 from Calcutta [70]. All these cases clinically had features of hemolytic anemia.

Cases of Lesch-Nyhan syndrome with features of choreoathetosis and self mutilation with elevated blood uric acid levels have been reported from Hyderabad [45] and Bangalore [59].

Scope for detection of inborn errors of metabolism

Is the detection of IEM purely of academic interest or does it have any practical utility? Considering that in case of PKU, mass screening of the newborn and institution of low phenylalanine therapy in indicated cases is more economical than otherwise, in most of the advanced centres in USA and Europe, mass screening of all newborns in hospitals has been made obligatory by law. Gratifying results have been reported from centres where such screening programmes are being done routinely [71]. Similarly early detection and early intervention in cases of galactosemia has also been found to be extremely rewarding and the infants grow up with no physical or mental abnormalities [71].

Based on these experiences attempts are being made to evolve speedy, reliable and economical tests for the detection of many forms of IEM [72].

However, there are certain other forms of IEM where biochemical anomalies are noted much earlier than the clinical signs and symptoms. These include cases of MPSes and lipidoses. In such cases prenatal detection and advocating medical termination of pregnancy has been found to be of some use in that it saves a lot of anxiety, discomfort and embarrassment for the mother. However, these involve socioethical considerations besides the cost-benefit aspects.

In a country where much of medical care for the population is to be borne by the government, it may be cost-ineffective to plan large scale screening programmes. But yet, in high risk families who have such cases, measures of early detection and early intervention might be utilitarian.

It is to be noted that several of the papers included in this review as well as publications on IEM from other centres in the world have discussed the cost-benefit aspects of screening programmes. As the outreach of medical facilities in our country improves in the manner in which they are proceeding now, a time may not be far off when genetic diseases (of which IEM is a part) would occupy the time and attention of the medical staff much more than at present and thus there would be need to develop facilities for detection of IEM. Hence, awareness of such genetic diseases would have far-reaching influence on future health planning.

Several of the papers reviewed in this article have indicated the presence or absence of consanguinity among the parents in affected families. One of the earliest reports from India on the possible biological significance of consanguinity in genetic diseases was made by Centerwall [73], [74]. Subsequently the role of consanguinity have been highlighted in the publications from Bangalore [75], [76], [77], [78].

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1.Eldjarn L, Jellum E & Stokke O, Inborn errors of metabolism: A Challenge to clinical chemist
Clinical Chemistry Page: 21: 63, 1975
2.Stanbury J B, Wyngaarden J B, Fredericksen D S, Goldstein D S & Brown M S, *The Metabolic Basis of Inherited Diseases. McGraw Hill Book Co., New York*1983
3.Rao B S S, *Some aspects relating to diagnosis and management of biochemical defects in India an*
Page: 23:35, 1990
4.Centerwall W R & Itteyrah T R, Phenylketonuria among mentally retarded in India
Lancet Page: 2: 93, 1966
5.Sinclair S, Familial mental retardation and parental consanguinity
Indian Journal of Medical Research Page: 60: 11 1718-1723, 1972
6.Gaind B N, Phenylketonuria
Indian Paediatrics Page: 49: 631, 1982
7.Joshua G E, Basu D K & Mathai K V, Sphingolipid errors in MR in Indian Children
Indian Journal of Medical Research Page: 63: 1521-1528, 1979
8.Kusuma Kumari C, Sujatha M, Usharani P, Isaac & Reddy P P, *Etiology of mental retardation in Me*
Page: 6-15, 1990
9.Chandra P, Thirupuram S & Raju B V, Phenylketonuria in Madras
Indian Paediatrics Page: 5: 209, 1968
10.Valmikinathan K, Phenylketonuria
Proceedings of Institute of Neurology Page: 65: 427, 1977
11.Ambani L M, Mental retardation: A study of 537 cases
*Paper read at seventh Annual Conference of Indian Society of Human Genetics, Ranchi*1980
12.Rao N A, Devi A R R, Savithri H S, Rao S V & Bittles A H, Neonatal screening for aminoacidopathies in Karnataka, South India
Clinical Genetics Page: 34: 60-63, 1988
13.Narasinga Rao B S, Three cases of homocystinuria

Journal of Association of Physicians of India Page: 27: 38-42, 1979
14.Verma I C, Sud N & Manerikar S, Homocystinuria: Report of two cases in siblings
Indian Paediatrics Page: 11: 753, 1974
15.Desai A D, Homocystinuria: one case with peripheral neuropathy
Neurology (India) Page: 22: 141-146, 1974
16.Valmikinathan K, Histidinemia
Proceedings of Institute of Neurology Page: 5 (27): 67-70, 1975
17.Reddy O S, Kumari K & Reddy P P, screening for aminoacidopathies in India
In: Genetic Research in India (Ed) Verma, I.C. Sagar Printers and Publ. New Delhi Page: 140-149, 1986
18.Srinivas K, Histidinemia with craniostenosis
Proceedings of Institute of Neurology Page: 5: 67-70, 1975
19.Dastur D K, Manghania D K, Joshi M K & Adair S V, Maple syrup urine disease in an Indian boy
Indian Journal of Medical Research Page: 54: 915-922, 1966
20.Valmikinathan K, Maple syrup urine disease
Proceedings of Institute of Neurology Page: 5 (27): 67-70, 1975
21.Kuttan R, Devarajan L V, Jadhav M, Radhakrishnan A N, Neonatal arginosuccinic aciduria
Indian Paediatrics Page: 18: 405-410, 1981
22.Reddy O S, Threoninemia
Journal of Paediatrics Page: 93: 814-816, 1978
23.Jyothy A & Reddy P P, Screening for aminoacid disorders in mental retardation
Indian Paediatrics Page: 21: 381-388, 1984
24.Somasundaram O S & Papakumari M, Hartnup's disease - Report of two siblings
Indian Paediatrics Page: 10:455-458, 1973
25.Srikantiah S G, Venkatachalam P S & Reddy V, Clinical and biochemical features of a case of Hartnup's disease
British Medical Journal Page: 1: 282-284, 1964
26.Nair K P B & Rao B S S, A case of Hartnup;s disease from Trichur
Indian Journal of Paediatrics Page: 35: 375-377, 1971
27.Kagalwala T Y, Bharucha B A, Kumta N B & Naik G R, The mucopolysaccharidoses. A study of 48 cases
Indian Journal of Paediatrics Page: 6: 919-925, 1988
28.Ganguly C, Ganguly P, Sarangi N N & Mukherjee K L, MPSes in Calcutta
Indian Journal of Paediatrics Page: 53: 263-270, 1986
29.Verma I C, MPS disorders in India: a commentary
Indian Journal of Paediatrics Page: 55: 999-1002, 1988
30.Puri R K & Verma I C, Mucopolysaccharidoses: Analysis of 41 cases of Pondicherry
*Proceedings of I Annual Conference of Indian Society of Human Genetics*1978
31.Joshua G E, Mental retardation in children
Indian Paediatrics Page: 11, 47-51, 1974
32.Rao B S S, Padmashree T S, Sudharshan N M & Jayasimha N, Utility of biochemical and genetic investigations in the diagnosis and management of some forms of mental retardation with a report of work carried out at National Institute of Mental Health & Neuro Sciences, Bangalore
Biological Mental Retardation Page: 3: 37-47, 1987
33.Savliwala A S, Gautami Naik, Bharucha B A, Khare R D & Kumta N B, Sandhoff's disease- GM2 gangliosidoses type 2
Indian Paediatrics Page: 20: 134-137, 1983

34.Kumta N B, Irani S F, Bhide A R, Punwani D V & Naik G, Hexosaminidase A deficiency
Medical Genetics in India (Ed) I C Verma, Auroma Enterprises, Pondicherry, Vol. 1 Page: 97-102, 1978
35.Vardkar A M, Mahale S D, Suchak R H, Patel Z M, Dhareshwar S & Ambani L M, GM2 gangliosidoses type 2
Indian Paediatrics Page: 5: 302-304, 1983
36.Bajaj R T & Master J M, Niemann Pick's disease - A case report
Indian Paediatrics Page: 13 (5): 375-378, 1976
37.Jaiswala R B, Khandelwal M K, Solanki B R & Parande A S, Niemann-Pick disease, a case report in an Indian Punjabi child
Indian Paediatrics Page: 4: 418, 1967
38.Ray R N, Chatterjee A K & Chatterjee J B, Niemann-Pick disease. Research communications
Bull. Cal. Sch. Trop. Med Page: 10: 160, 1962
39.Warey P, Tarmer S K, Agarwal S K & Chaturvedi V, Niemann-Pick disease
Indian Paediatrics Page: 20: 613, 1983
40.Parande A S, A report of four cases of Gaucher's disease
Procedings of Annual Conference of Indian Paediatrics Page: 28, 1970
41.Dayal R S, Prasad R & Mathur G P, Galactosemia: A study of two cases
Indian Journal of Paediatrics Page: 28: 429, 1961
42.Shah P M & Mathurkar S D, Galactosemia: A report of two cases
Indian Paediatrics Page: 1: 58, 1964
43.Kumta N B, Irani S F, Salgaonkar S & Naik G, Galactosemia and its variants in Bombay
In: Medical Genetics in India (Ed) I C Verma, Auroma Enterprises, Pondicherry, vol. 1 Page: 83-90, 1978
44.Joshi N C, Desai M P, Shah K N & Babar S S, Galactosemia. Report of two cases
Pediatric Clinics of India Page: 6: 205, 1971
45.Reddy P P & Shoba Rani A, *Genetic Diseases. Institute of Genetics Publ. Hyderabad*1989
46.Manchanda S S & Lal S K, Congenital galactosemia
Indian Journal of Child Health Page: 2: 611, 1956
47.Kulkarni R D, Sadre N L, Shinde N K & Amin R, Galactosemia
Indian Journal of Medical Research Page: 12: 938, 1958
48.Bhakoo O N, Walia B N S & Paulose P I, Galactosemia
Journal of Indian Medical Association Page: 30: 87, 1963
49.Purohit K R & Dwarkabai Y, A case of galactosemia
Indian Paediatrics Page: 4: 454, 1967
50.Anand V R, Galactosemia. A case report
Indian Paediatrics Page: 3: 325, 1979
51.Bajpai S, Galactosemia
Indian Journal of Paediatrics Page: 4: 450, 1971
52.Indira A & Punekar B D, Results of routine screening for phenylketonuria and galactosemia in MR
Indian Paediatrics Page: 5: 205, 1968
53.Chandrashekar S, Venkatesan K, Rajgopal C, Subramanian, Ranganathan P, Rajan R & Ramakrishna S, Galactosemia - A combination of classical and Duarte variant in a family
JAPI Page: 23: 447, 1975
54.Phadke M A, Kate S L, Joshi A S & Hiremath L M, Clinical and genetic study of mentally retarded. Bombay

*Precongress Workshop of combined Asian regional and commonwealth congress on mental deficiency*1981
55.Kulkarni P S, Alcaptonuria. A report of 3 cases from a family
Journal of Post Graduate Medicine Page: 19: 37, 1973
56.Reddy Y R, Acaptonuria in siblings
Journal of Paediatrics Page: 40: 330, 1973
57.Haiya P P, Balaji N K, Sukumar I P & George Cherian, Teratology of fallout and alcaptonuria in successive generations
Indian Paediatrics Page: 17 (1): 83-85, 1980
58.Parande A S, Tyrosinemia
Lancet Page: 2: 1254-1255, 1965
59.Rao B S S, Inborn errors of metabolism - mental retardation
In: Genetic Diseases (Eds) Reddy P P & Shoba Rani A. Institute of Genetics, Publ. Hyderabad Page: 45-47, 1989
60.Merchant R H, Menke's kinky hair syndrome
Indian Paediatrics Page: 18: 347-349, 1981
61.Gupta A, Arora N K, Desai N, Bagga A & Seth V, Menke's disease
Indian Journal of Paediatrics Page: 55: 445-447, 1988
62a.Wadia N H & Dastur D K, Wilson's diseasein four Indian families (clinical, genetic and biochemical aspects)
Neurology (India) Page: 11: 1, 1983
62b.Dastur D K & Manghani D K, *Wilson's disease in Scientific Approaches to Clinical Neurology Vol.* Page: 1033, 1977
63.Bhave S & Pandit A, Hepatic presentation of Wilson's disease
Indian Paediatrics Page: 23: 807, 1986
64.Reddi O S, Reddy S U & Reddy K R, Familial incidence of L-xylosuria
Human Genetics Page: 39: 143, 1977
65.Sundaravalli N, Ranganathan G, Sushila R & Raju V B, Von Gierke's disease - A case report
Indian Paediatrics Page: 12: 359-360, 1974
66.Singh M, Glycogen storage disease - type I
Indian Paediatrics Page: 8: 645, 1983
67.Kalra V, Glycogen storage disease type IV - A familial cirrhosis diagnosed by electron microscopy
Indian Paediatrics Page: 17: 453-455, 1980
68.Joshi R M, Mohire, Bharucha B A, Kumta N B, Desai A P & Desai A D, Pompe's disease
Indian Paediatrics Page: 22: 315-317, 1985
69.Rao P R, Thirty four cases of glucose-6-phosphate dehydrogenase deficiency
Indian Journal of Medical Research Page: 70: 807-813, 1979
70.Mitra S S, Seven cases of glucose-6-phosphate dehydrogenase deficiency
Indian Journal of Medical Research Page: 66: 253-258, 1977
71.Wiley A M, Carter T P, Kelly S & Porter I, *Clinical genetics:problems in diagnosis and counselling. Academic Press, New York*1982
72.Kolodny E H & Cable W J L, Inborn errors of metabolism
Annals of Neurology Page: 11: 221, 1982
73.Centerwall W R & Centerwall S A, Consanguinity and congenital studies in South India
Indian Journal of Medical Research Page: 54: 1160-1167, 1966
74.Centerwall W R, Consanguinity and MR

*Proc. 7th World Congress of IASSMD, New Delhi*1985
75.Rao B S S, Narayanan H S & Reddy G N N, A clinical and biochemical survey of 729 cases of MR
British Journal of Psychiatry Page: 118: 505, 1971
76.Rao B S S & Narayanan H S, Consanguinity & familial MR
Journal of Medicine Genetics Page: 13: 27, 1976
77.Narayanan H S & Rao B S S, Parental consanguinity and MR
*In: Medical Genetics in India Vol. 1 (Ed) Verma I C. Auroma Enterprises, Pondicherry*1978
78.Rao B S S & Padmashree T S, Consanguinity and MR
Malaysian Journal of Report on Health Page: 4: 105, 1986