Outcome of PKU due to DHPR deficiency in a pair of Siblings

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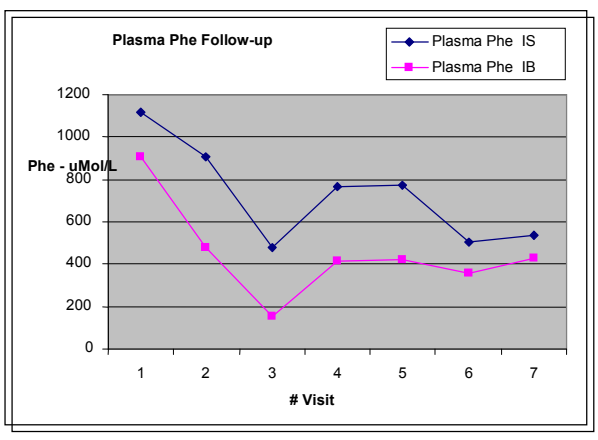
Introduction: - PKU is probably the most well known Inborn Error of Metabolism and all over the world active efforts are being made to screen this entity in newborn period by NBS. Since there is no newborn screening in India even though there are 28 million babies born every year, the real incidence is unknown. It is relatively more common in South India (Approx. 1 in 18,000 – Radharama Devi et.al.). Most of the cases of PKU are due to deficiency of enzyme "Phenylalanine Hydroxylase" but some are due to defects in Biopterin metabolism e.g. "DHPR" (Dihydro-pteridine Reductase) enzyme deficiency [OMIM # 261630]. Clinical features are complicated due to defects in neurotransmitter metabolism as well. These cases are quite rare in India.

Case report: - We report here on DHPR deficient sibs with their clinical and biochemical features. IS (43 Months) & IB (30 Months) are two sibs born to a Muslim family out of 3rd degree consanguineous marriage, hailing from South India. Both were full term normal delivery, normal weight and cried immediately after birth.

	IS Elder sib	IB Younger Sib
Age at presentation	**22 Months**	**10 Months**
Milestones	**Grossly delayed**	**Minor delays**
Rigidity	**++**	**+**
Convulsions	**++**	**+**
Dystonia	**++**	**+**
Hypopigmented hair	**+**	**+**
EEG	**Generalised epileptiform**	**Abnormal**
MRI of Brain	**Normal**	**Normal**
1st Pl. Phenylalanine [NR : 0–150 uMol/L]	**1,118 umol/L**	**909 umol/L**
CSF Phenylalanine NR < 20 umol/L	**379 umol/L**	**131 umol/L**
DHRPR mU/mg HB [NR : 1.8 – 3.8]	**< 0.05**	**< 0.05**
Neopterin – nmol/G Hb [NR : 0.31 – 4.45]	**0.99**	**0.56**
BH4 nmol/G Hb [NR : 0.15 – 2.91]	**1.11**	**0.63**
% BH4 [NR : 14 – 78]	**53.0**	**52.8**

Fig. 1: Plasma Phe Follow-up:-



Both the children started receiving treatment of phenylalanine restricted diet, special PKU diet, dopamine + carbidopa (Syndopa), folinic Acid & anti-convulsant – sodium Valproate, within 15 days of diagnosis. Soon after initiation with Syndopa, dystonia and rigidity disappeared. Slowly the convulsions stopped and both of them showed gain in milestones. They are following up regularly and we are monitoring with blood plasma phenylalanine levels. [Fig. 1]. The younger sib who was picked-up quite early in the illness and was started therapy much earlier that his elder sib, shows very good clinical outcome (the alert looking child with mother is the younger sib).

Outcome	IS (4.5 Yrs)	IB (3.5 Yrs)
Head Circum.	**48 cms**	**49 cms**
Milestones	**Delayed but recovering**	**Normal - activity**
Convulsions	**Occasional**	**Stopped**
Dystonic movements	**Occasional**	**No**
Hypertonia and Rigidity	**Disappeared**	**Disappeared**
IQ	**Low**	**Normal – Goes to Nursery School**

Discussion: - DHPR deficiency presents with progressive neurological illness, that donot respond to phe-restricted diet. Basal ganglia symptoms develop due to deficiency of dopamine. Woody et.al (1989) pointed out that without Folinic acid therapy as a source of tetrahydrofilate, patients with DHPR deficiency show progressive basal ganglia and other subcortical calcification (1). Prognosis and outcome strongly depend on the age when the diagnosis is made and treatment introduced, but also on the type of mutation (2).

References:-

1. Internet resource – Online Mendelian Inheritance in Man: OMIMhttp://www.ncbi.nlm.nih.gov/entrez/dispomim.cgi?cmd=entry&id=261630

2. Nenad Blau, Marinus Duran, Disorders of Phenylalanine and Tetrahydrobiopterin Metabolism, Physician's Guide to Laboratory diagnosis of Metabolic Diseases, 2nd Edition, 89 – 106.

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