Abstract: Phenylketonuria is an autosomal recessive metabolic disorder which occurs due to the deficiency of enzyme phenylalanine hydroxylase. PAH deficiency leads to high plasma concentration of phenylalanine and excretion of its metabolites (phenylalanine pyruvate, phenylalanine lactate) in urine. The severity of hyperphenylalaninemia depends on the degree of enzyme deficiency. Here we report a case of phenylketonuria in an infant presented with developmental delay, microcephaly and refractory seizure.

Keyword: Phenylketonuria, hyperphenylalaninemia, inborn error of metabolism, mousey odor, mental retardation

INTRODUCTION
Phenylketonuria is an inborn errors of metabolism involving impaired metabolism of the amino acid phenylalanine. It is due to the deficiency of the enzyme phenylalanine hydroxylase. Affected child is usually asymptomatic at birth [1]. Profound mental retardation develops gradually if the infant remains untreated. Phenylketonuria can be confirmed by high plasma concentration of phenylalanine. If the condition was not diagnosed early and a special diet started the individual will suffer irreversible brain damage.

CASE REPORT
A 6 months old female child born second to third degree consanguinous parents, brought with c/o multiple episodes of generalized tonic clonic seizure since two months of age. Child was apparently normal till two months of age, then child developed GTCS multiple episodes, each episode lasted for 3 minutes, child was on multiple antiepileptic drugs. Seizures was not controlled in spite of multiple Anti-epileptic drugs. No H/o fever, vomiting, ear discharge, trauma. Antenatal H/o : uneventful Birth H/o: FTND, birth weight – 2.8kg, cried soon after birth. No H/o perinatal asphyxia and NICU admission. Developmental H/o : Not attained social smile, and neck control. Immunized up to age. Family H/o: third degree consanguineous parents. Elder sibling 2 ½ years old female child who is normal. No significant illness in family members.

General examination
Child was awake, afebrile, some pallor, hypo pigmented hair + microcephaly +, HC-35.4cm (<-3 SD) no facial dysmorphism, no neurocutaneous markers, fixes and follows light, turns on hearing sounds.

Systemic examination
Central nervous system examination
Motor – bulk of the muscle in both UL and LL normal. Tone decreased in both UL and LL. Power > 2/5 in both UL and LL. DTR ++ both UL and LL. Plantar B/L extensor No neck stiffness. Other systems (CVS, RS, abdomen) – normal

INVESTIGATIONS
Basic blood investigations were normal. Serum calcium, ionized calcium, urine metabolic screening were normal. CT Brain was normal. Ophthalmic examination was normal. EEG was normal study.TMS was done which showed elevated blood phenylalanine & phenylalanine/tyrosine ratio, suggestive of...
DISCUSSION

Phenylalanine is an essential amino acid, deficiency of the enzyme phenylalanine hydroxylase or of its cofactor tetrahydrobiopterin causes accumulation of phenylalanine in body fluids and in brain. The severity of hyperphenylalaninemia depends on the degree of enzyme deficiency and may vary from very high plasma concentrations (>20mg/dl), classic phenylketonuria to mildly elevated levels (2-6mg/dl). In affected infants with plasma concentration >20mg/dl, excess phenylalanine is metabolized to phenyl ketones (phenyl pyruvate and phenyl lactate) which can be detected in urine [2]. These metabolites have no role in pathogenesis of CNS damage in patients with PKU. Their presence in the body fluids simply signifies the severity of the condition. The term hyperphenylalaninemia implies lower plasma levels (<20mg/dl) of phenylalanine. Tyrosine is a conditionally essential amino acid for PKU patients because without PAH it cannot be produced in the body through the breakdown of PA. Tyrosine is necessary for the production of neurotransmitter [3]. Brain is the main organ affected by hyperphenylalaninemia. The CNS damage in affected patients is caused by the elevated concentration of phenylalanine in brain tissue. Phenylalanine is a large, neutral amino acid (LNAA) which competes for transport across the blood brain barrier via the large neutral amino acid transporter. If phenylalanine is excess in the blood, it will saturate the transporter. Excessive PA tend to decrease other LNAA, necessary for protein and neurotransmitter synthesis and hinders the development of brain causing intellectual disability [4].

CLINICAL MANIFESTATIONS:
The affected infant is normal at birth. Profound mental retardation develops gradually if the infant remains untreated. In untreated patients, 50 to 70% will have an IQ below 35 and 88-90% below 65. Only 2 to 5% of untreated patients will have normal intelligence. Vomiting may be an early symptom. Older untreated children become hyper-active with autistic behaviors including purposeless hand movements, rhythmic rocking and athetosis. The infants are lighter in their complexion than unaffected siblings. Some may have a seborrheic or eczematoid rash which usually mild and disappears as the child grows older. These children have an unpleasant odour (musty or mousey) of phenyl acetic acid in urine. Neurologic signs include seizure, spasticity, hyperreflexia, and tremor. More than 50% have EEG abnormality. Macrocephaly, prominent maxillae with widely spaced teeth and growth retardation are other common findings in untreated children.

DIAGNOSIS

Early detection of PKU can be done by neonatal screening. In countries and places where such programmes are not in effect, identification of phenyl ketones in the urine by ferric chloride may offer a simple test for diagnosis of infants with developmental and neurologic abnormalities. Method of choice is TMS which identifies all forms of hyperphenylalaninemia with a low false positive rate [5].

An Initiative of The Tamil Nadu Dr. M.G.R. Medical University University Journal of Surgery and Surgical Specialties