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## Inherited metabolic disorders presenting as hypoxic ischaemic encephalopathy: A case series of patients presenting at a tertiary care hospital in Pakistan

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### Abstract

In spite of the efforts and interventions by the Government of Pakistan and The World Health Organization, the neonatal mortality in Pakistan has declined by only 0.9% as compared to the global average decline of 2.1% between 2000 and 2010. This has resulted in failure to achieve the global Millennium Development Goal 4. Hypoxic-ischaemic encephalopathy, still birth, sepsis, pneumonia, diarrhoea and birth defects are commonly attributed as leading causes of neonatal mortality in Pakistan. Inherited metabolic disorders often present at the time of birth or the first few days of life. The clinical presentation of the inherited metabolic disorders including hypotonia, seizure and lactic acidosis overlap with clinical features of hypoxic-ischaemic encephalopathy and sepsis. Thus, these disorders are often either missed or wrongly diagnosed as hypoxic-ischaemic encephalopathy or sepsis unless the physicians actively investigate for the underlying inherited metabolic disorders. We present 4 neonates who had received the diagnosis of hypoxic-ischaemic encephalopathy and eventually were diagnosed to have various inherited metabolic disorders. Neonates with sepsis and hypoxic-ischaemic encephalopathy-like clinical presentation should be evaluated for inherited metabolic disorders.

**Keywords:** Hypoxic-ischemic encephalopathy, Molybdenum cofactor deficiency, Pyruvate carboxylase deficiency, Zellweger syndrome, Non-ketotic hypoglycaemia.

### Introduction

Hypoxic Ischaemic Encephalopathy (HIE) remains a problem of great concern worldwide especially in developing countries. HIE occurs in neonates who display signs of perinatal distress, entail resuscitation at birth, and

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develop neurological symptoms within 24 hours after delivery.<sup>1</sup> At delivery, HIE neonates may have low APGAR scores with associated bradycardia, poor respiratory effort, hypotonia, decreased alertness, weak or absent cry, and abnormal skin colour. The presence of metabolic acidosis in cord blood with pH <7 is highly suggestive of HIE. Currently, perinatal asphyxia associated with moderate to severe HIE affects between 1-2/1,000 live births in the developed countries and between 10-20/1,000 live births in the developing countries. HIE is reported to contribute to 1/3 of the neonatal mortality.<sup>2</sup> Inherited Metabolic Disorders (IMDs) are a heterogeneous group of disorders, which cumulatively affect approximately 1 in 800 neonates.<sup>3</sup> A number of IMD present with HIE-like symptoms. Thus, IMD should be included in the differential diagnosis of neonates who present with nonspecific features suggestive of HIE. We report four neonates who had HIE-like presentation and were diagnosed to have IMD.

### Case Report

#### Patient 1

A boy who was born at term after an uneventful pregnancy was noted to have poor suckling, excessive crying and jitteriness on day 1 of life (D1OL). He developed seizures on the D2OL and required ventilator support for 5 days. He was discharged on D16OL on three anti-convulsants with the diagnosis of HIE.

At 2.5 month of age he was seen at our metabolic clinic at Aga Khan University Hospital in 2016 for intractable epilepsy and absence of social smile, eye contact and face regard for the mother. On examination, his weight was 4.7kg (25th percentile), length 59.5cm (75th percentile) and Fronto-Occipital Circumference (OFC) 38cm (10th percentile). He was noted to have hypotonia and depressed reflexes. As part of screen for metabolic disorders, biochemical labs were done, which showed normal plasma lactate and ammonia. Mildly elevated methionine and taurine, markedly low cysteine levels on plasma amino acid analysis (PAA) were noted along with significant hypouricaemia. Brain MRI showed cystic encephalomalacia. Based on the clinical features, hypouricaemia and hypocystinaemia prompted the

**Table-1:** History of the 4 patients with IMD presenting as HIE.

Patient	1	2	3	4
Gestational age (weeks)	38	37	36 + 3 days	37
Prenatal complications	None	Hydrocephalus on ultrasound scans	IUGR	None
Parental consanguinity	First-cousins	First-cousins	First-cousins	First-cousins
History of Sibling with similar presentation	Twins, one had hypotonia and seizures, died D20L and the other had delayed milestones and seizures, died at 6 months of age	One sibling died with similar presentation but no antenatal diagnosis	Death of a sibling on D70L with "Brain anomaly" and birth asphyxia	One sibling died of a similar presentation on D70L

**Table-2:** Clinical features of the 4 patients with IMD presenting as HIE.

Patient	1	2	3	4
Birth weight(kg)	2.8 (10th percentile)	2.8 (5th percentile)	1.8 (<2nd percentile)	2.8 (10th percentile)
Birth length(cm)	49 (50th percentile)	49 (50th percentile)	NA	50.5 (75th percentile)
Birth OFC(cm)	35 (25th percentile)	37 (>97th percentile)	30(<3rd percentile)	34 (50th percentile)
APGAR Score	NA	8 at 1 min, 9 at 5 min	NA	8 at 1 min, 9 at 5 min
Clinical Features	+ Hypotonia + Jitteriness on D10L and seizures on D20L	+ Hypotonia +Grunting soon after birth	+ Hypotonia + Poor suckling	+ Hypotonia + Poor suckling
Current status (Alive/Dead)	Alive- 1 year old	Patient expired on 4th day of life	Patient expired at the age of 4 months	Patient expired at the age of 1.5 months

**Table-3: Biochemical and molecular findings of the 4 patients with IMD presenting as HIE.**

Patient	1	2	3	4
Relevant Biochemical & Radiological Labs	Plasma L.A:2.0 (N:0.5-2.2mmol/L) Plasma NH4:49 (N:<100 µmol/L) Plasma Methionine:79 (N:5-32 µmol/L) Plasma Taurine:179 (N:11-93µmol/L)  Plasma Cystine: 6 (N:33-57µmol/L)  Plasma Uric acid: <0.5 (N: 2-5 mg/dl). Urinary Sulphocysteine: 216 (N:<43µmol/mmolcreatinine) Urinary xanthine: 182 (N:0-45 µmol/mmolcreatinine) Urinary hypoxanthine:162 (0-48 µmol/mmolcreatinine)	Plasma L.A:17.9 (N: 0.5-2.2mmol/L) Plasma NH4:842 (N:<100 µmol/L) Plasma citrulline:150 (N: 5-33µmol/L) Plasma lysine:443 (N: 67-291µmol/L)  Plasma Glutamine:173 (N: 198-886µmol/L)	Plasma L.A: 2.1 (N: 0.5-2.2 mmol/l). Plasma NH4:184 (N: <100 µmol/L) C24:0 1.5282 (N: <1.529) C26:0 0.5101 (N: <0.085) Babygram: Punctate discrete calcification in the patella. Fig. 1 Plasma fatty acids:	Plasma L.A:7.7 (N: 0.5-2.2mmol/L) Plasma NH4:68 (<100 µmol/L). Plasma Glycine:1591 (N: 101-317 µmol/L) CSF Glycine:387.6 (N: 3-8.3 µmol/L)  CSF Glycine: Plasma Glycine ratio: 0.24 (N: <0.02) Electroencephalogram: Burst suppression pattern
Molecular Results	ND	Homozygous deletion of 2 bp in exon 22 in PC gene <sup>^</sup> .	Homozygous c.2875C>T (p.Arg959*) in the PEX1 gene <sup>^</sup> .	ND
Diagnosis	Molybdenum cofactor deficiency	Pyruvate carboxylase deficiency	Zellweger syndrome	Non-ketotichyperglycinemia

differential diagnosis of Molybdenum cofactor deficiency (MoCD), which was confirmed on the classical pattern of urine purine analysis (raised xanthine and hypoxanthine) with elevated urinary sulphocysteine.

## Patient 2

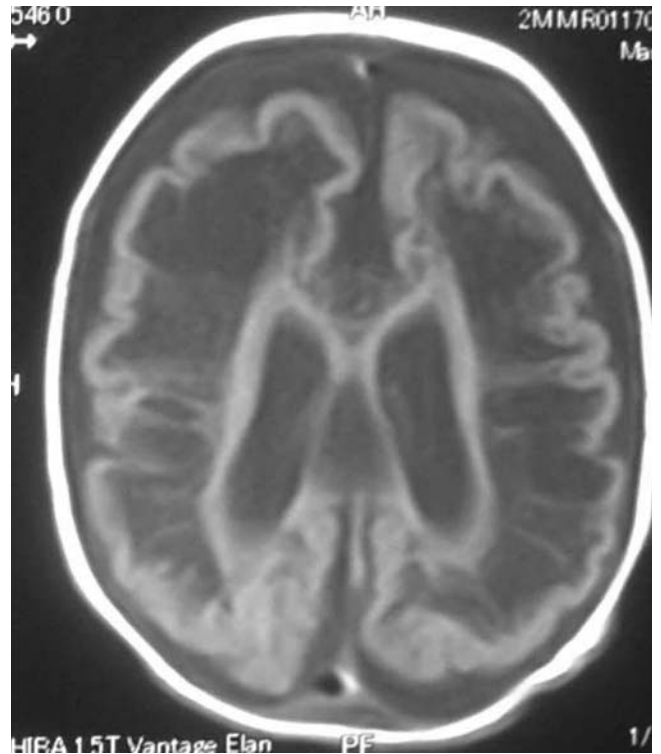
A girl was born at term by Lower Segment Caesarean Section (LSCS), due to increased OFC at Aga Khan University Hospital in 2015. Examination revealed open

**Table-4:** Brain MRI findings of the 4 patients with IMD presenting as HIE.

Patient	1	2	3	4
MRI Brain Findings	Cystic encephalomalacia. Fig 2a.	Bilateral periventricular and subependymal cysts in the caudothalamic groove and dilated lateral ventricles. Fig 2b. NMRS: Large peak of 2 hydroxy butyric acid and small peaks of acetoacetic acid and pyruvic acid. Fig 2 b.	Polymicrogyria in the frontal lobes, cavumseptumpallidum and mild hypoplasia of the inferior vermis. Fig 2c. NMRS: marked excretion of lipids	Normal
Diagnosis	Molybdenum cofactor deficiency	Pyruvate carboxylase deficiency	Zellweger syndrome	Non-ketotichyperglycinemia

**Figure-1:** Babygram of Patient 3, showing punctate discrete calcification in the patella).

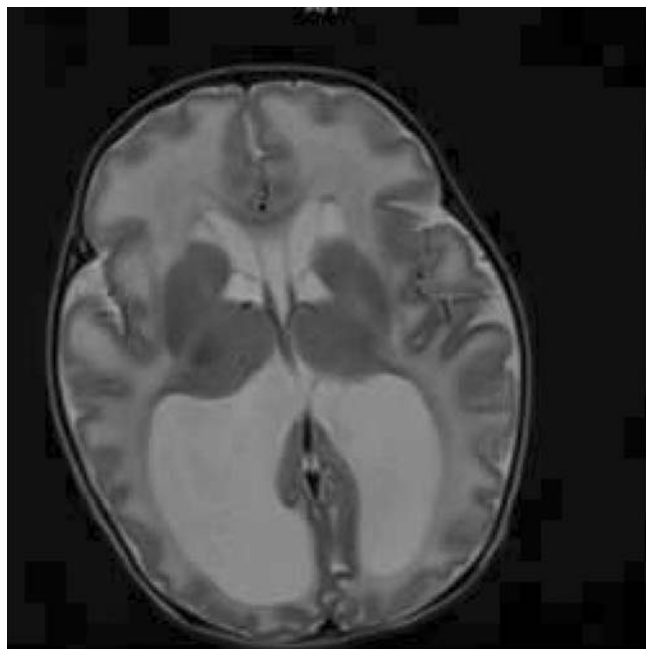
and flat anterior fontanelle, depressed neonatal reflexes and unremarkable systemic examination. The baby was shifted to the NICU after few hours due to grunting, tachypnea and hypotonia. The patient was investigated and managed along the lines of apparent HIE. HIE biochemical markers including serum creatine phosphokinase (CPK), lactate dehydrogenase (LDH), creatinine were raised. Other laboratory workup revealed lactic acidemia and hyperammonaemia. Urine organic acid (UOA) analysis showed ketosis. PAA revealed high levels of citrulline and lysine and decreased glutamine levels. Brain MRI revealed bilateral periventricular cysts and subependymal cysts in the caudothalamic groove along with dilated lateral

**Figure-2a:** MRI brain of Patient 1 showing Cystic encephalomalacia).

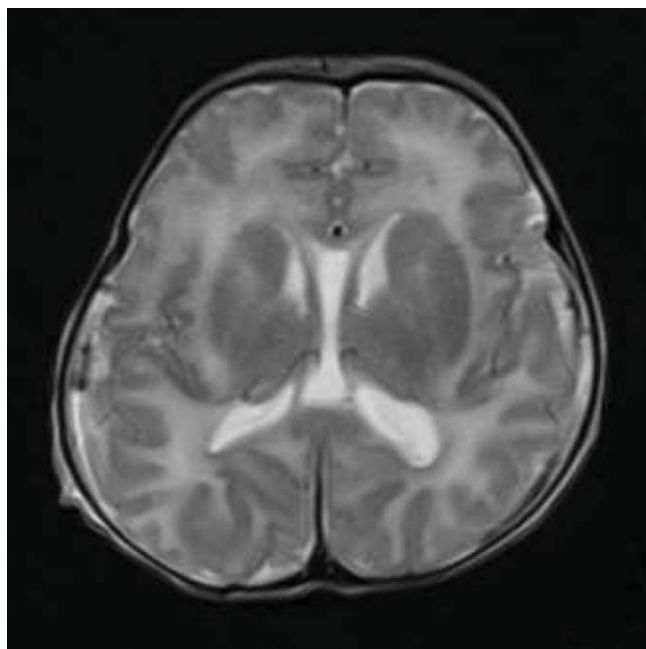
ventricles. Lactic acidosis and PAA along with the MRI findings prompted the differential diagnosis of pyruvate carboxylase deficiency (PCD), which was confirmed by PC gene sequencing.

### Patient 3

A boy was born at term by LSCS, due to intrauterine growth retardation (IUGR). He had poor suckling and hypotonia and was discharged on D9OL with the diagnosis of HIE. He presented at our metabolic clinic on D12OL at Aga Khan University Hospital in 2016 with complaints of poor feeding from birth and generalized hypotonia. Examination of the patient revealed a tower-like skull with large, open anterior and posterior fontanelles. There was severe hypotonia and hypo-reflexes. Based on the clinical features suggestive of



**Figure-2b:** MRI brain of patient showing Bilateral periventricular and subependymal cysts in the caudothalamic groove and dilated lateral ventricles).



**Figure-2c:** MRI brain of Patient 3 showing Polymicrogyria in the frontal lobes, septum pallidumcavum and mild hypoplasia of the inferior vermis.

Zellweger spectrum-disorder (ZSD), baby-gram was done, which showed patellar calcification. Brain MRI revealed polymicrogyria in the frontal lobes, cavumseptumpallidum and mild hypoplasia of cerebral vermis. For the biochemical confirmation of ZSD, very long chain fatty acids (VLCFA) were

done, which were elevated. ZSD was confirmed by PEX1 gene sequencing.

#### Patient 4

A girl was born at term by LSCS, due to decreased foetal movements. The newborn developed decreased activity, poor suckling and hypotonia on D2OL progressing to respiratory distress on D5OL requiring ventilator support and was shifted to our hospital with the diagnosis of HIE. HIE biochemical markers were raised. On arrival at Aga Khan University Hospital in 2016, the baby was noted to have severe hypotonia, hyporeflexia and depressed neonatal reflexes. Electroencephalogram showed burst suppression pattern. Brain MRI including corpus callosum was normal. Hyperglycinaemia and raised CSF glycine: Plasma glycine ratio strongly supported the diagnosis of non-ketotic hyperglycinaemia (NKH). The family declined molecular confirmation of the NKH due to financial constraints.

#### Discussion

IMD may present at or soon after birth with dysmorphic features, seizures and severe hypotonia. Neonates presenting with neurological abnormalities at or soon after birth, particularly the ones with persistent lactic acidosis and early-onset fits, are often misdiagnosed as HIE. More than 800 IMDs are known. A number of IMD present in the early neonatal age with non-specific symptoms of sepsis-like illness or HIE-presentation.<sup>4</sup> In local setting, neonates with HIE are rarely investigated for an underlying IMD. Investigations should include analysis of plasma ammonia, plasma lactate, plasma uric acid, blood and CSF lactate, paired plasma and CSF aminoacids, plasma very-long-chain fatty acids, urine ketone bodies and organic acids, urine sulphite, urinary sulphocysteine, and urine purines and pyrimidines.<sup>5</sup> Martinelloet al published a practical diagnostic algorithm for the evaluation of patients in whom the diagnosis of HIE is not confirmed.<sup>6</sup> The essence of this practical algorithm in this paper is that all newborns with HIE should be investigated for IMD, which is especially applied in our local context as the most new-borns who receive the diagnosis of HIE, the critical parameter of metabolic acidosis with pH<7.0 in cord blood and APGAR score information at birth is missing. Moreover, differentiation of true HIE and other pathologies like an underlying IMD or other genetic condition like neuromuscular disorder causing secondary HIE, is not possible based on the parameters like metabolic acidosis with pH <7.0 in cord blood and poor APGAR score. Pattern of brain injury on brain MRI due to HIE depends on the gestational age, severity and duration of HIE. Preterm neonates suffer periventricular white matter injury, term neonates sustain damage primarily in

the cortex and underlying subcortical and periventricular white matter. Severe HIE may show hyperintense signal in the thalamus and putamen (with relative sparing of the anterior putamen). Brain MRI in many IMDs have disease specific pattern, which if promptly recognized can lead to an accurate diagnosis.<sup>7</sup>

MoCD, PCD, ZSD and NKH are few IMDs, which are known to present as HIE and often are missed if not investigated properly. All four patients had initially received diagnosis of HIE, which eventually turned to be various IMD. Presence of parental consanguinity, family history of intellectual disability, cerebral palsy, seizure, sudden infant deaths, neonatal or early infancy death with symptoms suggestive of an IMD, history of non-immune hydropsfoetalis in previous pregnancy are some pointers, which should alert the physicians for a possible IMD in neonates presenting as HIE. However, absence of these parameter cannot exclude IMD as the primary cause in neonates presenting as HIE. The critical message is that all neonates with HIE needs a diagnostic evaluation for IMD. The Task Force on Neonatal Encephalopathy published guidelines in 2014, according to which "If a comprehensive etiologic evaluation is not possible, the term hypoxic-ischaemic encephalopathy should best be replaced by neonatal encephalopathy because neither hypoxia nor ischaemia can be assumed to have been the unique initiating causal mechanism".<sup>8</sup> Appropriate evaluation of HIE provides the family a chance of a correct diagnosis, proper genetic counseling and future

reproductive options.

**Disclaimer:** None to declare.

**Conflict of Interest:** None to declare.

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