FUEL FOR THOUGHT : Series of Indian Beta-Ketothiolase Patients Presenting with Metabolic Encephalopathy

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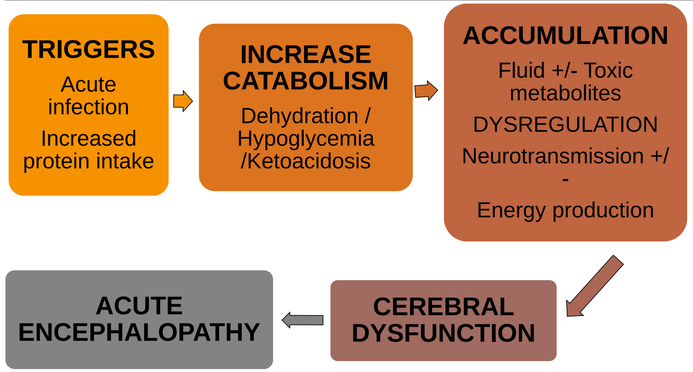
INTRODUCTION

- Metabolic encephalopathy - clinical state of global cerebral dysfunction due to systemic stress
- Clinical presentation varies from mild executive dysfunction to deep coma
- Underlying etiologies are diverse and include Inborn Errors of Metabolism (IEM)
- Management = acute stabilization + Specific measures based on etiology



ß- KETOTHIOLASE DEFICIENCY

- Affects ketone body metabolism and isoleucine catabolism.
- Presentation is during metabolic crisis with ketoacidosis
- In IEMs with defects in energy production or utilization - metabolic crisis manifests as acute encephalopathy
- Diagnosis is by urine organic acid profile and molecular testing.
- Most have a favorable outcome.

MRI Brain of Patient - **C**

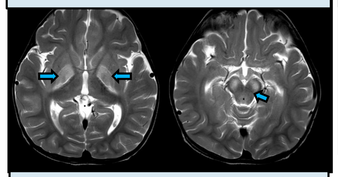


Fig.3: T2 Hyperintensity in Caudate, Putamen and Substantia Nigra

MRI Brain of Patient - **B**

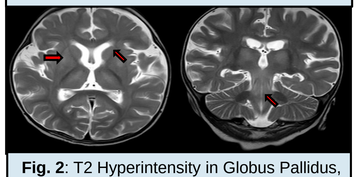


Fig. 2: T2 Hyperintensity in Globus Pallidus, Putamen, Venterolateral Thalami, Caudate nuclei and Midbrain

CLINICAL PROFILE AND INVESTIGATIONS

PATIENT	A	B	C	D
Age/Sex	12 months / F	11 months/ F	1.5 years/ M	11 MONTHS/ F
Development	Appropriate	Appropriate	Appropriate	No
Onset	2 days	5 days	3 days	2 days
Clinical features	Diarrhoea Tachypnea	Diarrhoea Tachypnea Encephalopathy	Diarrhoea Tachypnea Encephalopathy	Diarrhoea Tachypnea

INVESTIGATIONS

pH	6.9	7.06	6.9	6.99
HCO3 (mmol/L)	1.5	3.4	3.8	4.3
Anion Gap	22	30	40	36
Urine Ketones	4+	4+	4+	3+
Hypoglycemia	-	**+**	-	No
Organ Dysfunction	No	**AKI Optic Atrophy**	**AKI**	No

METABOLIC WORKUP

PATIENT	A	B	C	D
TMS	C4OH elevated	C4OH elevated	Normal	Elevation of C4OH, C5OH
Urine Organic Acid	**Acetoacetic acid 3-hydroxy butyric acid 2-hydroxy butyric acid, 2-hydroxy isovaleric acid Tiglylglycine**	Lactic acid **3 - hydroxybutyric acid 3 - hydroxyisovaleric acid**	**Hydroxybutyrate 2-Methyl-3-Hydroxybutyrate Acetoacetate Methylacetoacetate** Glutarate Lactate	Lactic acid **3-hydroxy propionic acid, acetoacetic acid** and other ketoacids **Tiglylglycine** 3-hydroxy-glutaric acid

CLINICAL EXOME

PATIENT	A	B	C
GENE	**ACAT1**	**ACAT1**	**ACAT1**
TYPE OF VARIANT	Compound/Double heterozygous? Variant	Homozygous variant	Compound heterozygous
CLASSIFICATION	Likely pathogenic	Likely pathogenic	Likely pathogenic
DISEASE	**ALPHA METHYL ACETOACETIC ACIDURIA**		

DISCUSSION

	Our Cases (A,B,C,D)	In literature
Onset	11 – 18 months	6 – 36 months (peak = 6-11)
Metabolic profile	Severe acidosis Pt A had single hypoglycemia post admission	Severe acidosis Mean blood sugar 7.51
Specific biochemistry	Atypical acylcarnitine 3/4	NBS known to miss C5OH/C5:1
Intervention	3 required VENTILATION + Peritoneal dialysis	~ 40% required Ventilation ~10% required dialysis
Deaths	¾	7/135
Neurological impairment	1	16 – prior to presentation

- Suspected metabolic encephalopathy after excluding CNS infection, structural disorders, toxin ingestion and trauma.
- Underlying etiologies are diverse → narrow down by clinical + lab clues.
- Metabolic crisis in Ketone metabolism defects present as acute encephalopathy.
- Other **neurological manifestations** reported
  - ➢ developmental delay, ataxia, myoclonus, and other extrapyramidal symptoms
  - ➢ caused as sequelae of severe metabolic crisis
  - ➢ often with basal ganglia lesions.
- **Management**
  - ➢ Acute : intravenous glucose + treatment of metabolic acidosis
  - ➢ Long-term: mild protein restriction(1.5–2 g/kg/day) + avoid fatty meal
  - ➢ ? Carnitine supplementation
- Early diagnosis by **Newborn screening** using C5OH/C5:1 may help in prevention of neurological sequelae

TAKE HOME MESSAGE

- Suspect Metabolic encephalopathy → evaluate for IEM
- Those with ketoacidosis → beta ketothiolase, SCOT deficiency, MHBD
- Neurological deficits known even before decompensation.
- Persistent / Recurrent ketoacidosis can result in neurological sequelae → poor prognosis.
- Early and apt diagnosis, Dietary control, Sick day management SAVES THE DAY!

REFERENCES

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