MITEM disorder- an entity to recognize

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- 1 year old male
- 1st born of 2 degree CM
- No significant antenatal/birth history and family history
- Referred to KKCTH with- recurrent non bilious, non projectile vomiting since early infancy
- Vomiting had worsened and had associated weight loss - 4kg in 2months

History:

- Vomiting - onset in early infancy but increasing in frequency over last 2 months
- Failure to thrive
- Admitted four times at different hospitals - Treated with intravenous fluids and anti emetics initially
- Clinical diagnosis of GERD – antireflux measures
- Milk scan: evidence of reflux of tracer into esophagus
- Poorly controlled vomiting
- CBC, RFT: normal
- USG abdomen - Normal except a mild fatty liver

Clinical Examination

Malnourished, Weight : 6kg (exp 10kg)

Features of *some* dehydration

Soft liver palpable 3 cm below RMCL

Hypotonia

On probing history …

- Head control and sitting without support were attained, but baby lost these milestones over past 2-3months.
- Apart from vomiting – mother also described some swallowing difficulty of late
- Detailed neuromotor examination in the wards after intravenous fluid rehydration:

1. Incomplete head control
2. Unable to sit without support – rounded back

Issues

- Recurrent Vomiting – unlikely to be a simple GERD
- Neuromotor issues
- Minimal fatty liver

- Could this be an inborn error of metabolism?
- Needs a detailed evaluation
- CBC, LFT, RFT, ammonia, lactate, pyruvate, urine ketones, urine and bloods for IEM

INVESTIGATIONS

- CBC- normal
- RFT – normal
- serum ammonia-normal, urine ketones were negative
- LFT showed elevated AST/ALT and GGTP
- Serum lactate was elevated(6.5mM)
- serum lactate pyruvate ratio of 23:1

LIVER ENZYMES…

	11/6/13	18/6/13
SGOT	351	250
SGPT	222	191
GGTP	252	119
TOTAL BILI	1.2	0.9
T.PROT/ ALB	6.2/3.9	5.7/3/7

Further work-up.....

- Barium UGI series done showed GER - anti reflux measures continued - not controlled
- Repeat USG abdomen showed mild hepatomegaly with fatty changes.

- Metabolic Conditions with recurrent vomiting:

1. Galactosemia
2. Urea cycle defects
3. Organic acidaemias
4. Mitochondrial diseases
5. Fatty acid oxidation defects
6. HFI

- Neurologist opinion for neuroregression & vomiting

1. MRI brain with spectroscopy - bilateral symmetric thalamic and putamen hyper intensity with loss of cerebral volume and increased lactate peak-s/o mitochondrial disorder.

2. CSF lactate was elevated

Further Work-up

- Urine for organic acidemia showed elevation of succinate, fumarate, malate and 2-ketoglutaric acid.
- Plasma amino acidogram suggested the possibility of Mitochondrial disease-mildly elevated alanine levels
- Liver biopsy was done-showed periportal fibrosis with septae and steatosis-s/o metabolic liver disease
- He developed seizures during hospital stay

- Diagnosis of LEIGH'S disease was strongly considered.

a/k/a *sub acute necrotizing encephalopathy*

Further course.....

- He was treated with metabolic drug cocktail with vitamins, carnitine & ubiq
- Parents were counseled regarding disease and prognosis was explained.
- Mutation analysis for *SURF 1 MUTATION* was sent.

Mitochondrial disease- a disease to recognize

What are problems in diagnosing:

- Notorious variability,
- Great Masquerader,
- nonspecific presentation,
- absence of a reliable biomarker specific for the screening or diagnosis of the disease,
- Ever increasing spectrum of recognized phenotypes.

As a general rule:

- the involvement of 3 or more organ systems without a unifying diagnosis should raise suspicion for mitochondrial disease

When to suspect:

- Mitochondrial disease may present with "any symptom in any organ at any age," but some symptoms and signs truly are more suggestive of a mitochondrial disorder than others.
- These "red-flag" features warrant the initiation of a baseline diagnostic evaluation for mitochondrial disease

Neurologic

1. Cerebral stroke-like lesions in a nonvascular pattern
2. Basal ganglia disease
3. Encephalopathy, recurrent or with receiving valproate
4. Neurodegeneration
5. Epilepsia Partialis Continua
6. Myoclonus
7. Ataxia
8. MRI findings consistent with Leigh disease
9. Characteristic MRS peaks
    a. Lactate peak at 1.3 ppm TE at 35 and 135
    b. Succinate peak at 2.4 ppm

Ophthalmologic

1. Retinal degeneration
2. Ophthalmoplegia/paresis
3. Fluctuating, dysconjugate eye movements
4. Ptosis
5. Sudden- or insidious-onset optic neuropathy/ atrophy

Gastroenterologic

1. Unexplained or valproate induced liver failure
2. Severe dysmotility
3. Pseudo-obstructive episodes

Cardiovascular

1. Hypertrophic cardiomyopathy with rhythm disturbance
2. Unexplained heart block in a child
3. Cardiomyopathy with lactic acidosis (> 5 mM)
4. Dilated cardiomyopathy with muscle weakness
5. Wolff-Parkinson-White arrhythmia

Other

1. Exercise intolerance out-of-proportion to weakness
2. Delayed waking from general anesthesia
3. Episodes of acute rhabdomyolysis
4. Unexplained hypotonia, failure-to-thrive, and acidosis

- the diagnostic evaluation is necessarily multitiered and broadbased with a focus on integrating information from many avenues:

1. the complete medical and family history,
2. clinical findings,
3. biochemical laboratory abnormalities,
4. tissue-biopsy evidence of abnormal electron-transport chain enzyme activity or impaired respiratory capacity - (liver, muscle, skin)
5. if possible, the identification of a pathogenic mtDNA or nDNAmutation

Conclusion……

- All vomiting in infancy is not GERD
- Barium or milk scan evidence of GERD should not prevent us from looking further into causes of vomiting
- Metabolic causes of vomiting are often missed unless we have a high index of suspicion
- Fatty liver in childhood needs detailed evaluation
- MITEM disorder should be suspected in children with multi system involvement – though some findings may be subtle….