All India Institute of Medical Sciences Rishikesh (AIIMSR)
Department of Paediatrics

Rishi Vansh

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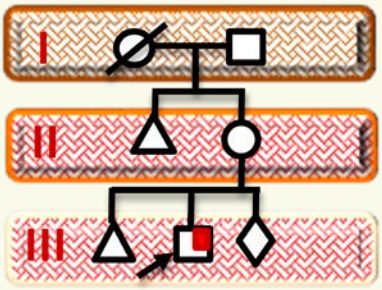
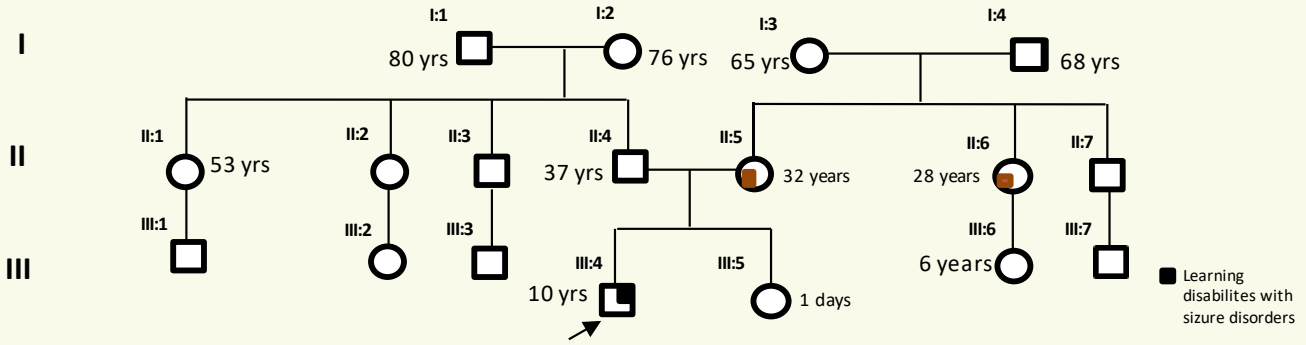
From the desk of Editor

The Department of Paediatrics is publishing a monthly newsletter for faculty and residents. The newsletter is related to genealogical parlance and a deliberate attempt to enhance awareness for genetic disorders with recent updates.

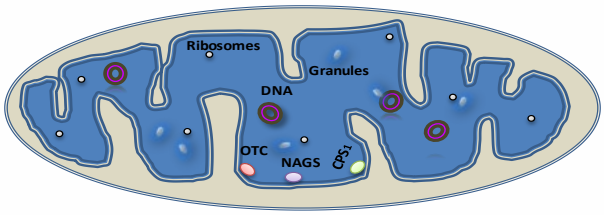


Inherited Metabolic Diseases

Neurometabolic/Intellectual Disability/ **X-Linked**/ Ornithine Transcarbamylase (**OTC**) Deficiency



Location of enzymes in mitochondria for UCP



Periportal hepatic mitochondria

UCP- urea cycle pathways
(Major pathway for NH3 metabolism)
NAGS- N-acetylglutamate synthase
CPS1- Carbamylphosphate synthetase 1
OTC - Ornithine transcarbamylase

Insight:

1. What are the management strategies for UCP disorders?
2. What is the cause for postpartum encephalopathy in cases II:5 and II:6?
3. What will be the various components of genetic counselling for the case III:4?
4. What is the critical level of ammonia that leads to permanent neurological damage in infancy?
5. What is the age of disease onset with total loss of enzyme function?
6. Is the genotype strongly follow the phenotype with OTC deficiency?

Plausible tenets:

Gene: OTC (Xp11.4); 68,919 bp & 10 Exons

- **Second enzyme of the principal pathway used for the detoxification of ammonia**
- Transcript (**1,522 bps)**, 3 transcripts (splice variants), 200 orthologues & 2 paralogues
- Protein**(354AA, 40 kD**) is changed to an active enzyme by fusion of three units of 36-kD by posttranslational modification
- **L-citrulline** is synthesized by fusion of carbamoyl phosphate with L-ornithine in the mitochondrial matrix
- Citrulline level in plasma is maintained by its synthesis in the intestinal tract through CPS1 and OTC activity and used by renal tubules to form arginine by argininosuccinate synthetase (ASS) and argininosuccinate lyase(ASL).
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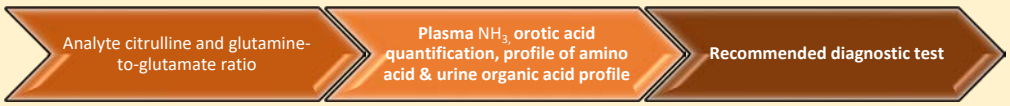
Clinical phenotypes: Simplified Genotype and Phenotype relationship

Gene expression	OTC activity	Hyperammonemiccrisis (symptomatic)	Sex	Treatment of choice for typical
Absent	**Absent**	**Neonatal (floppy, encephalopathy)**	**Male**	**Liver transplantation**
Fractional	**Partial**	**Post-Neonatal**	**M>F**	**Preventive**

- **Management:** depend upon hyperammonemia, disease stage, and co-morbidity
- **Consequences**, if standard treatment not followed: **1.** progressive dysfunction of higher cognitive function: delayed milestones, learning disabilities, attention-deficit/hyperactivity disorder, inexplicable cerebral palsy **2**. Other neurological features such as headache, migraine

Acute	**NH_3 - ≤200 µmol/L rapidly with +/_ dialysis, NH_3 scavenger, stopping catabolism; protect from neurologic damage**
Chronic	**dietary protein restriction, medications to stimulate substitute pathway, citrulline/arginine, frequent testing of NH_3 and amino acids levels, nutrition supplementations, liver function & neurological evaluation and avoid precipitating factors for catabolic state as fasting and stress & hepatotoxic drugs including systemic corticosteroids, Valproate & haloperidol.**

Steps for New-born screening (NBS) by dried blood spots (DBS) for OTC deficiency



UCD - overall incidence has been estimated to be 1 in 10,000 -35,000 births

The most important sources of NH3-Alanine and glutamine are **internal** while generated by urease-positive bacteria of the gut on dietary amino acids as a fuel are **external.**

Age of disease onset with absent gene expression - **2nd to 3rd day of life**

First case published by Russell and coworkers in 1962

Included in the USA NBS panel

First beneficial OTC gene therapy trial with (DTX301) was done on Simon Smith in August 2017

Specific observations in few UCD

Deficiency	Specific observations
Arginase deficiency	Progressive spastic tetraplegia
Argininosuccinate Lyase Deficiency, citrin deficiency and, OTC deficiency	Substantial liver disease
Argininosuccinate Lyase Deficiency	Trichorrhexis Nodosa
Citrin deficiency associated with	Neonatal intrahepatic cholestasis
Citrullinaemia type-II	Gastrointestinal symptoms & Failure to thrive and

Pregnancy should be managed as a catabolic state, even after delivery in the asymptomatic carrier.

Diagnosis by any one of technique:

	Technique	Comments
1.	**Molecular**	**Presence of pathological variant**
2.	**Biochemical**	**Random urinary sample - Orotic acid excretion ≥20 umol/mmol creatinine)***
3.	Enzyme activity in hepatocyte	**Fail to detect carrier status**

*Alternately in older cases, presence constant biochemical characteristics of OTC deficiency as elevated ammonia, elevated glutamine and low-to-normal citrulline, and high Orotic acid after an allopurinol challenge test

Genetic counselling components with case III:4

Understand family's psychological condition→ first confirm the disease → define the disease course and its management → discuss future treatment including Gene therapy surveillance guidelines → haploinsufficiency and stress phenomenon → antenatal diagnosis in the subsequent pregnancy

Thought Riveting:

- ***Can ammonia be used as a future medicine for tumor suppression?***
- ***Is there any protein in the body which do not have posttranslational modification?***
- ***What is the crucial role of tertiary protein structure in the success of gene therapy?***
- ***For a low resource center, what could be the best NBS strategy for detecting the UCD?***
- ***Does ammonia have teratogenic effects at the early embryonic stage, especially on the neuroectodermal growth plate and synaptogenesis?***

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