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

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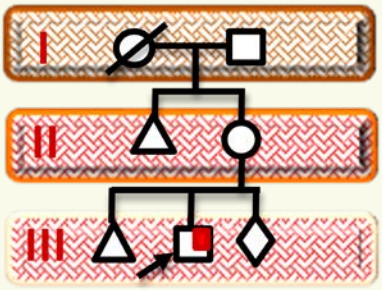
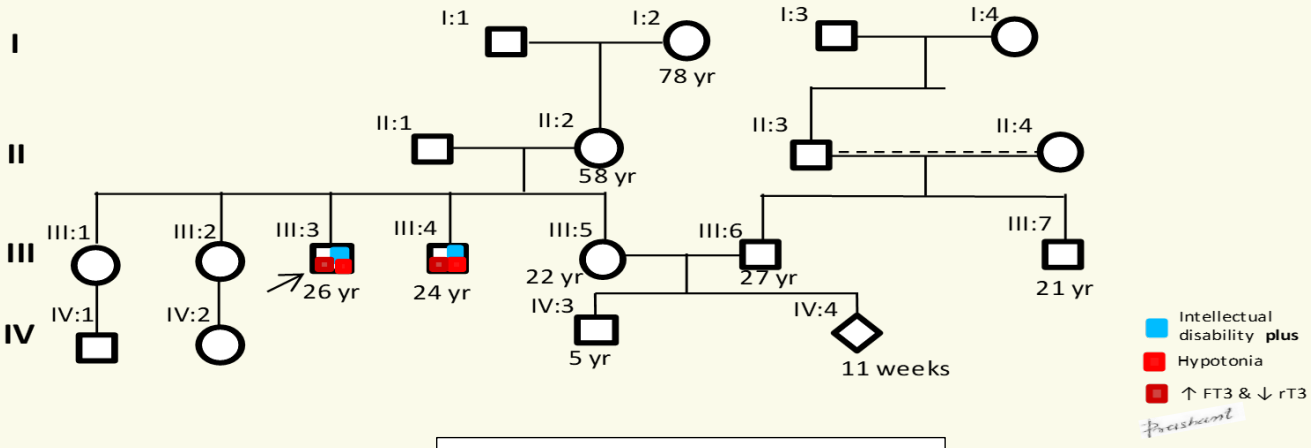
From the desk of Editor

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.

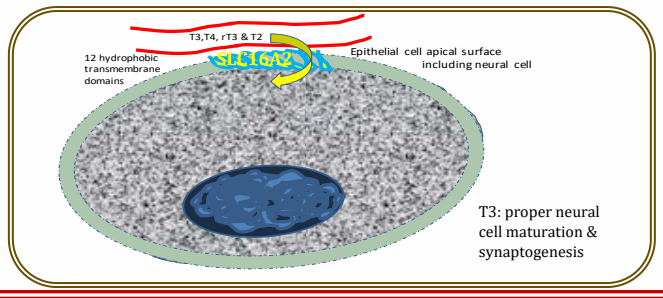


Inherited Metabolic Diseases

Neurometabolic/Intellectual Disability/ **X-Linked/ Allan-Herndon-Dudley** Syndrome (**AHDS**)/**T3 resistance**



Transcellular Role of SLC16A2



- Enables intracellular transportation of thyroxine (T4), triiodothyronine (T3), reverse triiodothyronine (rT3) & diidothyronine (T2)
- Peripheral tissues also have another transporter besides SLC16A2 for thyroid hormone

Insight:

1. Is there any diagnostic role of thyroid function test (**TFT**) for X-linked Mental retardation?
2. What are the key characteristic features of AHDS?
3. What should be the counselling plan for case IV:4?
4. What are the Monocarboxylate Transporters & their operations?
5. Can a T3 analog, as TRIAC (acide 3,3',5-triiodothyroacetique), help in the management of AHDS?

Plausible tenets:

Gene: SLC16A2 (Xq13.2); 6 Exons [location also known for having X-inactivation center (XIC)]

- **A member of the solute carrier family 16 member 2, one of the monocarboxylate transporter (MCT)**
- Transcript (**4,128 bps)**, has three splice variants, 256 orthologues & 13 paralogues; 27 domains & features
- Protein MCT8 **(539 AA, 67 kD)**: an essential transporter for thyroid hormone in neural cells in the course of development. Other peripheral tissue does not show features of abnormal transportation
- Indirectly help in neurodevelopment through enabling appropriate intracellular levels of thyroid hormone.

Clinical phenotypes: Simplified Age-dependent Phenotype (**MOI- X linked recessive, Prevalence 1:70 000 males**)

Age	Presenting **complex neurological Phenotype** beside **dysthyroidism**
Infancy	Significant hypotonia (Floppy infant) & delayed mile stones +/- Seizures
Early childhood	Developmental delay +/- Seizures +/- **Extrapyramidalsigns*(EPS)**
Late childhood	Moderate to severe Intellectual disability (**ID**)
Adolescent	ID plus Truncal hypotonia & peripheral hypertonia + **Pyramidal signs(PS)**
Adult	ID + PS + EPS +/- Seizure
* Paroxysmal movement disorder(**kinesigenic dyskinesias-** stimulus triggerred abnormal movements ≈ tetany), athetoid, dystonia, choreoathetosis, hypokinesia, ataxia, tremor	

- No abnormal behavior phenotype reported & life span usually unaffected
- A well defined genotype & phenotype correlation identified with different types of mutations based on the mechanism for loss of function
- Up to 25 % of carrier female has milder TFT abnormalities but no neurologic phenotype

Management:

- **Investigation:** TFT-↑ T3 & ↓ rT3; **FT3/T4 = >0.75 [***also + with nongoitrous congenital hypothyroidism-6* **(CHNG6)]**
- **Management: follow survillance guidelines (**https://www.ncbi.nlm.nih.gov/books/NBK26373/#thctd.Management**) &** Symptomatic treatment & individualized education plan (**IEP**) for selected cases with social support
- Enroll the case in international clinical trial of T3 analog TRIAC (acide 3,3',5-triiodothyroacetique)

Dysthyroidism with MCT8 transporter defect: *chronic*
Cerebral hypothyroidism & peripheral thyrotoxicosis
CNS- hypomyelination & arcane neurodegenerative changes
Peripheral- weight & muscle mass loss, tachycardia, loose motions, hypermetabolism, sweating
Rx:
- symptomatic
- Methimazole not useful, propylthiouracil is contraindicated

Triiodothyroacetic acid (Triac), an analog of thyroid hormone, enters the cell without MCT8 help. Restores thyroid level in CNS

- Decrease TSH secretion by negative feedback & indirectly reduce features of peripheral thyrotoxicosis
- Early administration reinstates myelination & neural development

The monocarboxylate transporter (MCT) family (14 subtypes of SLC16): transcellular transporter of various small molecules.

MCT	Transport function known in human
MCTs 1–4	monocarboxylate drugs, short-chain fatty acids, Pyruvate & lactate
MCT6	xenobiotics such as bumetanide, nateglinide, & probenecid
MCT7	ketone bodies
MCT8	transport thyroid hormones
MCT9	carnitine efflux transporter
MCT12	creatine transporter

Nonsyndromic Role: Increased expression has been noted in several cancers especially MCTs 1 & 4
Novel target therapy: altering the transportation for cancer cells & enhancing drug absorption as MCT1 has its high expression in the gut.

Genetic counseling for IV:4- 1. Proband needs to be confirmed by molecular testing, 2. Mother's TFT will not help to rule out carrier status completely, 3. ONLY molecular testing is strongly recommended for her. 4. If positive, the fetus needs to be tested antenatally by any of the procedure as CVS > amniocentesis (depends upon the mother's selection for the procedure & available resources)

Thought Riveting:

- ***Is there any tissue-specific non-transporter function of SLC16A2 in the brain?***
- ***Which cancers can be targeted with MCT-based personalized therapy?***
- ***Can TFT be used universally as one of the preconception screening tests due to its low cost & availability?***
- ***Can TRIAC be used in other demyelinating diseases or as a booster for neurodevelopment in normal infant?***
- ***Is there any direct correlation between elevated serum T3 levels & the severity of intellectual disabilities?***

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