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

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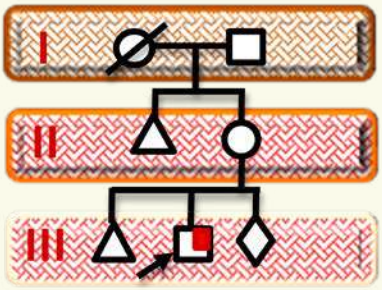
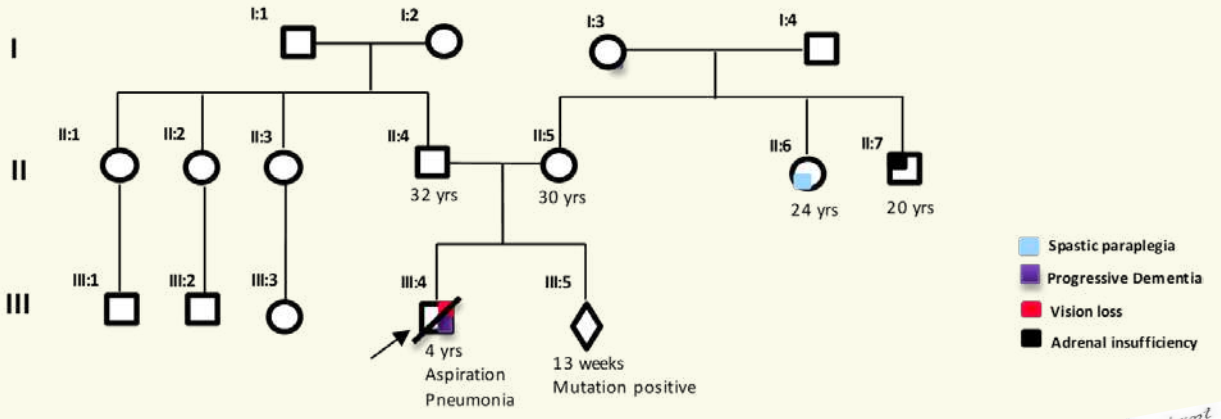
From the desk of Editor

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



Inherited Metabolic Diseases

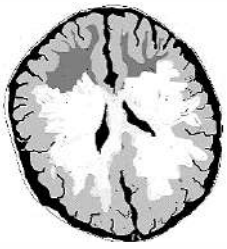
Neurometabolic/Intellectual Disability/ ***X-Linked***/ Adrenoleukodystrophy (**ALD**)



Characteristics clinical features

Parieto-occipital region

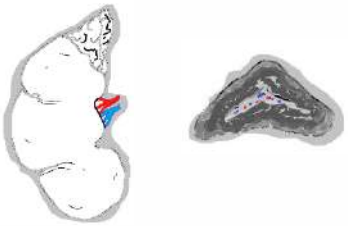
Symmetric enhanced signal in T2



Primary adrenocortical insufficiency

+/- variable degree of neurologic abnormality

Targeted organs by raised VLCFA



Insight:

1. What is the clinical phenotypic spectrum of ABCD1 disease & age-related phenotypic variation?
2. What is the three-tiered algorithm panel for Newborn screening of ALD?
3. What will be the counselling plan for case III:5?
4. How would you counsel the case II:5? Are there any specific investigation guidelines for her?
5. What is "Lorenzo's oil"?

Plausible tenets:

Gene: ATP-Binding Cassette Sub-Family D Member 1; ABCD1 (Xq28); 19.905 kb, 10 Exons & 16 domains

- **Belong to ATP-binding cassette (ABC) transporters (Superfamily) which transport various molecules**
- ABCC7/**CFTR** also belong to the same family & excess expression had been noticed in cancers
- **Function**: Protein **(745 AA) Subfamily ALD** that transport free very-long-chain fatty acids (**VLCFAs**) as well as their CoA-esters across the peroxisomal membrane; β-oxidation of fatty acids(**FA**); elongation of microsomal FA
- Severe phenotypes occur with missense mutations in comparison to large deletions
- X linked inheritance (95 % familial & 4.1 % de novo mutations)& affected females with less severity
- ABCD2 & 3 are the other ATP-binding cassette (ABC) transporters in the peroxisomal membrane
- **<1% obligate carrier** might **have a negative molecular test by leukocyte DNA** due to germline mosaicism

Clinical phenotypes: A lipid-storage disease with Triad of **myelin**, **adrenal cortex** and, the **Leydig *cells*** involvement,

- **Phenotypes**
  - **Symptom set 1** (childhood cerebral forms; ~35% of affected individuals) after 3 years of age, **Symptom set 2** (adrenomyeloneuropathy [AMN]; ~40%-45%) in twenties or middle age, **Symptom set 3** (Addison disease only; ~10%) between 2 years to adulthood, **Symptom set 4 to 7** (variable symptoms & more complex neurological picture like localized signs or psychiatric disorders)**, Symptom set 8 -** do not have any symptoms
- Inter & intrafamilial phenotypic variability very common, especially age of onset, so unpredictable phenotype even after genotyping; disease severity directly correlated with VLCFA levels which increase with time
- ℞: As per gudilines, MRI & adrenal function tests need to be done **repeatedly** & Hematopoietic stem cell transplantation (HSCT) for an asymptomatic case (**early stage**). Lorenzo's oil is still used as a **trial therapy**. Gene therapy under trial

- In **late 1980s**, **first time** used by parents (**Augusto & Michaela Odone**) for their ALD kid named **Lorenzo Odone**

- **Lorenzo's oil** - Mix of glyceryl trioleate & glyceryl trierucate **(4:1)** prepared from **rapeseed & olive oil, might Inhibit endogenous VLCFA synthesis**

- **Better** to start in pre-symptomatic results

- **February 2016**, **added** in Newborn screening panel in USA as **three-tiered algorithm**

Very long chain fatty acids (VLCFA): fatty acid with ≥ 22 carbons atoms

- Raised, in defective metabolism by peroxisomes **or** increase synthesis **or** both as in ALD
- Concentration of C26:0, C24:0/ C22:0 & C26:0/C22:0 is increased
- Raised C26:C22 fatty acids - indicator for peroxisomal dysfunction
- 20 % carrier female have normal level

Age wise phenotypic presentation with variable adrenal insufficiency

Boys	Young or middle-aged men	Adult women
Progressive dementia & behavioral disorders, loss of vision & coordination	Progressive spastic paraparesis, & sexual dysfunction, behavioral changes	Slowly progressive spastic paraparesis & peripheral neuropathy

Standard **Three-tiered algorithm** of Newborn screening: (It could be modified if needed)
1st: Biochemical test used as in routine for NBS have low cut off value of biochemical marker (**BCM**) for increased sensitivity [a high-throughput technique as FIA–MS/MS*
2nd: Biochemical test with definitive cut off value of BCM has increased specificity as **HPLC-MS/MS#**
3rd: Genomic study for confirming the diagnosis
*FIA–MS/MS- Flow injection analysis tandem mass spectrometry, #- HPLC- high-performance liquid chromatography

Genetic counselling for case II:5 & III:5 -
Step 1: Confirm the Phenotype in II**:6 & II:7**
Step 2: Explain the disease phenotypes & **pleiotropy** (effect of various unrelated body systems due to a disease)
Step 3: Discuss possible disease course & management plan alongside their limitation
Step 4: Family should be given time to discuss & imbibe; & follow up appointment
Step 5: Psychological referral

Thought Riveting:

- ***Is there any accurate phenotypic predictor for a specific ABCD1 gene mutation?***
- ***What could be the different modifier pathways for the variable phenotype of ALD among females?***
- ***Can there be separate newborn screening strategies for low resource centers for ALD?***
- ***What is the alteration in cell membrane function with high-level circulatory VLCFA?***
- ***How is an alteration in the plasma membrane microviscosity beneficial in early or late-onset metabolic syndromes?***
- ***Theoretically, what other disorders could benefit from "Lorenzo's oil"?***

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