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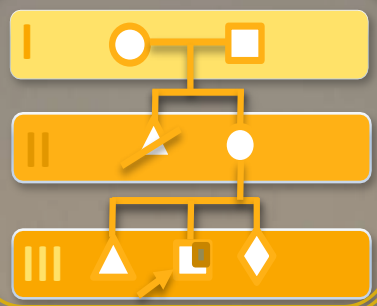

From the desk of Editor

The genetic division of the Pediatric Department publishes a monthly newsletter for all Medical Professionals. The newsletter is related to genealogical parlance and is a deliberate attempt to enhance awareness of genetic disorders with recent updates.

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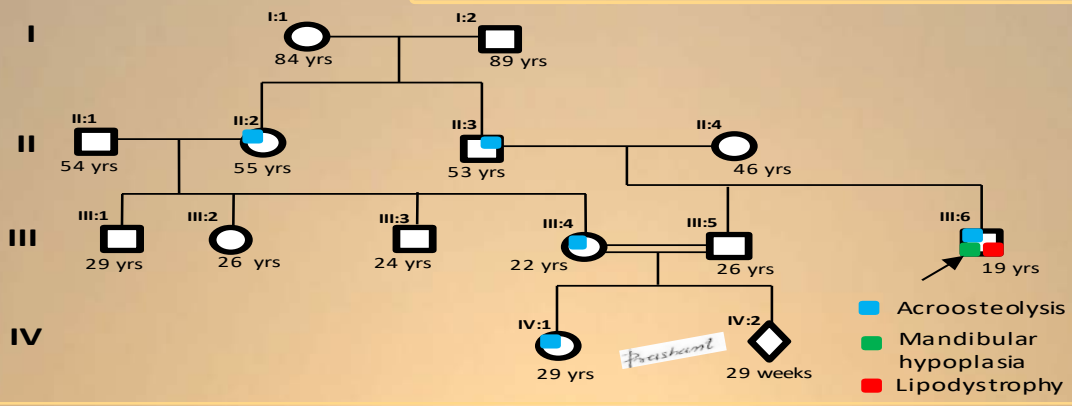
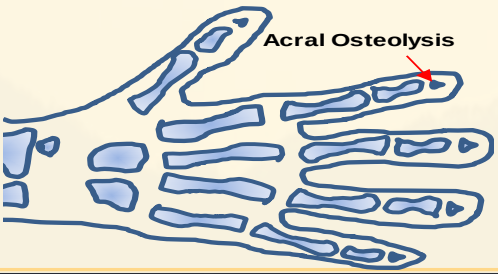
Progeroid Syndromes Like (PSL)-III / LAMIN A/C related disorders/ Mandibuloacral dysplasia type A lipodystrophy (MADA)



Acro-osteolysis



- Acro: tip/end; and osteolysis: bone resorption
- Radiologically diagnosed as distal phalangeal and clavicle osteolysis
- Etiologies: congenital or acquired (external or internal causes)
- Swelling (Clubbing) or atrophic changes in adjacent tissues
- Classification: (A) Based on radiological changes noticed in the bone (three types): terminal tuft (longitudinal type), midshaft (transverse type), and both together (longitudinal & transverse bone reabsorption); (B) Anatomical involvement: Localize versus systemic, single digit versus multiple, upper limb versus lower limb, or both

Insight:

1. Why is it called mandibuloacral dysplasia?
2. What are the principal differences between MADA and Hutchinson-Gilford progeria?
3. How would you counsel the family for Case IV: 2?
4. What is the possible explanation for acro-osteolysis?
5. How would you approach a case of acro-osteolysis?

Plausible tenets:

- **Osteolysis:** over activity of osteoclasts leads to the destruction of bone matrix over time.
- **Osteolysis with Laminopathies:** Probably by significantly higher levels (approximately 4.7-fold) of the active enzyme forms of **MMP9 (metalloproteinases).**
- OMIM search shows 37 entries by "osteolysis" with clinical synopsis, **33 entries** with **"acro-osteolysis OR acroosteolysis,"** and **seven entries besides laminopathies** (Mandibuloacral Dysplasia with Type A Lipodystrophy, Restrictive Dermopathy 2, MADA, Lipodystrophy, Familial Partial, Type 2; FPLD2, & Hutchinson-Gilford progeria) with **"clavicle AND acro-osteolysis OR acroosteolysis".**

Syndromes with clavicle anomaly AND acro-osteolysis OR acroosteolysis:

No.	Phenotype	MIM No.	Gene / Function / **MOI**	Additional key findings
1.	Pycnodysostosis [from Greek: πυκνός (puknos) meaning "dense", Dys ("defective"), and ostosis ("condition of the bone"]	#265800	Cathepsin K gene (CTSK)/ cysteine proteinases in osteoclast cells/ **AR**	Growth hormone therapy in selected cases
2.	**Mandibuloacral Dysplasia With Type B Lipodystrophy; MADB**	#608612	ZMPSTE24/ an endoprotease, conversion of prelamin A/ **AR**	Renal involvement, skin nodules
3.	Multicentric Carpotarsal Osteolysis Syndrome; MCTO	#166300	MAFB/ dual function transcription factors/ **AD**	CKD, JRA like radiological pictures
4.	Hypertrophic Osteoarthropathy, Primary, Autosomal Recessive, 1; PHOAR1	#259100	HPGD/ 15-hydroxyprostaglandin dehydrogenase (degradation of PGs) / **AR**	Marfanoid habitus, furrowing of the forehead, large clavicle
5.	Osteosclerotic Metaphyseal Dysplasia; OSMD	#615198	LRRK1/ maturation of osteoclasts/ **AR**	Osteosclerosis of clavicle & other bones, raised AST
6.	Cleidocranial Dysplasia 1; CLCD1	#119600	RUNX2/ Transcription factor, maturation of osteoblasts/ **AD**	Not a true acro-osteolysis
7.	Melnick-Needles Syndrome; MNS	#309350	FLNA/ interacting filaments at various level/ **XLD**	Short clavicles, cleft palate, CHD

- Other more specific head-toe findings with MADA **besides common laminopathies phenotypes include** wormian bones, wide cranial sutures, micrognathia, mandibular hypoplasia, progressive osteolysis of the distal phalanges and clavicles (acroosteolysis), hypoplastic clavicles, **hypomorhic progeroid phenotypes**, and restricted joint mobility.
- Overlapping phenotypic syndromes: Hajdu-Cheney syndrome (**NOTCH2**), Hallermann-Streiff syndrome (?), Gottron type acrogeria (?), Werner syndrome (**RECQL2**)

- **Matrix MetalloProteinase 9(MMP9), Gelatinase B (**GELB): a zinc metalloprotease, helps in leukocyte migration besides having proteolytic enzymes activities against extracellular matrix proteins (PubMed: 1480034, 2551898, and 12879005), like bone matrix resorption by cleavage of various collagen fibers**.**
- Phenotype: **Metaphyseal anadysplasia 2 (Ana = prefix meaning return), (MOI-AR),** an early-onset metaphyseal dysplasia with spontaneous regression with age: infantile genu varum (bowlegs) with scoliosis, and metaphyseal fraying of the distal femurs and distal tibias. **Post-toddlerhood, all abnormalities start to resolve themselves without affecting the final height.**

Counsel the family for antenatal diagnosis of case IV: 2- At 29 weeks, without abnormalities in all previous antenatal investigations, we need to re-evaluate for specific anomalies as directed by an expert. Phenotyping of the proband and all other affected family members can help to reach a clinical impression. Possibilities for disease in the fetus cannot be discussed during counseling without a confirmed diagnosis; it can significantly affect fetal and maternal health. Additionally, discussion on possibilities without evidence can have consultation irregularities and legal implications.

Thought Riveting:

- *Is aging a slowly adaptive cellular behavior against the surrounding environment of the cell?*
- *How could aging be reversed in a specific environment, specifically in the absence of mutagenic or extreme environmental situations?*
- *Can specific viral infections accelerate or deaccelerate the aging process?*
- *What is the effect of a high MMP9 levels on the cellular level in other tissues? Is there any role for a MMP9 inhibitor* ***(CAS number 1177749-58-4) or Mangiferin****?*
- *Can augmentation of the* ***ZMPSTE24*** *protein rescue the LMNA-associated phenotype?*