A rare cause of hypophosphatemia: Raine Syndrome

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- A 9-month-old male was referred for hypophosphatemia
- Birth weight of 3800 g from non-consanguineous parents
- Prenatal USG demonstrated nasal bone agenesis
- Family history was unremarkable
- Tracheostomy at 48 days of age
- Percutaneous endoscopic gastrostomy at 5.5 months of age
- Ventriculoperitoneal shunt operation at 9 months of age
- At presentation, his height at -1.1 SDS, weight at -2.14 SDS, and head circumference at -0.62 SDS.
- Physical examination:
  - ✓A large anterior fontanel (5x6 cm),
  - ✓Frontal bossing,
  - ✓Exophthalmos, corneal opacification
  - ✓Hypoplastic nose,
  - ✓High arched palate,
  - ✓Low set ear,
  - ✓Triangular mouth
- The ophthalmological examination: Optic atrophy.
- Skeletal X-rays *(Figure):*
  - ✓Diffuse osteosclerosis at birth
  - ✓Gradually resolved by the age of 5 months
    - ✓Medullary space of long bone could be distinguishable with bone-in-bone appearance.
  - ✓At 9 month of age hand X-ray revealed cupping of ulna with loose radial bone margin with minimal fraying and osteopenia.
- Cranial CT scan showed bilateral periventricular calcification with cerebral atrophy *(Figure)*.
- After an initial assessment, oral phosphate and calcitriol therapy were initiated.
  - ✓No significant improvement was observed in laboratory findings during the six-month follow-up despite of good compliance, gradual dose increase and close follow-up *(Table)*
  - ✓But, ALP decreased and rickets signs improved on radiographs
- The clinical, laboratory and radiological examinations were consistent with RS.

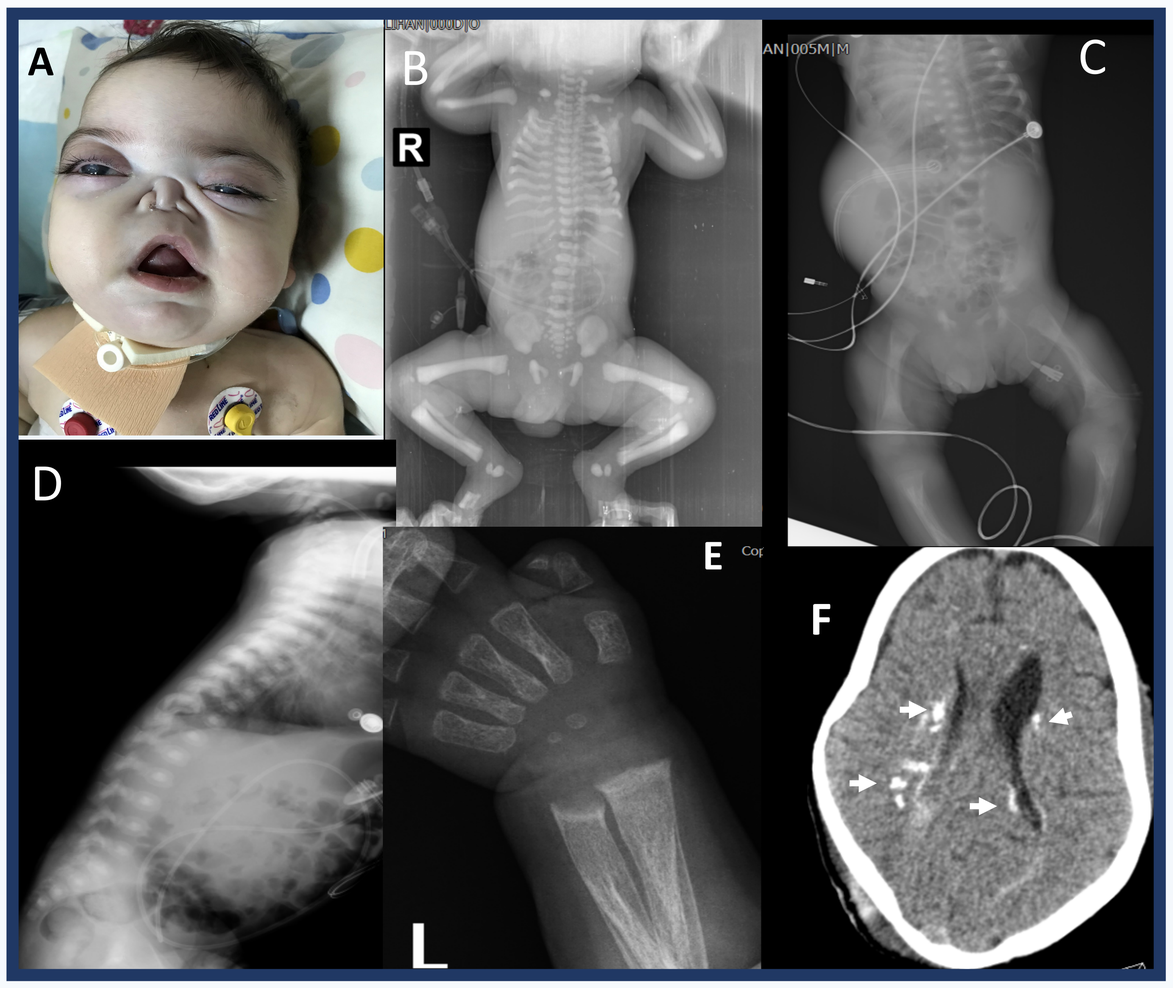

Figure. (A) Typical facial dysmorphism at 9-month-old, (B,C) Osteosclerosis at newborn and 4 month-old respectively, (E) cupping of ulna with loose radial bone margin with minimal fraying and osteopenia and bone in bone appearances at 9 month-old (D ,E) (F) bilateral periventricular calcification with cerebral atrophy at 9 month-old

Table. Laboratory follow-up of the patient

	First Evaluation (9 month-old)	15. Day	1.month	1,5. month	2. month	3. month	4. month	5.month	6. month
P (mg/dL) (4-6.5)	2	2.3	1.7	2.4	2.6	2.8	3.3	2.5	2.2
Ca (mg/dL) (9-11)	9.6	9.9	8.6	9.9	9.4	10.1	9.4	9.2	10.1
ALP (U/L) (116-450)	950	745	280	380	467	671	575	329	561
PTH (ng/L) (15-65)	84.47	142	119.1	86.04	86.97	58.15	95.48	-	73.8
25-OHD (ug/L) (30-100)	28.05	23.63	20.69	-	38.28	33.29	33.03	22.53	30.61
Spot urine Ca/Cr (0.03-0.8 mg/mg)	0.22	0.06	0.007	0.06	-	0.3	0.06	0.007	0.18
TRP (%85-100)	94	87.5	94.7	86.7	-	91.8	89.2	88.3	66
TmP/GFR (4.8-8)	2.31	2.02	2	2.04	-	2.9	3.09	2.26	1.46
Calcitiriol(µg)/Phosphorus (mg/kg)	-	0.25/ 30	0.25/ 30	0.5/ 35	0.75/ 35	0.75/35	0.75/ 40	1.0/40	1.0/45

Molecular analyses

✓ Compound heterozygous mutation in *FAM20C* gene (a known pathogenic mutation, c.1645C>T, p.Arg549Trp; and a novel mutation, c.863+5G>C)

Learning Points:

✓ Although rare, RS should be considered in differential diagnosis of hypophosphatemia in patients with typical craniofacial abnormalities.

✓ Inactivating mutations of *FAM20C* gene may cause non-lethal RS and hypophosphotemia without typical craniofacial abnormalities.