Clinical and Genetic Characterization of Tunisian Children with Hereditary Hypophosphatemic rickets (HHR).

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INTRODUCTION

• Hypophosphatemic rickets (HHR) is a vitamin D-resistant rickets and results in children in variable degrees of delayed walking, waddling gait, leg bowing, enlarged cartilages, bone pain, craniostenosis and growth failure.

• There are both inherited and acquired forms, where FGF23-dependent forms with X-linked dominant hypophosphatemic rickets (XLH) head of the list is the most prevalent genetic form; molecular defects of the sodium-phosphate co-transporter NPT2c unrelated to a FGF23 disturbance may cause hypophosphatemic rickets with hypercalciuria (HHRH).

PATIENTS AND METHODS

We report four cases of HHR and retrospectively studied the clinical features, laboratory findings, genetic defects, as well as responses to treatment.

RESULTS

Four patients from 2 families one case with yet described FGF23-activating mutation and Three related cases with new mutation of the SLC34A1 gene witch encodes the type II sodium-dependent phosphate co-transporter NPT2a

Case N° 1 :

•Rania is a girl who has been diagnosed at the age of 2 years and 10 months due to a gait disorder. She was from a non-consanguineous marriage and Vit D was taken correctly according to the Tunisian protocol against rickets (i.e: 200.000 UI of Vit D3 respectively at 15 days, 6 month, 1 year an 18 months old). The clinical, radiological and biological assessment was compatible with hypophosphatemic rickets without hypercalciuria. In fact laboratory evaluation disclosed hypophosphatemia (0,87 mmol/l) but normal age-adjusted serum levels of calcium (2.27 mmol/l), serum 25-hydroxyvitamin D [25(OH)D] (63 nmol/l), serum 1,25(OH)2D (53 pmol/l) and PTH (36 pg/ml); Total alkaline phosphatase was elevated at 2400 UI/l (60–485 U/l). The fasting tubular reabsorption of phosphate (TRP) was low at 57%(<80%). The radiological assessment was characteristic (fig1,2and 3). The genetic study confirmed the diagnosis of Autosomal dominant hypophosphatemic rickets with heterozygous mutation (p.Arg179Trp) on Exon 3 of the FGF23 gene. The child was supplemented by Phosphate : 30 mg/kg/day and Un-alfa 0,1µg : 35 ng/kg/day and the follow-up was marked by a partial improvement of rickets (fig 4).

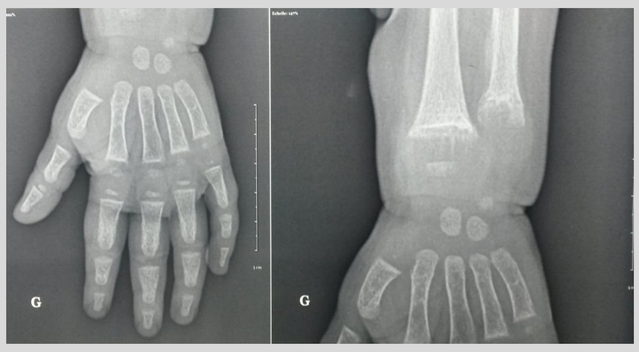

Figure 1: X-ray of the left wrist : cupping and flared appearance of the metaphyses.

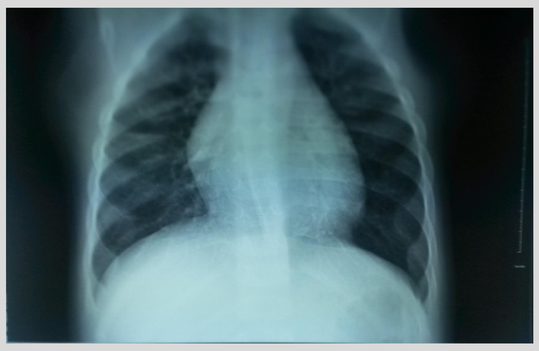

Figure 2: frontal chest x-ray: widening of the chondrocostal junctions without cortical bone demineralization.

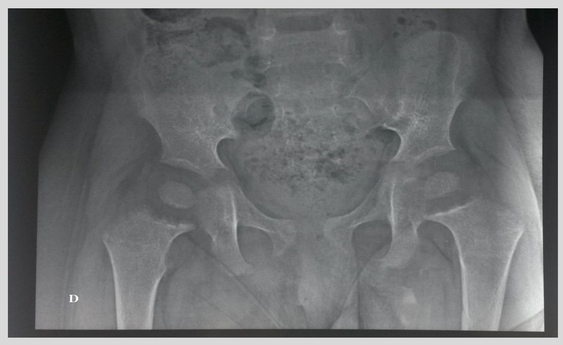

Figure 3: pelvic x-ray square iliac wings and enlargement with abnormalities of the femoral necks.

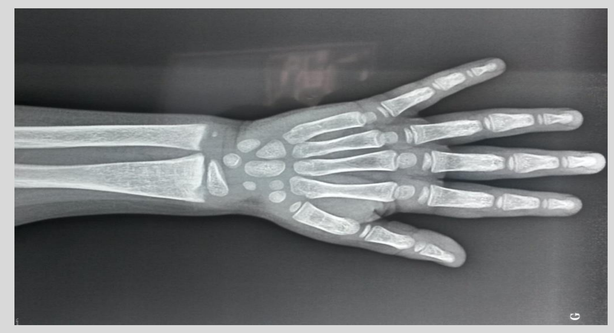

Figure 4: radiography of the left hand and wrist after 2 years of follow-up: radiological improvement, although irregularity in the radioulnar metaphyses coexists.

Case N° 2, 3 and 4 :

• Three children (two girls and one boy) who are from the same family.Vit D was taken correctly according to the Tunisian protocol against rickets. Hypophosphatemia was found in both children and parents, and in the latter was also found the concept of urinary lithiasis . The diagnosis was made in the two sisters after the age of two years and their clinico-biological tables were compatible with hypophosphatemic rickets with hypercalciuria. The radiological assessment was characteristic (fig5) and kidney ultrasounds showed severe bilateral nephrocalcinosis. At the brother's, the diagnosis was suspected at the age of two months in front of the family history and the discovery of a nephrocalcinosis. The boy has the peculiarity of having his renal function already altered at the first evaluation. The genetic study carried out in one of the two girls as well as in the boy, confirmed the diagnosis of HHRH, of recessive transmission, showing a homozygous mutation in the SLC34A1 gene. At the present state of our knowledge, this is the first mutation in the SLC34A1 gene causing HHRH, which is reported in the literature.

•The evolution was fatal for the older sister related to poorly therapeutic adherence.The other siblings was supplemented by phosphate: (30mg / kg / day) and the evolution was marked on 3 years-follow-up by an acceleration of growth velocity (see growth curve, fig.6)), disappearance of epiphyseal bulges and absence of limb deformity. On the radiological level, rickets were improved and ultrasonographic control showed an improvement in nephrocalcinosis from stage 3 to stage 2

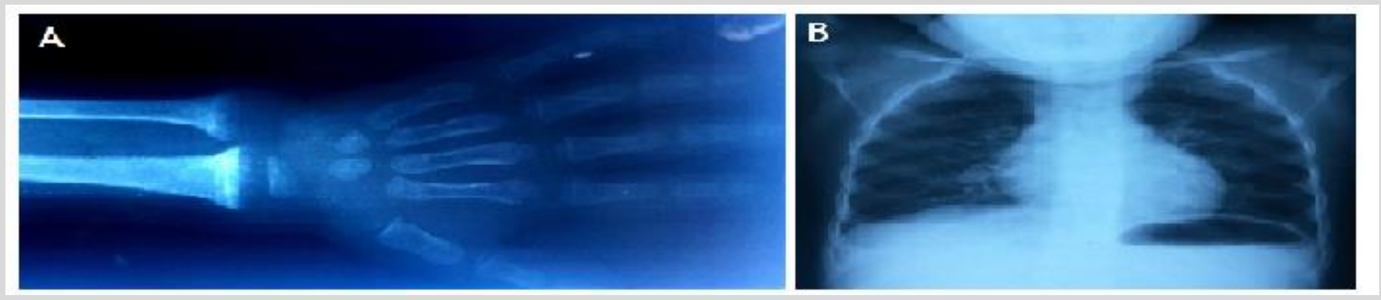

Figure 5: radiological assessment at first evaluation of case 2 . A: X-ray of the left wrist : Widening and cupping of the metaphyseal regions of the radius and ulna bones .B : chest X-ray: Enlargment of costochondral junction of ribs giving the appearance of beads, .

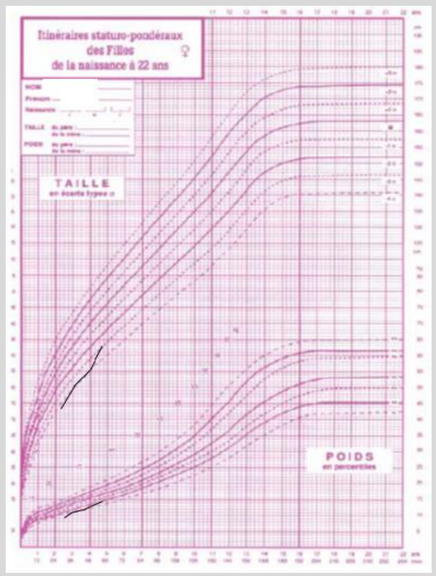

Figure 6: growth curve of the second girl with phosphate supplementation .

CONCLUSION

- On clinical, radiological and biological level our cases are representative for 2 different genetic forms of hypophosphatemic rickets.
- These results confirm the role of FGF23 in ADHR physiopathology and report for the first time HHRH caused by a homozygous SLC34A1 mutation, thereby further documenting the key role of the renal cotransporter NPT2a in the phosphocalcic metabolism.

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Bone, growth plate and mineral metabolism

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