INCREASED PREVALENCE OF OVERWEIGHT AND OBESITY AND ITS CLINICAL PREDICTORS IN CHILDREN AFFECTED BY X-LINKED HYPOPHOSPHATEMIA

Volha V. Zhukouskaya[1,2], Anya Rothenbuhler[1,3], Annamaria Colao[2], Carolina Di Somma[2,4], Peter Kamenicky[1,5,10], Séverine Trabado[6,10], Dominique Prié[7,8], Christelle Audrain[1], Anna Barosi[1], Christèle Kyheng[9], Anne-Sophie Lambert[1,3], Agnès Linglart[1,3,10]

Affiliations:

[1]APHP, Reference Center for Rare Disorders of the Calcium and Phosphate Metabolism, Filiere OSCAR and Platform of expertise for rare diseases Paris-Sud, Bicêtre Paris-Sud Hospital, Le Kremlin Bicêtre, France; [2]Department of Clinical Medicine and Surgery, Division of Endocrinology, University of Naples Federico II, Naples, Italy; [3]APHP, Department of Endocrinology and Diabetology for children, Bicêtre Paris Sud Hospital, Le Kremlin- Bicêtre, France; [4]IRCCS SDN, Naples, Italy; [5]APHP, Department of Endocrinology and Reproductive Diseases, Bicêtre Paris Sud Hospital, Le Kremlin- Bicêtre, France; [6]APHP, Department of Molecular Genetics, Pharmacogenetics and Hormonology, Bicêtre Paris-Sud Hospital, Le Kremlin Bicêtre, France; [7]Université Paris V, Faculté de Médecine, Paris, France; [8]Hôpital Necker Enfants Malades APHP, INSERM U1151, Paris, France; [9]APHP, Department of Adolescent Medicine, Bicêtre Paris Sud Hospital, Le Kremlin- Bicêtre, France; [10]Paris Sud – Paris Saclay University, Faculté de Médecine, Le Kremlin- Bicêtre, France.

Background / aim

- **X-linked hypophosphatemia (XLH**) is a rare disease caused by inactivating mutations in the phosphate-regulating endopeptidase homolog X-linked (*PHEX*) gene, characterized by **chronic hypophosphatemia** (1-2)
- Clinically, XLH patients are characterized by progressive skeletal deformities (leg bowing, poor growth, disproportional short stature), dental abscesses, craniosynostosis and typical radiographic changes of rickets *(Figure 1)* (1-2)
- Most affected children have been treated so far with multiple daily phosphate supplements and oral active vitamin D analogs. This therapy corrects clinical, biochemical and radiographic signs of rickets, nonetheless, does not restore stable level of serum phosphate (1)
- Scientific evidences support **the role of serum phosphate level in fat mass acquisition, i.e. obesity, in the general population**. Elevated Body Mass Index (BMI) is recurrently reported in series of adult XLH patients (3). In addition, XLH patients display chronic hypophosphatemia despite treatment
- Therefore we decided to address the clinical metabolic phenotype, beyond the abnormal skeletal phenotype, in children affected with XLH

The aim of our longitudinal observational study was to investigate the prevalence of obesity and associated factors in a large cohort of children with XLH

Patients / methods

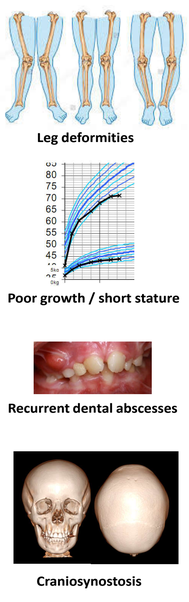
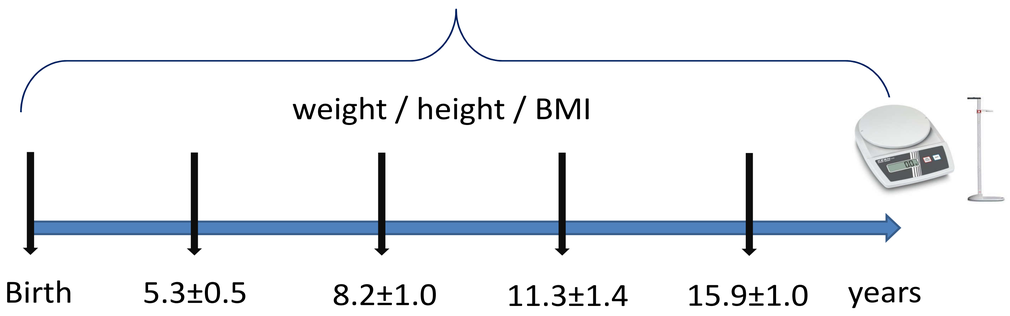


Figure 1

172 children affected by XLH (113 girls / 59 boys) of age 5-20 years

Longitudinal follow-up of anthropometric parameters



In each age group, subjects were classified based on International Obesity Taskforce (IOTF) cut off values of BMI for age and sex as overweight or obese (IOTF 25-30 or ≥30 kg/m2, respectively)

Results

I. Description of the cohort of children affected by XLH

Parameter	Absolute number or % (n) or Mean±SD
Number of subjects	172
Boys / girls	34.3 (59) / 65.7 (113)
Subjects carrying a *PHEX*-mutation	88.4 (130)
Subjects with positive XLH-family history	59.7 (92)
Diagnosis of XLH, years	3.0±2.9
Duration of follow-up, years	10.9±4.0
Gestational age, weeks	39.0±1.3
Birth weight, kg (SDS)	3.3±0.5 (0.0±0.0)
Birth length, cm (SDS)	49.5±2.1 (0.4±4.2)
Subjects born SGA	6.9 (9)

II. Prevalence of overweight/obesity in XLH:

in each age-group, almost 1/3 of XLH-patients are classified as overweight / obese (29.4% → 28.7% → 27.5% → 36.7% for each age-group) *(Figure 2)*

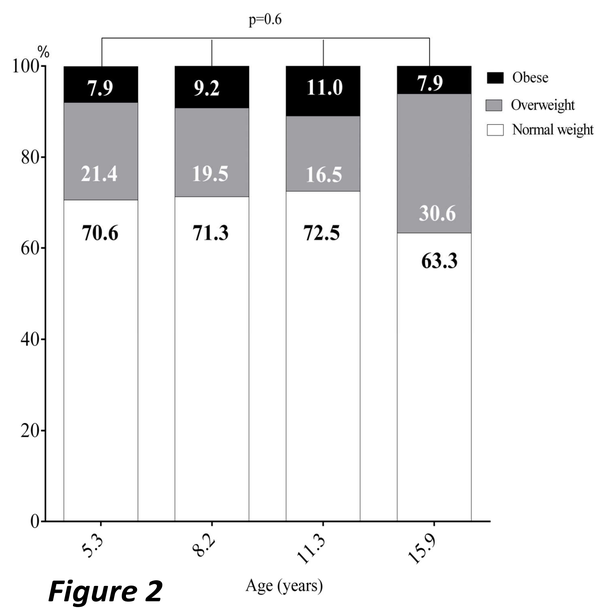


Figure 2

III. Evolution of BMI-SDS in XLH:

both girls and boys showed a similar pattern of BMI-SDS evolution characterized by stable trend nearby +1.0 SDS over time *(Figure 3)*

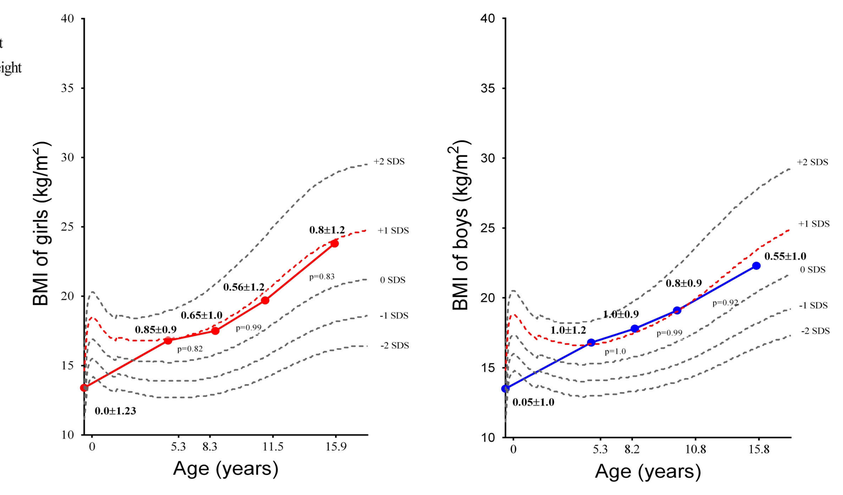


Figure 3

IV. Evolution of BMI-IOTF in XLH:

trend of progressive increment of BMI-IOTF over time *(Figure 4)*

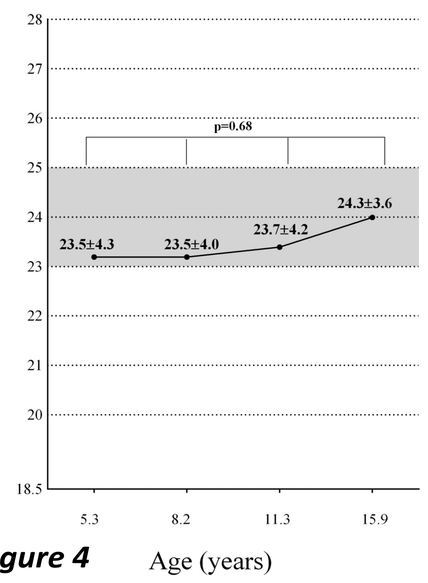


Figure 4

V. Clinical factors associated with higher BMI-IOTF in XLH:

- Children without XLH-family history have higher BMI-IOTF at every point of follow-up, compared to those with positive XLH-family history ***(****Figure 5)*
- BMI-IOTF is increasing with increment of treatment duration *(Figure 6)*
- Multiple regression analysis confirmed that treatment length and lack of XLH-family history are positively associated with higher BMI-IOTF (β=0.17, 95%CI=0.30-1.73, p=0.005 for treatment length; β= -0.13, 95%CI= -0.12 - -2.21, p=0.029 for XLH-family history)

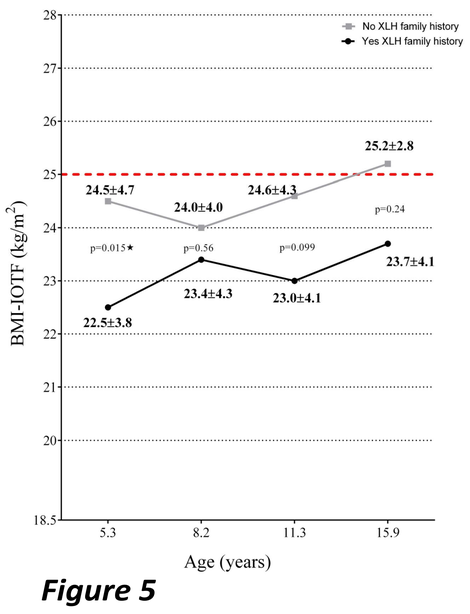


Figure 5

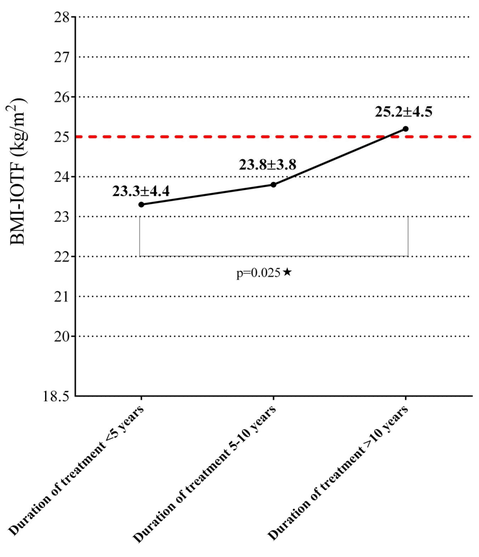
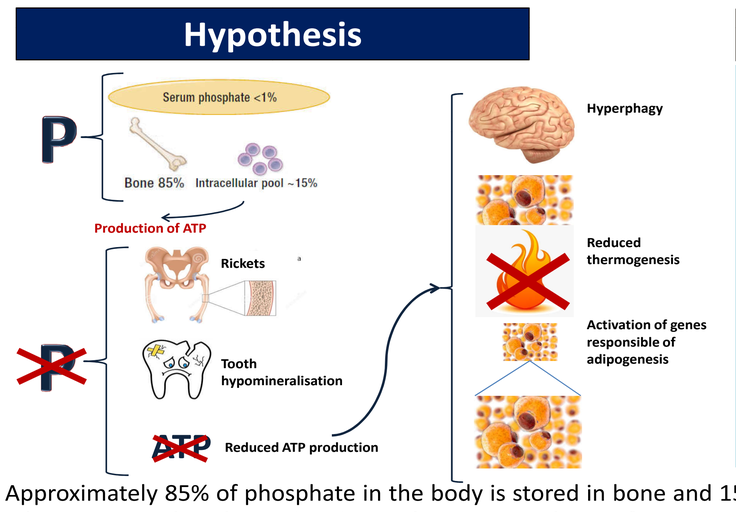


Figure 6

Hypothesis

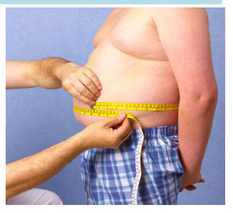


Approximately 85% of phosphate in the body is stored in bone and 15% in the intracellular space (2) which is needed for adenosine triphosphate (ATP) production. Decline of ATP production, especially at hepatic level, due to hypophosphatemia, transduces the signals to the central nervous system which leads to increased food intake. Secondly, low ATP production decreases thermogenesis and energy expenditure (3). Animal models (4) demonstrated that high-phosphate diet suppresses the activity of white adipose tissue by increasing lipolytic gene expression and decreasing lipogenic gene expression, and vice versa. Thus, this is a hypothesis on how low phosphorus status may contribute to the development of obesity through the regulation of food intake, thermogenesis and energy expenditure.

Regardless of conventional therapy in XLH, however, chronic phosphate supplementation is not sufficient to restore the phosphate deficit in bone tissue and in other cells at the same time, thus, leading to progressive fat mass gain in XLH.

Conclusion

1) Almost 1/3 of XLH-children have phenotypically unfavourable metabolic profile expressed as progressively increased prevalence of overweight/obesity , despite phosphate supplementation
2) Lack of XLH family history and length of treatment could be considered as clinical factors associated with higher BMI-IOTF
3) BMI should be carefully followed in children, and later in adults, with XLH



1. Linglart A et al. Endocrine Connections 2014
2.Kinoshita Y et al. Endocrine Reviews 2018
3. Obeid OA. Obesity reviews 2013
4. Imi Y et al. J Clin Biochem Nutr 2018

58ESPE P1-023

Bone, growth plate and mineral metabolism

Volha Zhukouskaya

Poster presented at: ESPE 2019 VIENNA

PosterSessionOnline.com