Fibroblastic growth factor 23 in infantile rickets

Protocol of a thesis

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CONTENTS

List of abbreviations

ADHR	Autosomal dominant hypophosphatemic rickets
ALP	Alkaline phosphatase
ARHP	Autosomal recessive hypophosphatemea
Ca	Calcium
CRF	Chronic renal failure
CSF	Cerebrospinal fluid
FGF-23	Fibroblastic growth factor 23
FGF-7	Fibroblastic growth factor 7
FHR	Familial hypophosphatemic rickets
HHRH	Hereditary hypophosphatemic rickets with hypercalciuria
HR	Hypophosphatemic rickets
Pi	Inorganic phosphorus
PHEX	Phosphate regulating gene with homologus to endopeptidase on the X-chromosome
PTH	Parathyroid hormone
PTR	Phosphorus tubular reabsorption
rhGH	Recombinant human growth hormone
sFRP-4	Secreted frizzed-related protein 4
TC	Tumor calcinosis
TIO	Tumor induced osteomalacia
XLH	X-linked hypophosphatemic rickets

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Introduction

Rickets is a disorder causing mineralization defect and bone and skeletal fragility, although production of bone matrix proteins and their architecture is not impaired. The disease is called rickets in children during skeletal development, respectively. Pathophysiology in rickets is defect in vitamin D actions and/or hypophosphatemia. Vitamin D deficiency, inability of activation of vitamin D in vivo or functional derangement in vitamin D receptor is involved in impaired actions of vitamin D **(Takeuchi Y 2007)**.

Avariety of factors regulate the efficiency of phosphate absorption in the intestine and phosphate reabsorption in kidney. Apart from the well- known regulators of phosphate homeostasis, namely parathyroid hormone and the vit D-endocrine system, a number of peptides collectively known as the "phosphatonins" have been recently identified as a result of the study of various diseases associated with hypophosphatemia. These factors, fibroblastic growth factor 23 (FGF23) , secreted frizzled-

related protein 4 (sFRP-4), fibroblast growth factor 7 (FGF-7) and matrix extracellular phophoglycoprotein (MEPE) , have been shown to play a role in the pathogenesis of various hypophosphatemic disorders. **(Shaikh A, et al Berndt T,2008)**

Fibroblast growth factor (FGF) 23 is a humoral factor that reduces serum phosphate and 1,25-dihydroxyvitamin D [1,25 (OH)(2)D] levels at least in part by suppressing proximal tubular phosphate reabsorption and 1,25 (OH)(2)D production. Measurement of circulatory FGF23 levels seems to be useful for diagnosis of these hypophosphatemic diseases. Novel therapeutic methods for these diseases may be developed by finding maneuvers to modulate FGF23 actions **(Fukumoto S. 2007).**

Hypothesis and Aim of the work

Fibroblast growth factor 23 (FGF 23) was described with the hypophosphatemic congenital rickets. What is the possible situation with vitamin D deficiency rickets that is known to be associated with hypophosphatemia?

The aim of this study is to estimate the levels of FGF 23 among infants suffering from vitamin D deficiency rickets and find out its relation to different variables.

Background

The origin of the word "rickets" is probably from the old English dialect word 'wrickken', to twist. The Greek derived word "rachitis" (meaning"inflammation of the spine") was later adapted as the scientific term for rickets, due to the words similarity in sound ***(Wekipedia, 2009).***

Rickets is softening of bones in children potentially leading to fractures and deformity. Rickets is among the most frequent childhood diseases in many developing countries. It reached epidemic proportions following the industrial revolution, which began in the 1750s. In the 19th century, before the importance of exposing children to sunlight was recognized, the majority of children that lived in cities with sunless, narrow alleyways and pollution developed rickets. An autopsy study done in Boston in the late 1800s showed that more than 80 percent of children had rickets ***(Miller, 2007).***

Rickets is a disease of growing bone that is unique to children and adolescents. It is caused by a failure of osteoid to calcify in a growing person. Failure of osteoid to calcify in adults is called osteomalacia. Vitamin D deficiency rickets occurs when the

metabolites of vitamin D are deficient. Less commonly, a dietary deficiency of calcium or phosphorus may also produce rickets. Vitamin D-3 (cholecalciferol) is formed in the skin from a derivative of cholesterol under the stimulus of ultraviolet-B light. Ultraviolet light or cod liver oil was the only significant source of vitamin D until early in the 20th century when ergosterol (vitamin D-2) was synthesized from irradiated plant steroids.

During the Industrial Revolution, rickets appeared in epidemic form in temperate zones where the pollution from factories blocked the sun's ultraviolet rays. Thus, rickets was probably the first childhood disease caused by environmental pollution ***(Greer and Laurence, 2008).***

Causes of Rickets:

Vitamin D Disorders

- Nutritional Vit D deficiency
- Secondary Vit D deficiency eg. Anticonvulsants therapy and endocrinal disorders.
- Vit D dependent rickets type 1

- Vit D dependent rickets type 2
- Chronic renal failure

Calcium Deficiency

- Low intake
- Malabsorption

Phosphorus Deficiency

- Inadequate intake

Renal Losses

- X-linked hypophosphatemic rickets
- Autosomal dominant hypophosphatemic rickets
- Hereditary hypophosphatemic rickets with hypercalciuria
- Overproduction of phosphatonin
- Fanconi syndrome

Renal Tubular Acidosis

(Greenbaum, 2007)

Differential Diagnosis

• Rare metabolic bone diseases, including hypophosphatasia have been confused with rickets in infancy.

• Jansen syndrome is a rare autosomal dominant form of short-limbed dwarfism in which infants present with metaphyseal chondroplasia.

• Severe calcium deficiency can also cause a syndrome that is confused with vitamin D deficiency rickets.

• In premature infants, severe phosphorus deficiency that occurs when human milk is used without mineral fortification presents with rickets.

• Hereditary disorders of vitamin D metabolism have also been described, such as hypophosphatemic vitamin D-resistant ricket ***(Greer, 2004).***

Vitamin D Deficiency Rickets

Vitamin D deficiency has re-emerged as a significant paediatric health issue, with complications including hypocalcaemic seizures, rickets, limb pain and fracture.