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Case Report

A 3 Years Old Boy with Transitory Hyperphosphatasemia, Short Stature, and Dysostosis Multiplex

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Abstract

Transient benign childhood hyperphosphatasemia (TBCH) affects children under five years of age, with no evidence of bone, liver or endocrine disease. The serum alkaline phosphatase can reach serum levels 2 - 50 times higher than the reference values for age. The return to normal occurs in an average period of four months.

Mucopolysaccharidoses type IV A (MPS IVA) or Morquio disease, results from mutations in the gene encoding galactosamine-6-sulfatase (GALNS). Clinically, we can find short stature, pectus carinatum, kyphoscoliosis and genu valgum in the first year of life.

The association of these two diseases are not described in the literature.

A 3 years old boy was sent to Metabolic consultation, because his blood test showed a high level of alkaline phosphatase (AF), -794 U/L (n: < 281), with calcium/phosphorus metabolism and parathormone in the normal range. Urine calcium and phosphorus were also normal. The AF normalized after 3 months (186 U/L). This evolution was compatible with TBCH. He has on his physical examination, macrocephaly, short stature, pectus carinatum with chest costal eversion and genu valgum. Skeletal x ray and brain MRI showed signs of storage disease. Molecular study confirmed the diagnosis of MPS IVA, with positive GALNS gene; c.115 116delGA; pAsp39ArgfsX6; EX1/CDS1, chr16:88923170..88923171; homozygous, likely pathogenic.

Keywords: *Transitory Hyperphosphatasemia; Short Stature; Dysostosis Multiplex; Morquio*

Introduction

The mucopolysaccharidoses (MPS) are caused by the deficiency of enzymes required for the gradual breakdown of glycosaminoglycans (GAGS). The incidence of all types of MPS is around 1 in 20,000 live births.

The inheritance is autosomal recessive, with the exception of MPS I or Hunter disease which is X linked.

They are classified as types I, II, III, IV, VI, VII and IX. The signs and symptoms are usually not present at birth, only in severe form of MPS VII.

Skeletal abnormalities known as dysostosis multiplex is typical findings: The long bones are short and thick. The distal radius and ulna have an abnormal angulation. The clavicle is curved with widened ends. The acetabulum is flattened and the genu is valgum. The metacarpals are breaking as same as vertebral bodies. The ribs have a characteristic "oar shape" with narrowing from the vertebral column and a broadening of the anterior distal end.

The skull is large and deformed due to craniosynostosis, with a thickened calvarium and an abnormal "j" or boot-shaped sella turcica. The basilar skull fuse with the cervical vertebra and cause narrowed spinal canal.

Case Report

A 3 years old boy was sent to Metabolic consultation, because his blood test showed a high level of alkaline phosphatase (AF), - 794 U/L (n: < 281), with calcium/phosphorus metabolism and parathormone in the normal range. Urine calcium and phosphorus were also normal. The hemogram, thyroid function and the rest of the biochemical test, were all normal. The blood study was done because of his short stature (83 cm - Percentile < 3), low growth velocity (1 cm/year) and pectus carinatum with chest costal eversion. The period before or during this abnormal level of AF, no episode of fever or diarrhea were reported. The AF normalized after 3 months (186 U/L). All the other blood tests were normal.

His past history revealed 2 episodes of febrile convulsion at 15 and 24 months old, generalized tonic-clonic presentation.

The parents are young and unrelated. Mother height is 153 cm and has hypothyroidism. Father height his 165 cm. His older sister has 6 years old with normal height.

Our case born by spontaneous delivery, with 41 weeks of gestational age, with Birth weight - 3.550g, height -52 cm and head circumference - 35 cm. Apgar 10/10/10.

On physical examination, the weight was 11.8 kg (Percentile 3) and Height - 83 cm (Percentile < 3). Macrocephaly, thorax carinatum with costal margin eversion noted. No heart murmur was observed (Figure 1). MRI of the brain showed mega cisterna magna (Figure 2). Abdomen was normal too. Abdomen - no hepatosplenomegaly or distension. He has genu valgum. The boy has normal intelligent.

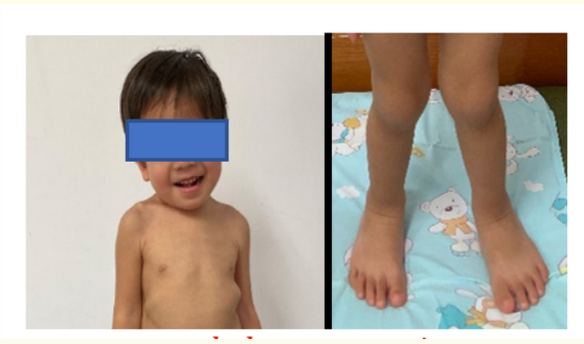

Figure 1: *Short stature, macrocephaly, pectus carinatum, genu valgum.*

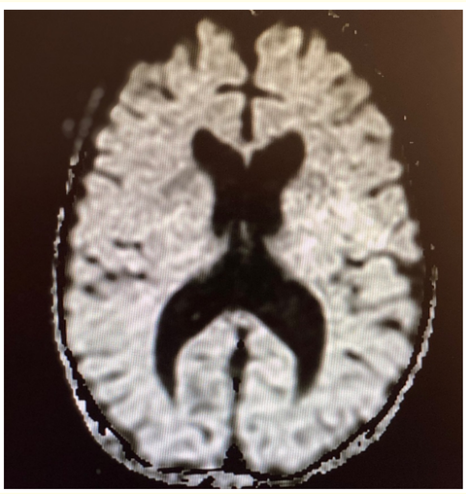

Figure 2: *Brain MRI - mega cisterna magna.*

Skeletal x ray revealed typical features of dysostosis multiplex with breaking metacarpals and lumbar vertebral bodies (Figure 3) genu valgum and flattened acetabulum (Figure 4). Cervical CT scan revealed flat cervical vertebra, hypoplasia of the odontoid process and the corresponding spinal canal is narrowed. Spinal stenosis in C1 (Figure 5). Abdomen ultrasound was normal. Heart echo showed mild redundant tricuspid leaflet with trivial regurgitation and also mitral regurgitation. GAGS in urine showed increase level: 31.5 umol/mmol Cr (n: < 15.7). Eyes and hearing screening examination showed normal result.

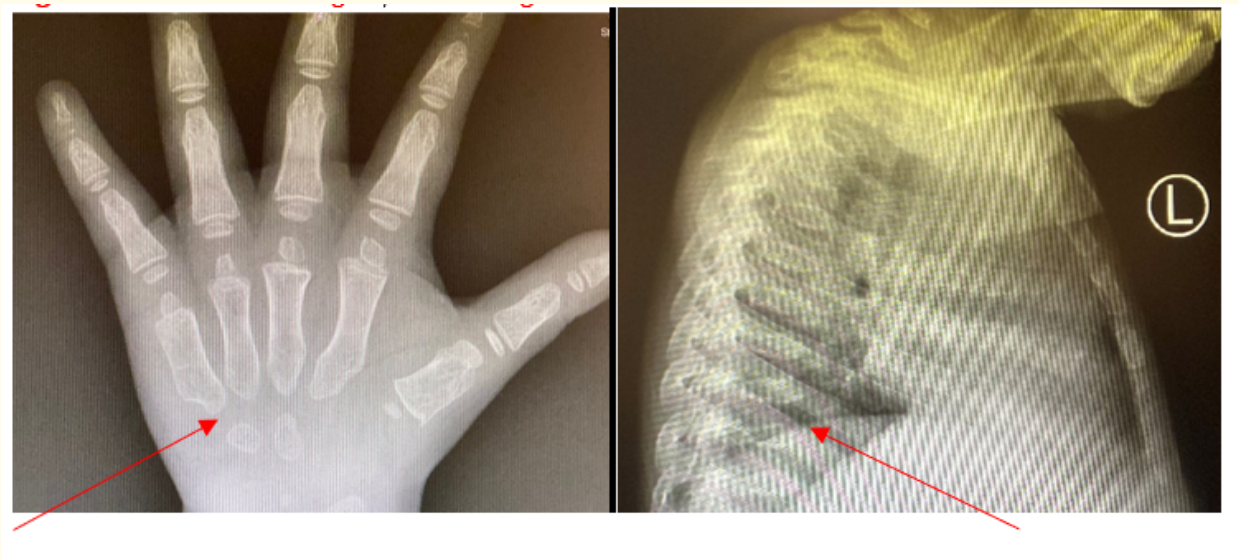

Figure 3: *Breaking metacarpals and lumbar vertebral bodies.*

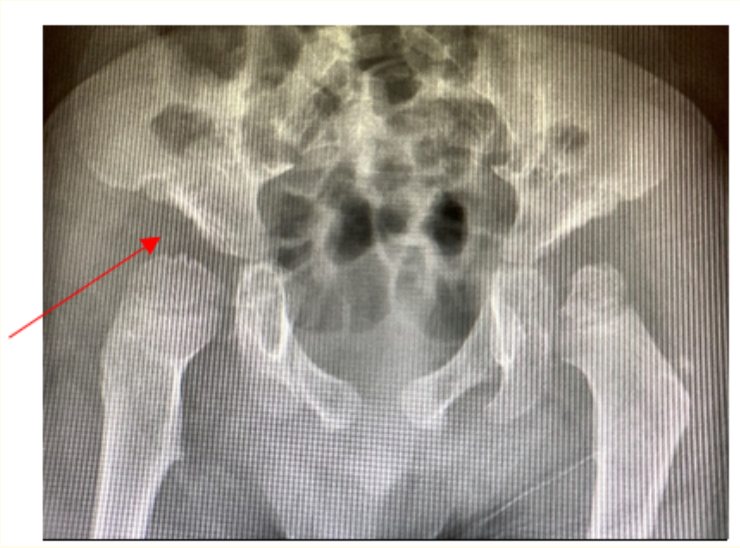

Figure 4: *Genu valgum and flattened acetabulum.*

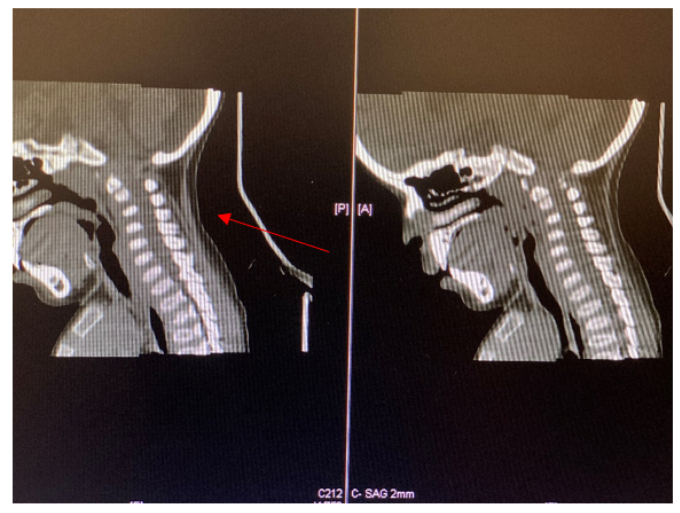

Figure 5: *Cervical CT scan revealed flat cervical vertebra, hypoplasia of the odontoid process and the corresponding spinal canal is narrowed. Spinal stenosis in C1.*

All clinical and radiological features pointed for a storage disease, like mucopolysaccharidoses type IV or Morquio disease. The DNA study confirm type A one: GALNS gene; c.115 116delGA; pAsp39ArgfsX6; EX1/CDS1, chr16:88923170..88923171; homozygous, likely pathogenic.

Discussion

The association of these two diseases, are so far not described in the literature.

Transient benign childhood hyperphosphatemia (TBCH) affects children under five years of age, with no evidence of bone, liver or endocrine disease, being characterized by the sudden and transient elevation of serum alkaline phosphatase in a healthy child alkaline phosphatase can reach serum levels 2 - 50 times higher than the reference values for age. The return to normal occurs in an average period of four months. Its etiology is still unknown, but the decrease in enzyme clearance circulation has been considered the most likely mechanism. There are reports in the literature relating the transient increase in alkaline phosphatase to upper airway infections or fever with diarrhea.

The diagnosis is usually made accidentally when requesting laboratory tests for other conditions. Our patient showed all laboratory evidence of TBCH but without a history of upper respiratory tract infection or fever with diarrhea. This was an accidental diagnosis like most cases in the literature [1].

Morquio disease or MPS IV has two types: A, more frequent and B that is less common. MPS IV A, results from mutations in the gene encoding galactosamine-6-sulfatase (GALNS), and MPS IV B is secondary to beta-galactosidase (GLB1) deficiency. The clinical features result from accumulation of keratan sulfate and chondroitin-6-sulfate. The incidences of MPS IV A and B are approximately 0.22 and 0.14 per 100,000 births, respectively. Clinically, at one year of age, we can find short stature, pectus carinatum, kyphoscoliosis and genu valgum. C1-C2 subluxation can result in cervical cord compression due to atlantoaxial instability and odontoid dysplasia, beginning with fatigue and progressing to weakness and later respiratory arrest. Mild corneal opacities, hepatosplenomegaly and valvular heart disease

may occur in Morquio disease. Some patients develop progressive hearing loss. Enamel hypoplasia is seen in MPS IV A but not IV B. In our case, the patient showed short stature, pectus carinatum, genu valgum, mild mitral and tricuspid regurgitation, but no eyes, hearing, liver or spleen involvement.

In MPS IV, analysis of urine may be negative, because keratan sulfate levels decline with age in this condition. In case of clinical suspicious, a normal GAGS in urine, will not rule out Morquio disease. Our case, the urine GAGS, was two times more than the reference level and associated with the clinical and radiological signs, was a good indicator for the diagnosis of MPS. Molecular analysis can be performed to confirm the diagnosis. Also can be used to identify carrier.

In our patient, the GALNS gene; c.115 116delGA; pAsp39ArgfsX6; EX1/CDS1, chr16:88923170..88923171; homozygous, although was likely pathogenic, all evidence was consistent with Morquio disease.

Patients brain magnetic resonance imaging (MRI) showed arachnoid cysts, enlarged cisterna magna, cerebellar hypoplasia, encephaloceles, and linear cyst-like structures in the subcortical white matter and corpus callosum. In our case, we found enlarged cisterna magna. Cervical CT scan of our patient showed all typical changes found in Morquio disease, with stenosis of C1, hypoplasia of odontoid process, spinal narrowed and flat cervical bodies.

Early cervical fusion is recommended in MPS IV patients and in other patients with cervical instability.

Deficient ossification of the superior acetabulum may result in progressive dislocation of the hip joint and erosions of the femoral neck. Joint replacement surgery is possible using a standard prosthesis [2,3].

The differential diagnosis is with other storage diseases, including the oligosaccharidoses (e.g. alpha- and beta- mannosidosis, fucosidosis, aspartylglucosaminuria), sphingolipidoses (e.g. Gaucher type II, Niemann Pick A), and mucolipidoses (e.g. I cell disease). Urinary analysis of glycosaminoglycans and oligosaccharides helps differentiate these disorders.

Elosulfase alfa (recombinant human N-acetylgalactosamine-6-sulfate sulfatase [rhGALNS]) is approved for the treatment of MPS IVA (Morquio A disease) The recommended dose is in Infants ≥ 9 months, Children and Adolescents: IV: 2 mg/kg once weekly.

In a randomized trial of 176 patients with MPS IVA, patients who received weekly infusions of elosulfase alfa for 24 weeks walked 22.5 meters farther in six minutes, on average, then patients who received placebo. Eight percent of patients had anaphylactic reactions during the infusions and premedication with an antihistamine, with or without an antipyretic, prior to infusion is recommended [4].

Our patient is a 3 years old boy with so far clinical, radiological and molecular confirmation of MPS IV A, with no heart or respiratory symptoms. He has criteria for starting ERT with elosulfase. Genetic counselling and prenatal diagnosis are recommended for future pregnancy.

Conclusion

The association between Transient benign childhood hyperphosphatemia and Morquio disease, are so far not described in the literature.

If we find a patient with high levels of alkaline phosphatase, with short stature and dysostosis multiplex, we have to exclude Morquio disease by testing GAGS in urine. If the result is normal, but the clinical signs are evident, further test like molecular study can be done for confirmation.

Bibliography

1. Alves C and Arruti R. "Hiperfosfatasemia transitória benigna da infância". *Acta Ortopédica Brasileira* 17.1 (2009).

2. Jones S and Wijburg F. "Mucopolysaccharidoses, oligosaccharidoses and sialic acid disorders". In: Inborn Metabolic Diseases: Diagnosis and Treatment, 6th edition, Saudubray JM, Baumgarter MR, Walter J (Eds), Springer, Berlin (2016): 577.

3. Hendriksz CJ., *et al*. "Efficacy and safety of enzyme replacement therapy with BMN 110 (elosulfase alfa) for Morquio A syndrome (mucopolysaccharidosis IVA): a phase 3 randomised placebo-controlled study". *Journal of Inherited Metabolic Disease* 37.6 (2014): 979-990.

4. "Vimizim (elosulfase alfa) [product monograph]". Toronto, Ontario, Canada: BioMarin Pharmaceutical (Canada) Inc (2016).

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