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Mucopolysaccharidoses type I and IVA: Clinical features and consanguinity in Tunisia

Les mucopolysaccharidoses de type I et IVA : aspects cliniques et consanguinité en Tunisie

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Abstract

Mucopolysaccharidoses (MPS) are a group of lysosomal storage disorders caused by the deficiency of specific enzymes which leads to the lysosomal accumulation of glycosaminoglycanes. Mucopolysaccharidosis type I or Hurler disease is characterized by the deficiency of alpha-L-iduronidase enzyme. Mucopolysaccharidosis type IVA or Morquio A disease is due to the lack of *N*-acetylgalactosamine-6-sulfate-sulfatase. Theses deficiencies result in a progressive accumulation of the substrates: dermatan and heparan sulfates for Mucopolysaccharidosis type I and keratan sulfate for MPS type IVA. This process leads to progressive and chronic course for visceral attacks of the affected organs such as lungs and heart. In the Hurler disease, the nervous system is particularly affected while in Morquio a disease, a skeletal dysplasia and a normal intelligence are characteristic.

Aim of the study. – This study was carried out on MPS type I and MPS type IVA unrelated families recruited from many regions of Tunisia in order to determine the relation between consanguinity and these types of disorders.

Patients and methods. – Clinical and molecular analyses confirmed the diagnosis for four MPS type I and five MPS type IVA studied families.

Results. – First cousins unions characterize all families except one Hurler family and one Morquio A family where the consanguinity is third cousin degree.

Conclusion. – MPS type I and type IVA seems to be associated with consanguinity in Tunisia.

Résumé

Les mucopolysaccharidoses (MPS) sont des maladies de surcharge lysosomale causées par la déficience d'enzymes spécifiques qui engendrent l'accumulation de glycosaminoglycanes dans les lysosomes. La mucopolysaccharidose de type I ou maladie de Hurler est caractérisée par la déficience de l'enzyme L-iduronidase tandis que la mucopolysaccharidose de type IVA ou maladie de Morquio A est due au déficit en enzyme *N*-acétylgalactosamine-6-sulfate sulfatase. Ces déficiences d'enzymes engendrent l'accumulation des substrats héparanes et dermatane sulfate pour la mucopolysaccharidose de type I et kératane sulfate pour la mucopolysaccharidose de type IVA. Des organes viscérales sont ainsi progressivement touchés tels que les poumons et le cœur. Le système nerveux est touché surtout dans le cas de la maladie de Hurler alors que la dysplasie osseuse et la conservation de l'intelligence caractérisent la maladie de Morquio A.

But de l'étude. – Cette étude a été réalisée sur des familles Hurler et des familles Morquio A, non apparentées, recrutées dans plusieurs régions de la Tunisie. Le but était de déterminer la relation entre la consanguinité et ces types de désordres.

Patients et méthodes. – Les analyses cliniques et moléculaires ont confirmé le diagnostic de MPS pour quatre familles Hurler et cinq familles Morquio A.

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Résultats. – Chez les familles étudiées, les unions sont entre parents cousins germains, à l'exception d'une famille Hurler et une autre Morquio A chez lesquelles la consanguinité est de troisième degré.
Conclusion. – Les MPS de type I et de type IVA semblent être associées à la consanguinité en Tunisie.

Keywords: Consanguinity; Clinical and molecular analyses; First cousin degree; Mucopolysaccharidosis type I; Mucopolysaccharidosis type IVA; Tunisian families

Mots clés : Consanguinité ; Analyses cliniques et moléculaires ; Cousins germains ; Mucopolysaccharidose de type I ; Mucopolysaccharidose de type IVA ; Familles tunisiennes

1. Introduction

Mucopolysaccharidoses (MPS) are a group of lysosomal storage diseases, autosomal recessive, caused by deficiency of the lysosomal enzymes needed to degrade glycosaminoglycanes (GAGs) such as dermatan sulfate (DS), heparan sulfate (HS) and keratan sulfate (KS). These undegraded or partially degraded GAGs are stored in lysosomes and excreted in urine. MPS type I or Hurler disease is caused by the alpha-L-iduronidase enzyme (IDUA, E.C.3.2.1.7.6; MIM 252800) deficiency and the intralysosomal accumulation of dermatan and heparan sulfates. Three subtypes are differentiated: the severe Hurler syndrome (onset before twelve months of age, survival no more than ten years and severe mental retardation; the Hurler–Scheie syndrome (onset between one and six years, survival variable and intermediate mental retardation but never before three years of age); the attenuated Scheie syndrome (onset after the age of five years, survival normal and normal intelligence) [1]. On the other hand, MPS IVA or Morquio A syndrome is characterized by the lack of *N*-acetylgalactosamine-6-sulfate-sulfatase (GALNS; E.C.3.1.6.4; MIM 253000) [2] and the accumulation of keratan sulfate and chondroitin-6-sulfate in the lysosomes [3,4]. On the basis of clinical signs, we distinguish three forms of Morquio disease: severe, intermediate and mild forms [3,5]. The severe form manifestations include coxa valga, short trunk dwarfism and hepatosplenomegaly. This form is characterized by severe skeletal odontoid dysplasia but without any mental retardation.

Consanguineous marriages are associated with a higher frequency of autosomal recessive disorders. Thus, an association between parental consanguinity and the frequency of MPS (particularly in Tunisia) will be reported and discussed.

The consanguinity is frequent in Tunisia and more precisely between first cousins. This rule, which characterizes the Arab world, results from particular traditions as a consequence of cultural and economical reasons.

2. Patients and methods

The study was carried out on four MPS I families (Fig. 1) and five MPS IVA families (Fig. 2) recruited in pediatric departments of different geographic areas of Tunisia (Central and Southern areas). The phenotypic and molecular diagnoses were confirmed in our laboratory of Biochemistry and Clinical Biology of Sousse in Tunisia.

2.1. Familial questionnaire

The families of MPS I and MPS IVA patients have been questioned to establish an inventory of the consanguineous unions and to determine the relation between consanguinity and the frequency of MPS I and IVA in Tunisia.

3. Results

The biological, enzymatic and molecular analyses confirmed the MPS diagnosis for all the studied patients. The clinical characteristics of patients MPS I and IVA were reported below.

3.1. MPS I patients

Patients from families 1, 2 and 4 had a severe Hurler phenotype while patients in family 3 had an intermediate phenotype (Hurler–Scheie phenotype) (Fig. 1).

3.1.1. Patients of family 1

We had identified the clinical parameters of the two male siblings probands explored in our laboratory. The first boy was diagnosed at the age of fifteen months. He developed coarse facial features, facial and body hypertrichosis, enlarged tongue, thick lips, bushy eyebrows, exophtalmos, noisy breathing and hearing loss. He also developed progressively a corneal clouding, an aortic valve disease, an inguinal hernia, dysostosis multiplex, spacing and shape teeth, enlarged tonsils, carpal tunnel syndrome, obstructive airway disease and sleep apnea. He had hepatomegaly and a severe mental retardation. He eventually deceased at five years old as a result of pulmonary and cardiac deficiencies. His brother's age of onset was six months and progressively presented severe developmental delay, hydrocephaly, heart disease, deafness, inguinal hernia and obstructive airway disease. He deceased at age of three years.

3.1.2. Patient of family 2

This girl, diagnosed at the age of eighteen months, developed facial dysmorphisms, scaphocephaly, skeletal dysplasia, spacing and shape teeth, enlarged tonsils, thick lips, bushy eyebrows, umbilical hernia, mitral valve regurgitation and coax valga. She had hepatosplenomegaly and cardiomegaly and deceased at four years of age. She also developed a severe mental retardation.