Aspartylglucosaminuria in a Tunisian family

Faouzia Khalidi, PhD, Mourad Besrour, MD, Samir Boukthir, MD.

ABSTRACT

We report on the first 4 cases of aspartylglucosaminuria (AGU) diagnosed in Tunisia. Four siblings with the clinical and laboratory findings of AGU were the products of a first cousins' mating. The index case was a 20 month old male who presented with heart failure and coarse features. He had a slow psychomotor development and skeletal changes consistent with numerous changes in small bones. Enzymatic assays in cultured skin fibroblasts showed aspartylglucosaminidase deficiency. His 2 sisters and his brother were 11, 3 and 8 1/2 years of age, respectively and also presented a slow psychomotor development and dysmorphia.

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Aspartylglucosaminuria (AGU) is an autosomal recessive lysosomal storage disorder characterized by slowly progressive mental retardation from infancy, urinary excretion of aspartyl-N-acetyl glucosamine (GLC-NAC-ASN) and decreased activity of the lysosomal enzyme, 1-aspartamid-8-N-acetyl-glucosamine amidohydrolase in body tissues and fluids. This inborn error of glycoprotein catabolism was first described in two mentally retarded English siblings. Additional reported cases have come from an extensive Finnish series. In this report, we describe the clinical and laboratory findings of four patients from Tunisia, the first North African described with this disorder.

Methods. Fibroblast cultures were established and maintained from skin biopsies of the patients and controls as previously described. The 4-B aspartylglucosaminylamidohydrolase (AAGase) was measured according to the method of Aula et al. The N-acetyl-B-D glucosaminidase (Hex) was determined as a control lysosomal enzyme activity. Urinary oligosaccharides were separated by thin-layer chromatography as described by Humbel and Collart.

Clinical reports. The pedigree of the family is shown in Fig. 1. The parents of the propositus were first cousins. The father and the mother were 43 and 33 years old, respectively and both were in good health. The patient V-5, a 20 month old white male, was a full term infant born after an uneventful delivery. His psychomotor development was slow. At 18 months old, he sat alone, but did not walk, had delayed speech and recurrent respiratory infections. He was referred to the Children's Hospital of Tunis for congestive heart failure. At admission, his weight and height were below the third percentile. Evidence of heart failure was present with heart rate 160 per min. He had dependent edema, hepatomegaly with the liver 4 cm below the right costal margin, and the spleen was 5 cm below the left costal margin. A grade 2/6 blowing systolic murmur radiating to the axilla was heard. A voluminous umbilical defect also was noted. He had coarse facial features with wide set eyes and thick lips (Fig. 2). The corneas were not clear and the fundi had no abnormal pigmentation. His neck was short and his right knee was in a valgus position. No gross neurologic abnormalities were noted except the absence of speech. Cardiomegaly was evident on x-rays and left ventricular dilatation and mild mitral insufficiency was demonstrated by echocardiogram. The heart defects were treated with digoxin and diuretics.

Normal blood concentrations of glucose, urea, electrolytes, calcium, phosphorus, uric acid, albumin were noted. The concentrations of SGOT (91 Wl, NV<30 Wl), SGPT (54 Wl, NV<70 Wl) and alkaline phosphatase (224 Wl, NV<142 Wl) were mildly elevated. The patient's radiographs showed thickening of the cortex of the skull, widened ribs, vertebral changes and the cortex of metacarpal or metatarsal bones was abnormally thin (Fig. 3). Metabolic screen of the urine was positive with quantitative excretion of GLC-NAC-ASN (972 μmol/l; normal values: 10 μmol/l).

The patient V-4 was a 3 years 7 month old girl born after an uneventful pregnancy. She sat at 14 months, took her first steps at 30 months. She had recurrent respiratory infections and delayed speech. Her weight and height were normal. Her traits were less coarse than those of her brother and sister. There was hepatomegaly without
Aspartylglucosaminuria in Tunisian family ... Khaldi & Boukthir

Figure 1 - Pedigree of the family

Figure 2a - Photographs of the patients: Patient V-5

Figure 2b - Photographs of the patients: Patient V-3

Figure 2c - Photographs of the patients: Patient V-2

hernia. Her cardiac, pulmonary and neurologic examinations were normal. She had right genu valgum. Ophthalmic examination was normal. Routine laboratory parameters were normal except for a mild anemia. Skull roentgenograms (Fig. 4) showed densification of skull bones, widened ribs and ovoid formed dorsal vertebra. Long bones were normal. Urinary excretion of GLc-NAc-ASN was increased (2395 μmol/l).

The patient V-3, was an 8 years 6 month-old boy who had a slow psychomotor development and a medical history of recurrent respiratory infections. His anthropometric measurements were normal. His facial features were milder than those of his other affected siblings (Fig. 2) and his somatic examination was normal except for a short neck and vagon genum. Routine biological parameters were normal except for mild anemia. Urinary GLc-NAc-ASN was excreted at about 2050 μmol/l with presence of heparin sulfate.

V-2 was an 11 year-old girl who was born after an uneventful pregnancy. Her psychomotor development was slow; she sat at 15 months, took her first steps at 4 years and had delayed speech. She had recurrent respiratory infections. At 11 years, her height was below the third percentile with normal weight and head circumference. She had wide mouth, wide nasal bridge, thick lips and macroglossia (Fig. 2). Cardiac and pulmonary functions were normal. She had hepatomegaly, a knee in valgus position and a short neck. Her corneas were cloudy and her fundi were normal. The results of routine laboratory hematology and chemistries were normal except for mild anemia. Roentgenograms showed dense skull bones, ovoid formed dorsal vertebra, widened ribs and normal long bones. Urinary excretion of GLc-NAc-ASN was increased (2140 μmol/l).

Results. The activity of AADGase in extracts of skin fibroblasts of the four patients was reduced or absent (Table 1). Cultured fibroblasts from the mother and father showed an intermediate enzyme activity compatible with heterozygosity for the AGU disease gene.

Discussion. The four siblings reported here expand the
occurrence of AGU. The AGU gene is particularly common in the Finnish population, among whom the disease is the most common lysosomal storage disorder. The incidence is estimated to 1 case per 30,000 births. However, patients from other ethnic groups have been reported from the United States, Italy, Canada and Puerto Rico, but to our knowledge no North African cases have been described.

Clinical and biochemical aspects of AGU have been well described. The age range of the patients at diagnosis is 1 to 5 years. The main physical findings are coarse facial appearance, mental retardation, skeletal abnormalities, cardiac manifestations. Coarse facial appearance, mental retardation and delayed speech are always present. They were observed in our 4 cases. Hepatomegaly was noticed in 3 out of our 4 subjects. Splenomegaly is less frequent and we had noticed it only once. Predisposition to infections, mainly respiratory and...
Aspartylglucosaminuria in Tunisian family: Khaled & Boukthir

digestive, is another frequent sign. Cardiac abnormalities resume to systolic murmur due to mitral insufficiency.19 Speech disturbances were observed in our 4 cases and in 19 out of the 23 subjects of autio series.14 Reported ophthalmic abnormalities have not been noticed in our subjects. Skeletal roentgenograms are important for diagnosis orientation. Skull thickening and frontal sinus agenesis, widened ribs flattened vertebral bodies, ovoid or trapezoid formed vertebrae are seen in 60 per cent of the literature.3,8,10 Changes in long bones and small bones include widening of diaphysis, increased tubulation, and coarsening of trabecular pattern. Certitude diagnosis of AGU is made by the identification of GLc-NAC-ASN excreted in urine in big amounts1,5,12 and the individualization of generalized aspartylglucosaminylaminohydrolase deficiency.4,5,12 In our series, large amounts of GLc-NAC-ASN >2000 μmol/l are excreted. Enzymatic activity is deficient in our 4 siblings. The distinction between a homozygote affected and a heterozygote unaffected did not pose difficulties because of the absent or very low residual activity in homozygotes.16 AGU is compatible with long life span. However patients are exposed to infections and skeletal complications such as genu valgum and spontaneous fractures.3 The treatment is purely symptomatic but the prevention of AGU is actually possible by prenatal diagnosis after amniocentesis and genetic counseling.16 The structural gene of AGU has been assigned to the region 4 q 21-4 qter of chromosome 4.17 In conclusion, AGU is not limited to individuals of Finnish background and should be considered in evocative context, regardless of ethnic background.

References

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