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Gaucher disease type 2 — Homozygosity for the mutation F331S in two unrelated consanguineous Muslim Arab patients with Gaucher disease from the Gaza and Jenin regions

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To the Editor:

Gaucher disease (GD) results from the deficiency of the lysosomal enzyme glucocerebrosidase. The phenotypes of patients with GD have been divided into three types, based on the presence and rate of progression of the neurologic manifestations. Both types 2 (GD2) and 3 (GD3) affect the central nervous system (CNS), but exhibit differing rates of neurological deterioration. Patients with GD2, the acute neuropathic form, present with symptoms either prenatally or during infancy, and all die before the age of 2 years, while GD3, the sub-acute neuropathic form, has a more protracted course. The three clinical forms are pan-ethnic in occurrence. The incidences of GD2 and GD3 in the general population are about 1 in 500,000 and 1 in 50,000 respectively [1].

We describe two Palestinian patients, one from Gaza and one from Jenin, which are two separate cities within the Palestinian Authority (PA) territories. They were evaluated at two different medical centers in Israel, both of which are tertiary centers for GD. Both patients had GD2 and both were found to be homozygous for the same novel mutation in the GBA gene, F331S.

Patient 1, an 8-month-old male infant, was evaluated for severe failure to thrive (FTT) and hepatosplenomegaly. He was microcephalic and regression in his developmental milestones was reported. He was the second child born to first-degree cousin parents of Muslim Arab origin, resident in Jenin. Their first child is a healthy boy, now aged 5 years. The proband began to exhibit neurologic deterioration at age of 3 months, when he developed opisthotonus, and by 8 months he was hypotonic with no eye contact. He had head lag, severe strabismus, and was not able to sit. At 8 months his weight was 6.5 kg (−4 SD), head circumference 40.5 cm (−4 SD) and length 64 cm (−3 SD). The abdomen was distended with liver and spleen palpable 6 cm and 8 cm respectively below the costal margin. Both skeletal survey and brain magnetic resonance imaging (MRI) were reported as normal. The lymphocyte beta-glucosidase level was 4 nmoles/mg protein/h (controls were 31 and 26), hemoglobin level was 10.3 g/dl, WBC 8290 m³, and platelets 182,000. He died at home at age of one year.

Patient 2, a 7-month old boy, was evaluated for FTT, massive hepatosplenomegaly and severe developmental delay. He was the seventh child born to first-degree cousin Muslim Arab parents from Gaza. They have four healthy children as well as two previous affected children, a boy and a girl with a similar clinical picture, both of whom died at the age of 11 months. Evaluation of one of the proband's affected siblings revealed a beta glucosidase level of 0.367 nmoles/mg protein/h (controls were 3.3-8.15), an increased chitotriosidase level of 22,641 mmol/ml/h, and mild brain atrophy on brain MRI. Physical examination of the proband at the age of 7 months revealed an irritable infant with significant FTT. His weight was 4868 gr (−4SD), and he reacted to noises but was unable to track. Neurological evaluation revealed hypertonicity of all four limbs and a constantly arched back. He had a grade 2/6 systolic murmur and hepatosplenomegaly — liver and spleen were both 5 cm below the costal margin. His blood count revealed a hemoglobin level of 8.1 gr/dl, leukocyte count 10,600/mm³ (25% neutrophils, 64% lymphocytes), platelets 124,000/mm³, and acid phosphatase 36u/l (normal up to 10). Beta glucosidase was 4 nmol/h/ mg (deficient control 2 and normal control 19). An abdominal ultrasound showed an enlarged liver with increased echogenicity (10.3 cm span) and an enlarged spleen (8.9 cm). MRI showed prominent cortical sulci and fissures indicating mild brain atrophy and delayed myelination. The child died several weeks later.

Genomic DNA was extracted from lymphocyte samples, including flanking intronic sequences and a 1 kb segment at the 5' promoter region, were amplified using primers complementary to the functional gene but not the pseudogene. PCR products were sequenced with primers specific for each exon [2].

Full sequencing of the GBA gene revealed homozygosity for the F331S (c.1109 TNC) mutation in both probands. The parents in each case were found to be F331S carriers. No other mutations were identified. This novel mutation was not seen in over 500 GBA alleles sequenced in controls and patients with GD.

While it is not known whether the two families were related, the relative proximity of their origins suggests the possibility of a founder mutation in this population. This mutation changes phenylalanine, an aromatic amino acid, to serine, a polar uncharged amino acid. This residue is conserved in 19 mammalian species [3] and analysis with Maestro software

(Schrödinger, Inc., New York) predicts this mutation to be pathogenic. F331S is located in exon 8 of GBA, a region involved in the catalytic activity of the enzyme [4], and is partially exposed at the surface. It makes hydrophobic contact with L296, so the serine mutant would disrupt this contact, which could render the mutant protein less stable.

In summary, from this report and the literature [5], F331S appears to be a severe mutation which, in the homozygous state, leads to a non-perinatal lethal form of GD2. As is known, ERT treatment has been shown not to be beneficial in GD2 [6-8], so this was not offered and the children received supportive care on their return to their homes in the PA territories.

We received the molecular analysis results after both families returned home, but despite repeat invitations for genetic counseling they were lost for follow up. Therefore, unfortunately, we could not enable these families to undergo prenatal diagnosis in future pregnancies.

The prevalence of GD2 in the Palestinian population is not reported in the literature. In view of these two patients, population screening in the Palestinian community is recommended to determine the prevalence of carriers of this mutation and to establish the need for genetic counseling and prenatal diagnosis.

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