

Electronic letter

J Med Genet 2000;37 (http://jmedgenet.com/cgi/content/full/37/11/e40)

Cardiovascular fibrosis, hydrocephalus, ophthalmoplegia, and visceral involvement in an American child with Gaucher disease

EDITOR—We have recently performed the molecular characterisation of the glucocerebrosidase alleles of a child with an unusual presentation of type 3 Gaucher disease. This patient was among the first described cases of Gaucher disease with cardiac involvement, oculomotor abnormalities, and hydrocephalus,¹ features that were subsequently described in patients from Japan,^{2,3} Israel,⁴ Spain,^{5,6} Turkey,^{7,8} Canada,⁹ and the USA^{10,11} (table 1). Interestingly, many of these patients were reported to be homozygous for the mutation D409H in the human glucocerebrosidase gene. Similar to the latest case with genotype D409H/D409H described in this journal by Chabás *et al*,⁵ our patient had early and aggressive visceral disease. However, unlike many of the other cases reported, pathological evaluation showed cardiovascular fibrosis, rather than calcification, and Gaucher cells were found scattered within the areas of fibrosis.

This child was diagnosed at 6 months of age with splenomegaly and abnormal saccadic eye movements were observed at 1 year of age. At 6 years of age, he was noted to have delayed growth (height and weight less than the 1st centile), scattered ecchymoses, a thoracolumbar gibbus deformity, and a grade 3/6 systolic ejection murmur. His liver extended 4 cm below the right costal margin, and his spleen was palpable at the left pelvic brim and extended across the midline. A neuro-ophthalmological evaluation

disclosed an ophthalmoplegia with absent saccadic movements. His gait was broad based, and the muscle tone was decreased in his lower extremities, with symmetrically hyperactive patellar and ankle reflexes. Laboratory evaluation was significant for a haemoglobin level of 10.1 g/dl and a platelet count of 105 000/mm³. Long bone surveys, chest x rays, an EKG, and an echocardiogram were reported as normal. An EEG was suggestive of mild bilateral cerebral dysfunction, and a cranial CT scan showed a compensated, communicating hydrocephalus. At 6½ years of age, the child developed acute pulmonary oedema. He experienced a respiratory arrest and subsequently a terminal cardiac arrest.¹

Necropsy showed unexpected cardiac ventricular hypertrophy, intimal fibrosis of the coronary arteries and aorta, and a grey fibrotic thickening of the intimal surface at the root of the aorta.¹ Gaucher cells were scattered along the intima and media of the aorta in the area of fibrosis.¹

Mutation analysis, performed by sequencing of DNA, showed that the patient was heterozygous for mutation D409H and a recombinant allele encompassing mutations L444P, A456P, and V460V (RecNciI). Southern blot analysis using the restriction enzymes *Ssp*I and *Sst*II confirmed that this was not a fusion allele. Because both mutant alleles contain sequence changes found in the pseudogene, an *Nci*I restriction digest of a PCR amplified fragment containing exons 8-11 was performed to determine which allele contained the L444P mutation. Analysis of both alleles after *Nci*I digestion, electrophoretic separation on an agarose gel, excision, and gel purification and sequencing confirmed that the D409H mutation was not present on the RecNciI allele. The RecNciI allele is most sequencing likely a null allele, since in the

Table 1 Patients with type 3 Gaucher disease and cardiovascular abnormalities

Report	Country of origin	No of cases	Age	Consanguinity	Genotype	Symptoms				
						Visceral	Neurological	Cardiac	Eye	Other
Chabás <i>et al</i> ⁵	Spain	3 sibs	10 16 17	No	D409H/ D409H	Mild Moderate	Abnormal saccades, one had tonic/clonic seizures	Calcifications of aortic and mitral valves and ascending aorta	Corneal opacities	NA
Abrahamov <i>et al</i> ⁴	Israel	12 pts in 3 families	2–20	Yes	D409H/ D409H	Mild	Absent saccades, mild dilatation of lateral ventricles	Calcification of valves	Corneal opacities	NA
Sharratt <i>et al</i> ⁹	Canada	1	12	Yes	NA	Moderate	NA	Calcifications of mitral and aortic valves and left atrium	NA	NA
Saraclar <i>et al</i> ⁸	Turkey	2 sibs	15 9	Yes	NA	Mild	NA	Mitral and aortic valve involvement	NA	NA
Uyama <i>et al</i> ^{2,3}	Japan	3 sibs	42 35 27	No	D409H/ D409H	Mild	Abnormal saccadic eye movements, leptomeningeal fibrosis	Mitral and aortic valve calcification, intimal fibrosis of ascending aorta	Corneal opacities	Azoospermia, progressive hearing loss, deformed toes, hyperextensible skin, hernias
Erduran <i>et al</i> ⁷	Turkey	1	12	Yes	NA	Mild	Communicating hydrocephalus, choreoathetoid movements of head	Left ventricular hypertrophy	Corneal opacities	Clinodactyly, sensorineural hearing loss
Beutler <i>et al</i> ¹⁰	Britain/ Germany	1	18	Yes	D409H/ D409H	Moderate	Hydrocephalus, oculomotor apraxia	“Cardiac disease”	NA	NA
This report and Wilson <i>et al</i> ¹	USA	1	6	No	D409H/ recombinant allele	Severe	Absent saccades, mild communicating hydrocephalus	Ventricular hypertrophy, aortic and coronary artery intimal fibrosis	NA	NA
Casta <i>et al</i> ¹¹	USA	1	15	NA	NA	Mild	NA	Calcification of ascending aorta, aortic and mitral valves	Corneal deposits	NA

NA - not available.

homozygous state it has only been observed in cases of Gaucher disease presenting as hydrops fetalis.¹²

Thus, our molecular findings in this young child with Gaucher disease provide strong support that the unusual manifestations of aortic and coronary artery involvement, hydrocephalus, and absent saccadic movements are associated with the D409H mutant allele, as observed in other cases.^{2-5 10} However, since severely affected patients with Gaucher disease do not generally present with the cardiovascular complications and hydrocephalus described here, it is unlikely that these unusual findings are solely the result of glucocerebrosidase deficiency. A more extensive characterisation of genes surrounding glucocerebrosidase,^{13 14} as well as other genetic and environmental factors, may help to explain the aetiology of this phenotype.

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