

RESEARCH REPORT

# Etiology of Vision Loss in Ganglioside GM3 Synthase Deficiency

**Fahhad Farukhi**

*Cole Eye Institute, Cleveland Clinic Foundation, Cleveland, OH, USA*

**Claudia Dakkouri**

*Alcona Health Clinic, Alpina, MI, USA*

**Heng Wang**

*DDC Clinic, Middlefield, OH, USA*

**Max Wiztnitzer**

*Case Western University Hospital, Cleveland, OH, USA*

**Elias I. Traboulsi**

*Cole Eye Institute, Cleveland Clinic Foundation, Cleveland, OH, USA*

**Purpose:** To investigate the cause of vision loss in patients with ganglioside GM3 synthase deficiency, a newly described rare autosomal recessive infantile-onset symptomatic epilepsy syndrome associated with developmental stagnation and blindness. **Methods:** We examined four children from two related Amish sibships. Molecular genetic analysis confirmed inheritance of the founder mutation. Electroretinography and fundus photography were obtained in two patients. **Results:** Despite an initial suspicion of retinal degeneration, retinal function was found to be preserved in both patients and ERG amplitudes were within normal limits. Ophthalmoscopy showed bilateral optic atrophy in all patients. **Conclusions:** Vision loss in GM3 synthase deficiency results from central nervous system and optic nerve involvement. Retinal function appears to be otherwise normal into the teenage years.

**Keywords** GM3 synthase deficiency; vision loss; retinal function; optic atrophy

## INTRODUCTION

Ganglioside GM3 synthase deficiency is an extremely rare autosomal recessive infantile-onset symptomatic epilepsy syndrome associated with developmental stagnation and blindness. The disorder was mapped to 2p12–p11.2 in a large Old Order Amish pedigree, and the defect was subsequently found to be the result of homozygosity for a nonsense mutation in SIAT9, leading to the premature termination of the GM3 synthase enzyme (also called lactosylceramide alpha-2,3 sialyltransferase). Although patients with GM3 synthase deficiency were described as blind from optic nerve atrophy in the original publication,<sup>1</sup> no details of the ocular examinations were given.

## CASE PRESENTATION

### Pedigree 1

Amish siblings, a 13-month-old girl (Fig. 1; IV:9; Child A) and a 6-year-old boy (Fig. 1; IV:6, proband; Child B), with an unknown progressive epilepsy syndrome presented in March 2005 due to concern about the status of their vision. Child A did not track or focus with her eyes, displayed uncoordinated as well as incongruent eye movements, and showed little to no visual attention to her surroundings. Child B was believed to be cortically blind. Both children experienced global developmental delay and EEG documented seizure activity. VA in Child A was 20/40 OD and 20/30 OS. VA in Child B was 20/30 in both eyes. Slit-lamp exam was normal in both children. Indirect ophthalmoscopy and digital fundus photography in both children showed optic disc pallor indicative of optic atrophy (Fig. 2). The possibility of retinal degeneration was raised in Child A because of the appearance of the fundus. Genetic

Accepted 8 June 2006.

Address correspondence to Dr. Elias I. Traboulsi, Cole Eye Institute, 132 9500 Euclid Avenue, Cleveland, OH 44195, USA. Tel: (216)-444-4363; Fax: (216)-445-2226; E-mail: traboue@ccf.org

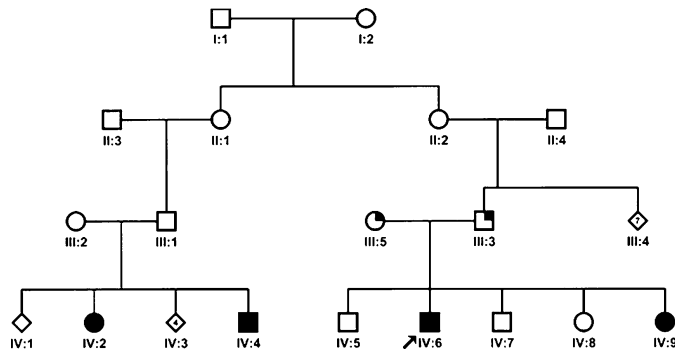


FIG. 1. Pedigree of Family 1. Circles, females; squares, males; filled symbols, affected; partially filled, obligate carriers; roman numerals, generation number; Arabic numerals, individual number.

mutation analysis established the diagnosis of GM3 synthase deficiency.

### Pedigree 2

Two siblings with GM3 synthase deficiency from the Simpson et al. study<sup>1</sup> of a family with nine affected individuals, including a 13-year-old boy (Child C) and 6-year-old boy (Child D), were then examined to determine the existence of optic nerve degeneration and the prospect of retinal degeneration. These children presented with a history of profound developmental delay, gastric dysmotility, generalized tonic-clonic seizures, poor eye contact, and visual dysfunction. Previous brain MRI in affected children from this family showed no structural abnormalities except for diffuse atrophy at older ages. Both children had mild bilateral ptosis. Slit-lamp exam was nor-



FIG. 2. Retcam<sup>®</sup> photograph of the right eye of patient IV:6 showing optic atrophy. The retinal vasculature is normal in caliber, and there are no evident pigmentary changes.

mal. Indirect ophthalmoscopy and digital fundus photography showed optic atrophy, but not pigmentary retinopathy. Scotopic and photopic ERG waveforms were normal.

The identical findings in both pedigrees prompted a thorough investigation of the relationship between the two pedigrees. Using the Swiss Anabaptist Genealogical Association, we were able to find multiple familial ties between both families including a sibling link that occurred five generations ago.<sup>2</sup>

### DISCUSSION

Gangliosides are a group of multifunctional molecules found on the surface of essentially all mammalian cells. They are particularly abundant in the central nervous system (CNS), where they represent about 10% of total lipid content. The roles of gangliosides in the developing and adult central nervous system are not fully understood, but they are believed to function in the regulation of receptor-mediated cell-signaling pathways. Ganglioside function has also been associated with apoptosis.<sup>3</sup> GM3 synthase catalyzes the initial step in the biosynthesis of most complex gangliosides from lactosylceramide. It is located on chromosome 2p12–p11.2 and a nonsense mutation in exon 8 of SIAT9 (694C>T) is believed to result in premature termination of this enzyme. Ganglioside GM3 is the precursor to more complex gangliosides such as a- and b-series. Early termination of GM3 synthase interrupts this synthesis and leads to an increase in lactosylceramide.<sup>1</sup> Mice exhibiting GM2 synthase deficiency experienced optic degeneration, whereas those with only GM3 synthase deficiency were phenotypically normal.<sup>4</sup> GM3 synthase deficiency has also been associated with enhanced insulin sensitivity and decreased retinal pericyte proliferation in bovine species.<sup>5</sup>

Prior to the present study, the children in Simpson's study were the only ones known to be affected with GM3 synthase deficiency. The actual prevalence of this disease is probably underestimated in the Amish community. Children with evidence of neurologic dysfunction and mental retardation in this population, especially those with the characteristic freckling, need genetic analysis for the common 694 C > T mutation as well as ophthalmologic examinations for the presence of optic atrophy. We were able to demonstrate normal retinal function using electroretinography, hence assigning the cause of vision loss to optic atrophy and possibly cortical visual impairment.

Because of the high prevalence of rare recessive genetic disorders that involve the visual system in the Amish community, ophthalmologists who care for Amish patients should familiarize themselves with these conditions, including among others Leber congenital amaurosis, Bardet-Biedl syndrome, Cohen syndrome, and GM3 synthase deficiency. Genetic testing is already available for some of these conditions, and in the future gene therapy will become possible, significantly improving the diagnostic and therapeutic armamentarium to handle these rare and devastating diseases.

## REFERENCES

1. Simpson MA, Cross H, Proukakis C, et al. Infantile-onset symptomatic epilepsy syndrome caused by a homozygous loss-of-function mutation of GM3 synthase. *Nat Genet.* 2004;36:1225-1229.
2. Swiss Anabaptist Genealogical Association. Database Access. Available at <http://www.omii.org>. Accessed July 1, 2005.
3. Watanabe R, Ohyama C, Aoki H, et al. Ganglioside G(M3) over-expression induces apoptosis and reduces malignant potential in murine bladder cancer. *Cancer Res.* 2002;62:3850-3854.
4. Yamashita T, Wu YP, Sandhoff R, et al. Interruption of ganglioside synthesis produces central nervous system degeneration and altered axon-glia interactions. *Proc Natl Acad Sci USA.* 2005;102:2725-2730.
5. Masson E, Troncy L, Ruggiero D, Wiernsperger N, Lagarde M, Bawab SE. a-Series gangliosides mediate the effects of advanced glycation end products on pericyte and mesangial cell proliferation: a common mediator for retinal and renal microangiopathy? *Diabetes.* 2005;54:220-227.