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Neuronal GM_1 Gangliosidosis in a Siamese Cat with β-Galactosidase Deficiency

Abstract. *A juvenile Siamese cat with severe, progressive motor disability was shown to have extensive neuronal degeneration caused by accumulation of GM_1 ganglioside. Tissues from brain and kidney were markedly deficient in β-galactosidase activity. The disease in this cat is thought to be inherited as an autosomal recessive trait, and is strikingly similar to juvenile GM_1 gangliosidosis of children.*

Inherited defects of sphingolipid metabolism cause devastating diseases in man. At least five such diseases are due to abnormalities in ganglioside metabolism, in which specific lysosomal hydrolases appear to be deficient or absent. Remarkable progress in unraveling these complex diseases has been made by the study of human patients (*1*), despite its limitations. However, suitable animal models are badly needed for intensive study of pathogenetic mechanisms and potential curative measures. Diseases analogous to the human gangliosidoses with respect to histology have been described for a few animal species (*2*), but the underlying biochemical defects in these diseases have not been well characterized. In this report we describe preliminary clinical, pathological, genetic, and biochemical studies of a disease in Siamese cats which shows striking similarities to juvenile GM_1 gangliosidosis (*3*) of children.

Table 1. Gangliosides in brain. Values are expressed as micrograms of NANA per gram wet weight of tissue.

Total ganglio-sides	Distribution of gangliosides			
	GM_1	GD_{1A}	GD_{1B}	GT_1
	Diseased cat			
2265	1411.1	231.0	151.8	188.0
	Control cat			
946	170.3	350.0	104.1	141.9

Table 2. Enzyme activity in brain and kidney. Activities are expressed as nanomoles of substrate cleaved per milligram protein per hour.

Source	β-Galactosidase	Arylsulfatase-A
	Diseased cat	
Brain	38	110
Kidney	20	223
	Control cat	
Brain	256	95
Kidney	105	183

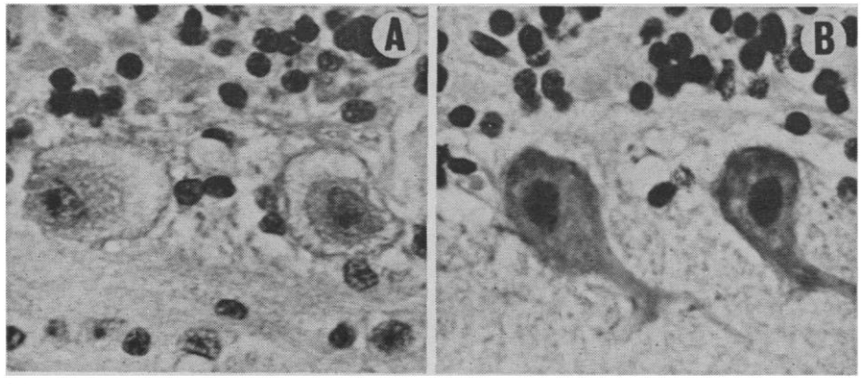

Fig. 1. Purkinje cells of diseased cat (A) and normal sibling (B). Sections of cerebellum are stained with hematoxylin-eosin (× 500).

A male Siamese cat developed normally until the age of 4 months, when he showed weakness and incoordination of his hind legs. General ataxia appeared and progressed until the animal was totally incapacitated at the age of 6 months when he was killed humanely. No gross lesions were found at necropsy. Histopathological examination of sections stained with hematoxylin-eosin revealed that neurons throughout the central nervous system, as well as those in sympathetic ganglia and retina, were enlarged and rounded, and had lost Nissl bodies from the cytoplasm (Fig. 1). Margination and chromatolysis of neuronal nuclei were frequent. In frozen sections the cytoplasm of neurons stained intensely with the periodic acid Schiff stain but weakly with oil red O and Sudan black B stains. Increased numbers of glial elements were evident throughout the brain, and there was occasional neuronophagia. Lesions outside the nervous system were limited to the spleen, where a few macrophages had foamy, vacuolated cytoplasm.

Gangliosides were extracted from brain by the method of Suzuki (*4*). The total amount of ganglioside extracted from brain was determined by measuring the *N*-acetylneuraminic acid (NANA) content, with the use of the resorcinol method as modified by Mietinen and Takki-Luukkainen (*5*). Individual gangliosides were separated by ascending thin-layer chromatography with a propanol : water (73 : 27 by volume) solvent system. After 6 hours of migration, gangliosides were located with resorcinol reagent, and the NANA content of each fraction was measured (*4*). Recovery of NANA from gangliosides exceeded 95 percent. Brain tissue from a normal Siamese cat, 6 months

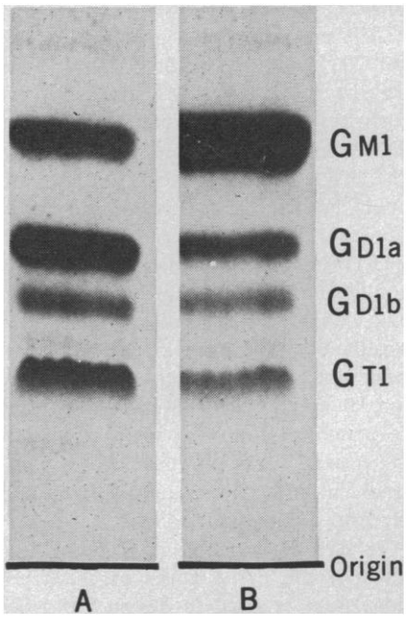

Fig. 2. Thin-layer chromatogram of gangliosides in brain from control (A) and diseased (B) cats.

in age, served as a control in ganglioside and enzyme analyses.

Total ganglioside content and the distribution of four major gangliosides in brains from diseased and normal cats are shown in Table 1. The total ganglioside content of diseased cat brain was more than twice that found in normal brain. The quantity of GM_1 ganglioside in diseased cat brain was more than eight times normal, but the quantities of other gangliosides were close to normal values (GD_{1A}, 66 percent of normal; GD_{1B}, 145 percent; GT_1, 132 percent). A thin-layer chromatogram showing distribution of gangliosides from brains of diseased and control animals is shown in Fig. 2.

Activities of β-galactosidase and arylsulfatase-A were measured in brain and kidney from diseased and control cats. Tissues were homogenized in 0.32*M* sucrose, sonicated, and centrifuged. The resulting supernatant was the source of the enzymes. The activity of arylsulfatase-A was measured by the method of Kaback and Howell (*6*); that of β-galactosidase was measured by the method of Pinsky *et al.* (*7*). The activities of β-galactosidase in the brain and kidney of the diseased cat were approximately 15 and 20 percent, respectively, of activities for the normal cat (Table 2). Activities of arylsulfatase-A in both brain and kidney of the diseased cat were equal to or slightly higher than control values.

A pedigree (Fig. 3) of the diseased cat's family shows that two full sisters (Nos. 6 and 13) exhibited clinical signs resembling those of the propositus (No. 14). Cat No. 6 died naturally at the age of 5 months, and cat No. 13 was destroyed humanely at the age of 3 months. Unfortunately, neither of these cats was studied by necropsy. All of the diseased cats were progeny of a female (No. 2) bred to her son (No. 3). Both parents were phenotypically normal. Of the siblings, two females (Nos. 10 and 12) and five males (Nos. 4, 5, 7, 8 and 11) were phenotypically normal. The clinical status of several other siblings is unknown at this time. Necropsy examination and enzyme analysis of tissues from cat No. 11 suggests that he was homozygous for the normal trait.

This pedigree strongly suggests that that feline GM_1 gangliosidosis is inherited as an autosomal recessive trait. (i) Both parents were phenotypically normal. (ii) Parents were consanguineous. (iii) Male and female siblings were affected. (iv) The ratio of diseased to phenotypically normal cats was consistent with that expected for autosomal recessive inheritance.

Table 3. Comparative features of human and feline GM_1 gangliosidoses.

Item	Generalized gangliosidosis (type I)	Juvenile gangliosidosis (type II)	Feline gangliosidosis
Age at onset	Birth	Juvenile	Juvenile
Motor retardation	+	+	+
Physical appearance	Altered	Normal	Normal
Hepatosplenomegaly	+	−	−
Neuronal lipidosis	+	+	+
Vacuolated macrophages	+	+	+
GM_1 ganglioside in brain	10 × normal	10 × normal	8 × normal
β-Galactosidase deficiency in brain	3% of normal	3% of normal	15% of normal
Autosomal recessive inheritance	+	+	Probable

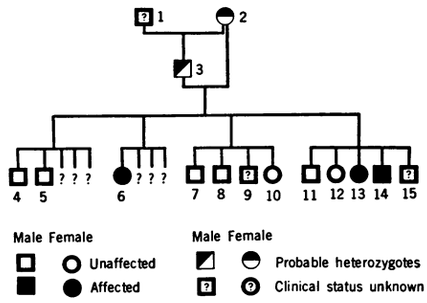

Fig. 3. The pedigree of a Siamese cat family.

Neuropathologic lesions found in cat No. 14 are very similar to those described for the human gangliosidoses (Table 3). Furthermore, the biochemical basis for the disease in cat No. 14 is identical to that found for the GM_1 gangliosidoses of man (*1*). Lack of significant visceral involvement in cat No. 14 differentiates this disease from generalized GM_1 gangliosidosis (type I, Norman-Landing disease). This feature, and several other aspects of the feline disease, more closely parallel the features of juvenile GM_1 gangliosidosis (type II, Derry's disease). This disease in cats has exceptional potential as an experimental model of the human gangliosidoses.

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