ANIMAL MODEL OF HUMAN DISEASE

Niemann–Pick Disease

Sphingomyelinosis of Siamese Cats

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Biologic Features

Sphingomyelinosis of Siamese cats is a rare and presumably heritable lysosomal disease that appears to be analogous to Niemann–Pick disease (NPD) in man.[1,2] The disease results from a profound deficiency of lysosomal sphingomyelinase activity, with resultant accumulations of sphingomyelin, cholesterol, and gangliosides in neurons and visceral cells of the mononuclear phagocyte system.[3] Kittens that are affected have progressive neurologic deterioration, starting at about 4 months of age, and usually die before they reach 1 year of age.[4]

The earliest recognized clinical features of feline NPD are retarded growth and occasional knuckling over in the rear legs. As the disease progresses, there is increased incoordination in the rear limbs, splaying of legs, and involvement of forelimbs. Later there is depression, apparent blindness, anorexia, and continuous bobbing movements of the head. Eventually total paresis and anorexia lead to death.

At necropsy all lymph nodes in the body are enlarged and yellow to tan. The liver is markedly swollen, pale yellow, and greasy. The spleen is enlarged and pale, and lymphoid tissue is indistinct. There is a deficiency of red marrow. Histologically, changes in the central and peripheral nervous systems are characterized by loss of Nissl substance, cytoplasmic swelling, and vacuolation of neurons (Figure 1). These changes are most marked in Purkinje cells of the cerebellum and neurons of the cerebellar roof nuclei and hippocampus, and in dorsal root and peripheral ganglion cells. Accumulations of large mononuclear cells with foamy cytoplasm are found most prominently in lymph nodes, liver, and spleen (Figure 2) but also are found readily in the bone marrow, adrenals, and lungs. These cells stain positively with oil red O and weakly positively with periodic acid–Schiff (PAS). In addition, endothelial cells in most organs have cytoplasmic swelling, and most lymphocytes and monocytes in blood smears contain clear cytoplasmic vacuoles.

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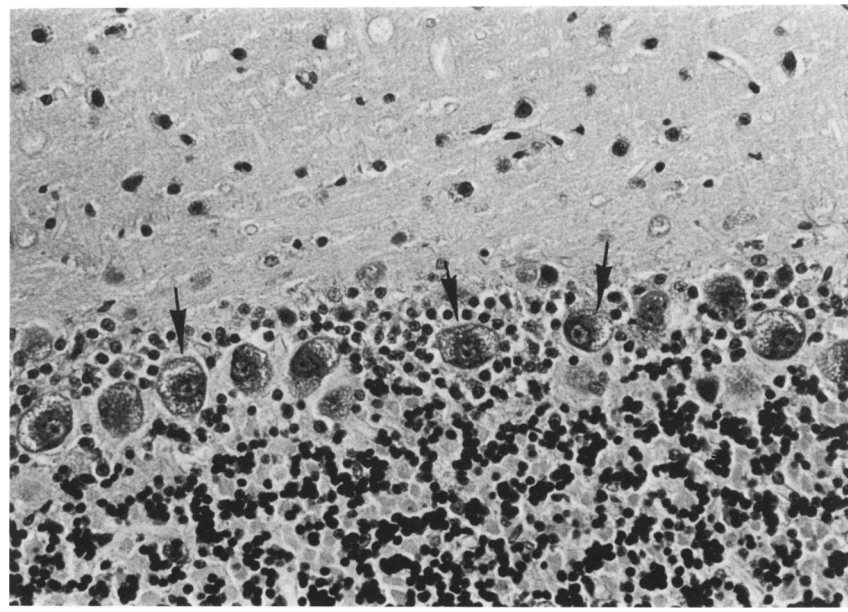

Figure 1—Cerebellar cortex from an affected kitten showing extensive cytoplasmic vacuolization of Purkinje cells (*arrows*).

Comparison With Human Disease

Feline sphingomyelinosis is analogous to human NPD Type A, and the clinical, morphologic, and biochemical features of the respective diseases are virtually identical.[4,5] One alteration in human NPD not yet found in affected cats is the macular "cherry red spot" seen ophthalmoscopically.[6] Although the human disease has been established as having an autosomal recessive mode of inheritance, the genetic basis for the disease in cats is not yet fully established. However, leukocyte sphingomyelinase levels that are about half of the normal level have been found in phenotypically normal littermates of affected kittens, strongly suggesting that feline sphingomyelinosis has an autosomal recessive mode of inheritance.

Usefulness of the Model

The clinical, morphologic, and biochemical defects all appear to be analogous in the human and feline subjects. Since cats are multiparous and readily can produce two or more litters of offspring per year,

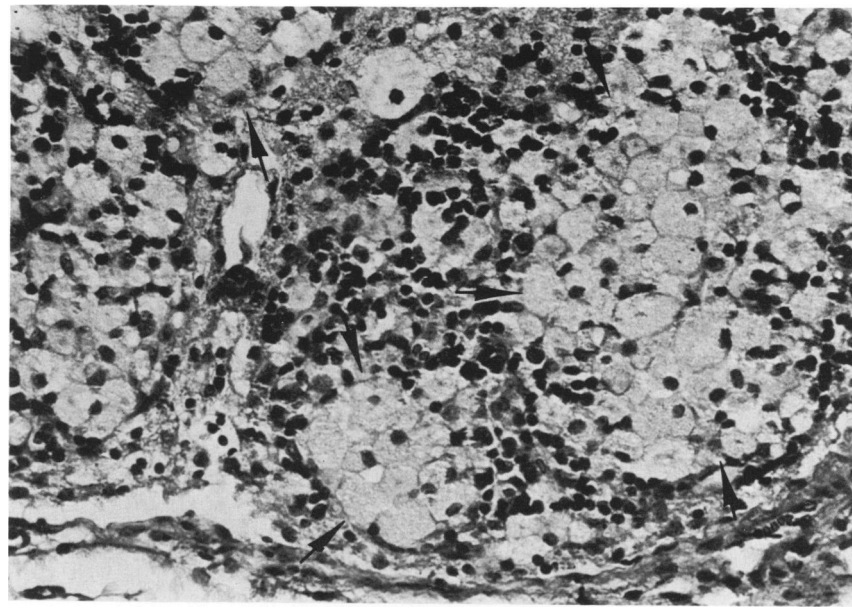

Figure 2—Spleen from a kitten with sphingomyelinosis containing aggregates of large, foamy macrophages (*arrows*).

there is great potential for the production of large numbers of kittens that are either homozygous or heterozygous for the trait. The availability of a genetic model for studies of the pathogenesis and treatment of this uniformly fatal disease of children would be preferable to the current use of drug-induced enzyme deficiency in rodents.[7,8]

Availability

It is believed that this and other lysosomal storage diseases are quite rare in the cat population at large.[9,10] We are currently mating suspected carriers of this trait (siblings and other close relatives of affected animals with low leukocyte sphingomyelinase levels) with the hope of establishing the mode of inheritance of feline NPD and increasing the number of affected animals. A colony of Siamese cats is being maintained by Dr. S. P. Snyder, Department of Veterinary Pathology, Colorado State University, Fort Collins, Colorado 80523.

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