ANIMAL MODEL OF HUMAN DISEASE

Mucopolysaccharidosis VI Maroteaux-Lamy Syndrome

Arylsulfatase B-Deficient Mucopolysaccharidosis in the Siamese Cat

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Biologic Features

Mucopolysaccharidosis (MPS) VI (Maroteaux-Lamy syndrome) has been reported in three families of Siamese cats.[1-4] Affected animals can be identified within a week after birth by the Berry spot test[5] for excessive urinary glycosaminoglycans (GAG), which has been shown to be dermatan sulfate by cellulose acetate electrophoresis.[2] Typical features of the syndrome are evident in animals by 6 weeks of age. These features include a broad flattened face, small ears, diffuse corneal clouding, large forepaws, and pectus excavatum (Figure 1). Affected animals are smaller than normal sex-matched relatives of the same age. Polymorphonuclear leukocytes in peripheral blood smears contain coarse granules that stain metachromatically with toluidine blue (Figure 2). Radiographic features of the disease are progressive epiphyseal dysplasia and bilateral hip subluxation, with eventual degeneration of joints and fusion of cervical vertebrae. Other features, seen in only a few animals, have included cutaneous nodules present over the face and head (which resolved within six weeks) and hind-limb paresis with depressed pain perception and increased extensor tone. Animals with hind-limb paresis retained some voluntary control of hind-limb movement and were not incontinent. Mentation is difficult to assess in animals; however, there have been no indications in any of the affected cats of deficits comparable to those defining mental retardation in man.

Figure 1—The facies of a Siamese cat with MPS VI. Note the depressed bridge of the nose, flattened facies, small ears and corneal clouding.

Significant pathologic changes are present in many systems.[4] The liver and spleen are of normal size.

Supported by NIH Genetics Center Grant GM-20138, NIH Grants AM-25759 and GM-25279 and the March of Dimes Birth Defects Foundation Grant 1-578.

Publication sponsored by the Registry of Comparative Pathology of the Armed Forces Institute of Pathology and supported by Public Health Service Grant RR-00301 from the Division of Research Resources, National Institutes of Health, under the auspices of Universities Associated for Research and Education in Pathology, Inc.

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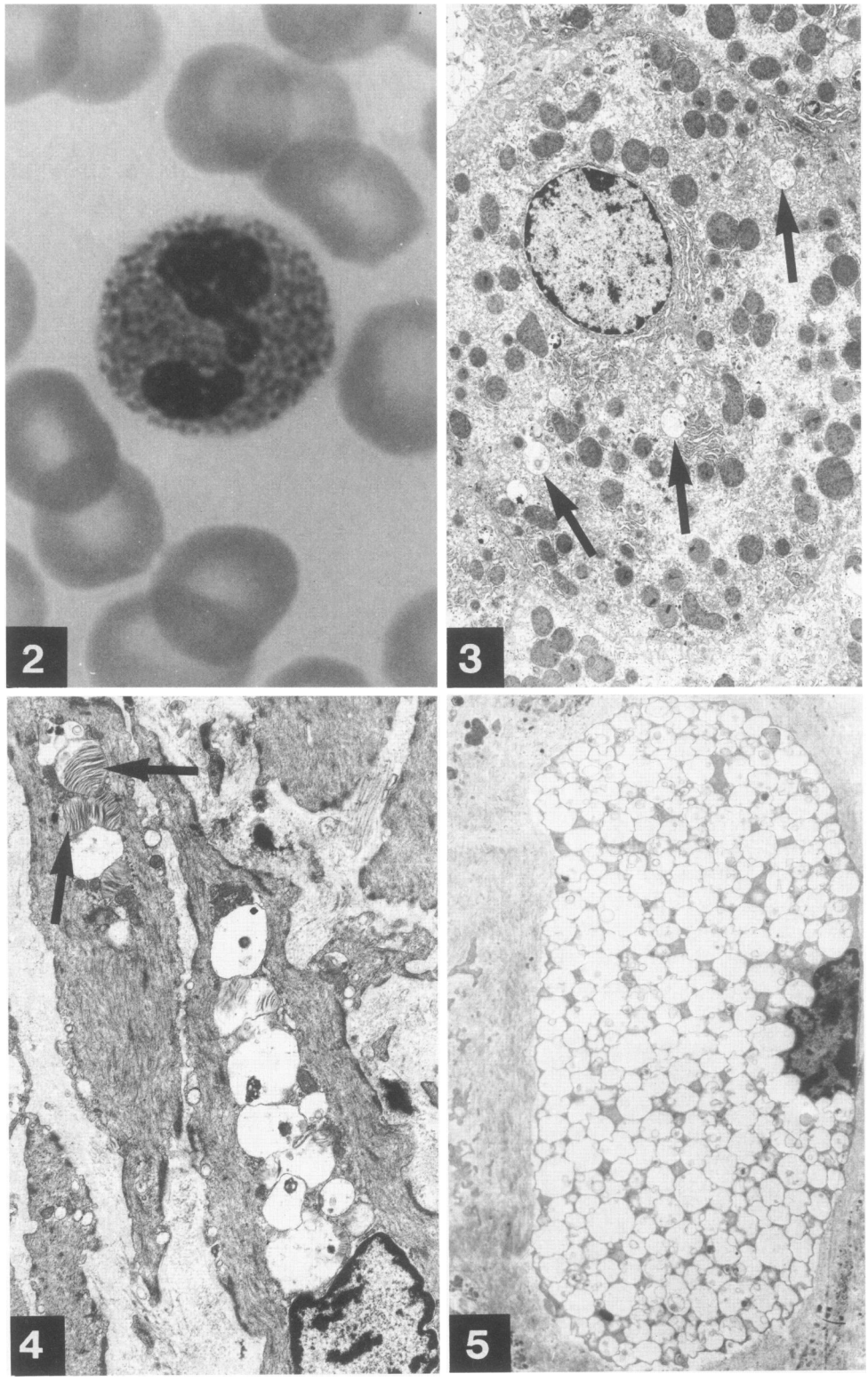

Figure 2—Light micrograph of a polymorphonuclear leucocyte with numerous metachromatic inclusions. (Toluidine blue, ×960) **Figure 3**—Electron micrograph of a hepatocyte that contains several small membrane-bound granular inclusions (*arrows*). (Lead citrate and uranyl acetate, ×4560) **Figure 4**—Electron micrograph of a smooth muscle cell in the spleen. Notice the membrane-bound cytoplasmic inclusions, some containing "zebra" bodies (*arrow*). (Lead citrate and uranyl acetate, ×10,080) **Figure 5**—Electron micrograph of a cartilage cell in a rib. The cytoplasm is filled with membrane-bound inclusions (Lead citrate and uranyl acetate, ×4750)

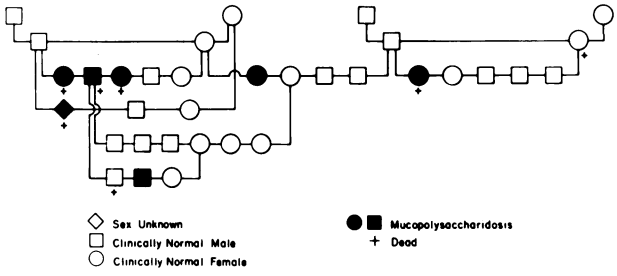

Figure 6—Pedigree of the several families of Siamese cats with MPS VI.

However, membrane-bound cytoplasmic vacuoles are present histologically in hepatocytes (Figure 3), Kupffer cells, and splenic smooth muscle cells (Figure 4). Similar vacuoles are present in ocular fibroblasts and ciliary epithelium, cartilage (Figure 5), dermal and atrioventricular heart valve fibroblasts, polymorphonuclear leukocytes, and aortic smooth muscle cells. Bone lesions consist of epiphyseal dysplasia with sclerosis and abnormal islands of cartilage, as well as fusion of cervical and lumbar vertebrae. Evidence of lysosomal storage within the central nervous system is limited to the perithelium of brain and cord and connective tissue cells of the meninges and choroid plexi. Spinal cord compression at T_{13}-L_2 was present in those animals with posterior paresis.

Accumulation of $^{35}SO_4$ by cultured fibroblasts is abnormal. The pattern is consistent with defective degradation of glycosaminoglycans.[2] Activity of the lysosomal enzyme arylsulfase B in peripheral blood granulocytes, cultured fibroblasts, and liver from homozygous affected cats is about 6% of that in normal cats, and obligate heterozygotes (parents of affected cats) have arylsulfatase B activities of an intermediate level compared with those of normal and affected cats.[2,3,6]

Pedigree information is consistent with autosomal recessive inheritance in independently ascertained families of cats with feline MPS VI, as well as in those bred within the animal colony at the University of Pennsylvania Veterinary School (Figure 6). Affected cats of both sexes have been bred successfully.

Comparison With Human Mucopolysaccharidosis VI

The clinical syndrome of MPS VI in the cat resembles quite closely the syndrome in man. Affected individuals of both species have facial dysmorphia, corneal clouding, epiphyseal dysplasia, peripheral leukocyte inclusions, urinary excretion of excessive amounts of dermatan sulfate, and less than 10% of normal arylsulfatase B activity.[7-9] Children with MPS VI are of normal intelligence; MPS VI cats have no demonstrable behavioral abnormalities that would indicate involvement of the central nervous system. Lesions of MPS VI in the cat and man are also similar, and in both species there is storage of glycosaminoglycans within membrane-bound cytoplasmic inclusions. The distribution of the lesions in the cat closely parallels that of the human mucopolysaccharidoses in general and MPS VI in particular. This naturally occurring animal model should prove to be useful in studies of the pathogenesis and therapy of lysosomal storage disease.

Availability

When the number of cats with feline mucopolysaccharidosis VI within this colony exceeds the research needs of the authors, animals will be made available to others with an interest in using this animal model of human disease.

References

1. Cowell KR, Jezyk PF, Haskins ME, Patterson DF: Mucopolysaccharidosis in a cat. J Am Vet Med Assoc 1976, 169:334-339
2. Jezyk PF, Haskins ME, Patterson DF, Mellman WJ, Greenstein M: Mucopolysaccharidosis in a cat with arylsulfatase-B deficiency: A model of Maroteaux-Lamy syndrome. Science 1977, 198:834-836
3. Haskins ME, Jezyk PF, Patterson DF: Mucopolysaccharide storage disease in three families of cats with arylsulfatase B deficiency: Leukocyte studies and carrier identification. Pediat Res 1979, 13:1203-1210
4. Haskins ME, Aguirre GD, Jezyk PF, Patterson DF: The pathology of the feline model of Mucopolysaccharidosis VI. Am J Pathol 1980, 101:657-674
5. Berry HK, Spinanger J: A paper spot test useful in the study of Hurler's Syndrome. J Lab Clin Med 1960, 55: 136
6. Vine DT, Jacovina MM, Haskins ME, Patterson DF, Desnick RJ: Characterization of the residual arylsulfatase B (ASB) activity in feline mucopolysaccharidosis (MPS) type VI. Am J Hum Genet 1979, 31:64A
7. Neufeld EF, Lim TW, Shapiro LJ: Inherited disorders of lysosomal metabolism. Ann Rev Biochem 1975, 44: 357-376
8. Dorfman A, Metalon R: The mucopolysaccharidoses (a review). Proc Natl Acad Sci USA 1976, 73:630-637
9. McKusick VA, Neufeld EF, Kelly TE: The mucopolysaccharide storage diseases, The Metabolic Basis of Inherited Disease. 4th edition. Edited by JB Stanbury, JB Wyngaarden, DS Frederickson. New York, McGraw-Hill, 1978, pp 1282-1307