REVIEW

Genetic Galactosylceramidase Deficiency (Globoid Cell Leukodystrophy, Krabbe Disease) in Different Mammalian Species

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ABSTRACT

Globoid cell leukodystrophy (Krabbe disease) in man is a rare genetic disorder caused by deficiency of galactosylceramidase activity. Clinical and pathological manifestations are almost exclusively confined to the nervous system, particularly to the white matter and the peripheral nerve. The disease also occurs in four other mammalian species: dog, cat, sheep and mouse. Except for the feline disease, for which enzymatic information is lacking, these animal models are genetically equivalent to the human disease. The clinical and pathological features are fundamentally similar in all species, as might be expected from the same underlying genetic defect. Nevertheless, significant species differences are observed in the clinical course, severity of pathological alterations, and analytical biochemistry. These genetically "authentic" animal models provide an invaluable tool for

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studies of the rare human genetic disorder. Results of studies already done and the future potentials are discussed.

**Index Entries:** Globoid cell leukodystrophy; Krabbe disease; hereditary disease; animal model; human; dog; cat; mouse; sheep; myelin; galactosylceramide; galactosylceramidase; psychosine; lactosylceramide; lysosomal disease.

**INTRODUCTION**

Globoid cell leukodystrophy (GLD)\(^\dagger\) in man is one of the classical genetic leukodystrophies known since the first definitive description by Krabbe in 1916 (Krabbe, 1916; see Suzuki and Suzuki, 1983a for an up-to-date review). The disease is caused by a genetically determined deficiency of a lysosomal hydrolase, galactosylceramidase (EC 3.2.1.46) (Suzuki and Suzuki, 1970). The enzyme normally catalyzes hydrolysis of the terminal β-galactosyl residue from galactosylceramide (the systematic name is D-galactosyl-N-acylsphingosine galactosylhydrolase). GLD caused by the same genetic galactosylceramidase deficiency occurs in three other mammalian species: the dog (Fankhauser et al., 1963; Fletcher et al., 1966; Jortner et al., 1968; Yajima et al., 1977; Suzuki et al., 1970), the sheep (Pritchard et al., 1980), and the mouse (Duchen et al., 1980; Kobayashi et al., 1980). In addition, a pathological description of typical GLD in the cat is in the literature (Johnson, 1970). Enzymatic verification, however, is lacking in the feline disease. To our knowledge, no colony of the sheep GLD has been established for research purposes and we are unaware of further studies since its original description. In contrast, a colony of the canine model was maintained for research purposes for many years at the School of Veterinary Medicine, University of Minnesota. Consequently, the morphology and biochemistry of the canine GLD have been investigated extensively (see Suzuki and Suzuki, 1983a for review). The murine mutant, the twitcher, was discovered relatively recently with details of morphology and enzymatic characterization, both published in 1980 (Duchen et al., 1980; Kobayashi et al., 1980). The advantages of the small size, rapid reproduction, and ease of maintenance are expected to result in a widespread use of the murine model as a research tool. Breeding pairs are commercially available from the Jackson Laboratory, Bar Harbor, Maine, and colonies have already been established in many laboratories throughout the world (Suzuki and Suzuki, 1983b).

Studies of rare human genetic disorders are limited by their uncommon incidence and by ethical considerations. Genetically and enzymatically authentic animal models can overcome many of the limitations in working with human patients. As expected from the same ge-

\(^\dagger\)Abbreviations: GLD, globoid cell leukodystrophy; CNS, central nervous system; PNS, peripheral nervous system.