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Pathologic studies of GM₁ gangliosidosis in Shiba dogs :
characteristic changes of central nervous system

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GM₁ gangliosidosis is a lysosomal storage disease that resulted from a deficiency of lysosomal acid beta-galactosidase. These genetic disorders are inherited as autosomal recessive trait. Previously, GM₁ gangliosidosis has been identified and studied in humans, cattle, cats, dogs, and sheep. In this study, we examined morphological changes of the central nervous system in five Shiba dogs affected with GM₁ gangliosidosis. They were euthanased and necropsied at 3, 6, 10, or 14 months of age. We also discussed the relationship between the neuropathologic findings and development of the main clinical signs.

The affected dogs showed progressive clinical signs of predominantly cerebellar ataxia and resting and intentional type of head tremor from approximately 6 months of age. After that clinical signs including hypermetria, tetraplegia, ataxic abasia and generalised muscle rigospasticity were also prominent and they developed lethargy at 14 months of age. Grossly, marked cerebral atrophy with yellow discoloration was recognized after 10 months of age. The width of cerebral white matter was decreased in all the examined dogs. Microscopic study revealed mild to severe distension of neurons due to cytoplasmic accumulation of storage materials related to the GM₁ gangliosidosis throughout the central nervous system. The most severe affected sites were cerebellar cortex, cerebral cortex and thalamus. The pathologic lesions were characterized by severe loss of Purkinje cells

in cerebellum, severe diffuse and/or perivascular infiltration of vacuolated macrophages in cerebral cortex and thalamus. The most of nuclei connected with cerebellum showed milder pathologic changes than the cerebral cortex in each examined dogs. The vacuolated macrophages in the cerebral cortex and thalamus increased in number as the age of the dogs increased. On the other hand, mature oligodendrocytes in the cerebral cortex markedly decreased in number in all the examined cases. Ultrastructurally, typical membranous cytoplasmic bodies (MCB) were observed in Purkinje cells and small granular cells at 3-month of age. The number and accumulation degree of MCB increased as the dogs grew older and MCB accumulated within dendrites as well as perikaryons at 6 months of age. There were also low-electron dense flocculent materials and vacuoles containing fine lamellae, suggesting storage of glycoproteins or oligosaccharides, recognized in lysosomes of vascular endothelial cells and pericytes after 10 months of age.

From these findings, Cerebellar Purkinje cells are suggested most consistently involved in Shiba dogs with GM₁ gangliosidosis. The neurological signs are interpreted to mainly reflect the primary distention and loss of cerebellar Purkinje cells caused by cytoplasmic accumulation of storage materials related to this disease. To our knowledge, severe perivascular accumulation of macrophages in the cerebrum has not been emphasized as the pa-

thologic changes in other breeds or animals affected with GM₁ gangliosidosis. This finding was considered as the characteristic lesion of severe GM₁ gangliosidosis in Shiba dogs, probably indicating that most of the storage materials accumulate within central nervous sys-

tem throughout the life. In addition, it is suggested that the affected dogs also have retardation of myelinogenesis (hypomyelinogenesis) associated with disturbance of oligodendroglial maturity.

Effects of culture media and cycloheximide treatment following electrical stimulation on parthenogenetic development of *in vitro*-matured porcine oocytes

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Recently, the birth of cloned piglets by somatic cell nuclear transfer has been reported, but the success rates are very low. This may be due to the inadequacy in the *in vitro* culture conditions for maturation and development, and activation treatment. To address this problem, the effects of media for maturation and subsequent development, and activation treatment on the parthenogenetic development of *in vitro*-matured porcine oocytes were examined.

First, *in vitro*-matured porcine oocytes were activated by electrical stimulation, and then cultured for 7 days either in NCSU-23 medium, which is widely used for porcine embryo culture system, or mSOF medium supplemented with 20 amino acids, which is successfully used for ovine and bovine embryo culture. Eighteen percent of parthenotes developed to blastocysts when they were cultured in NCSU-23, while parthenotes ceased to develop at the 2-4 cell stage when they were cultured in mSOF. Secondly, *in vitro*-matured porcine oocytes were activated by electrical stimulation combined with or with-

out exposure to 10 µg/ml cycloheximide (CHX) for 6 hr, and then cultured in NCSU-23 for 7 days. Combined treatment of electrical stimulation with CHX caused higher frequency of cleavage (63%) and blastocyst formation (54%) than electrical stimulation alone (32 and 19%, respectively). Next experiment was conducted to examine effects of supplementation with epidermal growth factor (10 ng/ml) to maturation medium on the development of parthenotes activated by electrical stimulation and CHX, but no beneficial effect was observed. To examine the effect of supplementation with fetal calf serum (FCS) to culture medium on parthenogenetic development, parthenotes were cultured in NCSU-23, and then transferred to NCSU-23 supplemented with 10% FCS at various time after electrical stimulation (0, 96 and 120 hr, respectively). When parthenotes were cultured in NCSU-23 supplemented with FCS from the beginning of culture or in FCS-free NCSU-23 until 96 hr after electrical stimulation then transferred to NCSU-23 supplemented with FCS, development to blastocysts