'Mad cow disease' in cattle can spread widely in ANS before detectable in CNS

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Bovine spongiform encephalopathy (BSE, or "mad cow disease") is a fatal disease in cattle that causes portions of the brain to turn sponge-like. This transmissible disease is caused by the propagation of a misfolded form of protein known as a prion, rather than by a bacterium or virus. The average time from infection to signs of illness is about 60 months. Little is known about the pathogenesis of BSE in the early incubation period. Previous research has reported that the autonomic nervous system (ANS) becomes affected by the disease only after the central nervous system (CNS) has been infected. In a new study published online in the August issue of The *American Journal of Pathology*, researchers found that the ANS can show signs of infection prior to involvement of the CNS.

"Our results clearly indicate that both pathways are involved in the early pathogenesis of BSE, but not necessarily simultaneously," reports lead investigator Martin H. Groschup, PhD, Institute for Novel and Emerging Infectious Diseases at the Friedrich-Loeffler-Institut, Riems, Germany.

To understand the pathogenesis of BSE, fifty-six calves between four and six months of age were infected orally with BSE from infected cattle. Eighteen calves were inoculated orally with BSE-negative material from calf brainstem as controls. The study also included samples collected from a calf that had died naturally of BSE. Tissue samples from the gut, the CNS, and the ANS were collected from animals every four months from 16 to 44 months after infection. The samples were examined for the presence of prions by immunohistochemistry. Samples

were also used to infect experimental mice that are highly sensitive to a BSE infection.

A distinct accumulation of the pathological prion protein was observed in the gut in almost all samples. BSE prions were found in the sympathetic ANS system, located in the thoracic and lumbar spinal cord, starting at 16 months after infection; and in the parasympathetic ANS, located in the sacral region of the spinal cord and the medulla, from 20 months post infection. There was little or no sign of infection in the CNS in these samples. The sympathetic part of the ANS was more widely involved in the early pathogenesis than its parasympathetic counterpart. More bovines showing clinical symptoms revealed signs of infection in the sympathetic nervous system structures at a higher degree than in the parasympathetic tissue samples. The earliest detection of BSE prions in the brainstem was at 24 months post infection. However, infection detected in the spinal cord of one animal at 16 months post infection suggests the existence of an additional pathway to the brain.

"The clear involvement of the sympathetic nervous system illustrates that it plays an important role in the pathogenesis of BSE in cattle," notes Dr. Groschup. "Nevertheless, our results also support earlier research that postulated an early parasympathetic route for BSE."

The results, Dr. Groschup says, indicate three possible neuronal routes for the ascension of BSE prions to the brain: sympathetic, parasympathetic, and spinal cord projections, in order of importance. "Our study sheds light on the pathogenesis of BSE in cattle during the early incubation period, with implications for diagnostic strategies and food-safety measures."

More information: “Spread of Classical BSE Prions from the Gut via the Peripheral Nervous System to the Brain,” M. Kaatz, C. Fast, U. Ziegler, A. Balkema-Buschmann, B. Hammerschmidt, M. Keller, A.

Oelschlegel, L. McIntyre, M. H. Groschup (DOI 10.1016/j.ajpath.2012.05.001). It appears online in advance of publication in *The American Journal of Pathology*, Volume 181, Issue 2 (August 2012)