New sporadic prion protein disease identified

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A new sporadic prion protein disease has been discovered. Variably protease-sensitive prionopathy (VPSPr), as it has been named, is the second type of complete sporadic disease to be identified since Creutzfeldt-Jakob disease (CJD) was reported in the 1920s. The landmark finding from the National Prion Disease Pathology Surveillance Center at Case Western Reserve University is published in the August issue of *Annals of Neurology*.

Normally, the human prion protein gene comes in three types due to its capability to encode prion proteins that contain only the amino acid methionine, commonly identified as M, both methionine and valine, commonly identified as V, or only for the amino acid valine at position 129. Therefore, when it comes to the prion protein gene unaffected people can be identified as 129MM, 129MV or 129VV. Sporadic CJD (sCJD), which is the most common human prion disease, can affect patients who have any one of the three types of the prion protein gene. In 2008, Pierluigi Gambetti, MD, and Wen-Quan Zou, MD, PhD, with collaborators, reported the discovery of this novel disease, which affected patients who exhibit only one of the three types of the prion protein gene. In this follow-up study, they discovered that all three genetic groups can be affected also by this novel disease which now joins sCJD in displaying this feature. However, VPSPr is associated with an abnormal prion protein that exhibits characteristics very different from those of sCJD, as well as other prion diseases, suggesting that it may be caused by a different mechanism, perhaps more akin to other neurodegenerative diseases, such as Alzheimer's disease. This finding may exemplify, for the first time, the possibility that the prion protein

affects the brain with different mechanisms.

While examining cases received at the National Prion Disease Pathology Surveillance Center where he is the director, Dr. Gambetti observed that a subset of cases had clinical and pathological features quite different from those of all known types of human prion diseases. Further, after being tested for prion proteins via the Western blot - the gold standard of prion disease diagnosis - the cases were negative. Dr. Gambetti then collaborated with Dr. Zou, associate director at the center, to solve the riddle of a disease that exhibited some features of a prion disease in histopathological examination but was negative using the standard Western blot test.

Dr. Zou's lab performed a full characterization of the disease and discovered that the VPSPr-associated abnormal prion protein formed a ladder-like electrophoretic profile on Western blot. "When I obtained the first Western blot result of these cases with a different antibody against prions, I was surprised that these cases consistently exhibited this particular profile; one that I had never seen in my more than 10 years of work on human prion diseases," Dr. Zou, assistant professor of pathology at Case Western Reserve School of Medicine, recalls. This ladder-like profile is quite distinctive and very different from the profile of common prion diseases. "Discovery of this unique type of prion provides solid evidence that this novel disease may possess a pathogenesis that is different from that of the major prion diseases currently known," Dr. Zou adds.

Despite extensive research, a relatively large group of neurodegenerative diseases associated with dementia remain undefined. Before being discovered and characterized, VPSPr was one of the undefined dementing diseases. The discovery of VPSPr is chipping away at that group. In the two years since its discovery, more than 30 cases have been reported.

"If, as the current evidence indicates, the VPSPr mechanism of affecting the brain is different from that of other sporadic prion diseases, such as sCJD, the discovery of VPSPr would also provide the first example that the prion protein may spontaneously damage the brain with different mechanisms," concludes Dr. Gambetti, professor of pathology at Case Western Reserve School of Medicine. "This might apply to other dementing illnesses as well, and has implications for the strategies that need to be followed to attain a cure."

Drs. Gambetti and Zou, along with their extensive research team, plan to further characterize the abnormal prion protein associated with VPSPr as well as other important features of the protein, such as the disease's propensity for transmission upon inoculation and its replication in test tubes. These features in VPSPr will be compared with those of sCJD to obtain a complete picture of how the abnormal prion protein attacks the brain in these two diseases.

Provided by Case Western Reserve University