

What finding prion proteins in skin means in the larger picture of what we already know about prion disease

The recent study by Orrú and colleagues that prions are found in the skin of CJD patients is understandably concerning for families. However, it is important to consider this finding in the broader context of what we already know about CJD through decades of research. Scientific discoveries often describe very specific scenarios that often are not applicable to real life situations. The multitude of “miracle” Alzheimer’s disease drugs that have shown promise in animal models but have not resulted in any positive human clinical trials is just one of many examples.

What did the researchers do in this study?

In this study, researchers assessed whether or not prions agents and prion infectivity were present in the skin of CJD patients. Skin samples from deceased sporadic and variant CJD patients (23 patients total) as well as autopsy or biopsy skin samples from non-CJD patients were taken. A diagnostic test (real time quaking induced conversion, RT-QuIC) that is able to detect extremely small amounts of prions through amplification techniques was conducted on skin samples. Infectivity was then investigated by injecting skin samples from two of the above patients directly into the brains of mice that were genetically modified to express the human prion protein. Importantly, such an experimental scenario (direct injection of prion samples into the brain) is not going to happen in the routine care and surgery of patients.

What did the researchers find in this study?

RT-QuIC was able to detect prion-seeding activity in skin from all CJD patients. Prion seeding activity in skin was approximately 1,000 to 100,000 times lower compared to performing RT-QuIC on brain samples of these patients. This is suggestive of very low levels of prions in skin. All mice that had skin samples from two CJD patients injected into their brains developed prion disease again suggesting that infectious prions were present in the skin of sCJD patients.

What does this mean for humans?

It is unclear what this means for humans at this time as these findings are not what we expected based on what we knew about prion disease from the last several decades of research. There currently is no compelling and consistent evidence that CJD can be transmitted through surgeries that do not involve the brain. Although many epidemiologic studies have examined this issue, the results have been controversial because results of studies varied widely and evidence was deemed to be of low quality. Clearly, this new finding suggests that further investigation is needed to help address this controversy.

How is prion disease transmitted in humans?

Less than 1% of all cases of CJD are due to an acquired infection. The reason for this is that very specific circumstances are required for transmission between individuals. In the past, CJD was transmitted through dura mater, corneal

transplants, pituitary gonadotropins, and human growth hormone that were acquired from cadavers presumably affected by prion disease. It has also been transmitted via neurosurgical instruments. These scenarios from these previous studies inform us that for transmission to occur, tissues were often taken from an affected individual's central nervous system and either consumed, injected, or placed within the brain of another individual. Fortunately, it was the successful identification of the correlation between the occurrence of CJD and medical contamination history that led to the cessation of the majority of these unsafe practices that no longer occur because of the precautions that were put in place.

An important point regarding neurosurgical transmission must also be considered. Only four cases of neurosurgical transmission have been recognized to date, all of which occurred in the last century. This suggests that although complete prion decontamination requires special sterilization procedures, it seems highly likely that current standard sterilization techniques does remove the majority of prion infectivity.

The one exception to the above scenarios is variant CJD. Variant CJD is different in that there is evidence that it can be transmitted between individuals by blood transfusion. Although there is the theoretical risk of blood contamination in other forms of CJD, there has been no human population study evidence that this occurs in any other prion disease except vCJD.

Am I at increased risk of contracting CJD by caring for my loved one or patients?

No, multiple studies have demonstrated that there is no evidence that healthcare professionals or caregivers are at any increased risk of prion disease compared to the general population.

What does this study actually suggest?

This study suggests that extremely small amounts of prion proteins can be found in the skin of deceased CJD patients and that they may be infectious in certain scenarios. It also suggests that further studies are needed to compare infectivity between the skin and the brain in CJD patients.

What are the positives of this study?

One positive outcome of this study is its demonstration of the high sensitivity of RT-QuIC, which allows it to detect very small amounts of prions. This may be another way to more definitely diagnose patients with prion disease in countries where autopsies are generally not performed for cultural reasons. It also may be expanded to develop better diagnostic tests for live patients.

What are the future directions for this project?

Further studies will attempt to validate findings from this study. They will also investigate why human population studies are variable and largely not suggestive of prion disease transmission through non-neurosurgical procedures. Future studies

will help us understand what it means to have small amounts of prions in skin with regard to diagnostic test results and infection risks.