Published in final edited form as:

Lancet Neurol. 2007 April ; 6(4): 294–295. doi:10.1016/S1474-4422(07)70064-9.

Reversibility of prion-induced neurodegeneration

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Transmissible spongiform encephalopathies (TSEs), also known as prion disorders, are a group of fatal, infectious, brain diseases that affect human beings and other animals. As in other more prevalent neurodegenerative disorders, such as Alzheimer's or Parkinson diseases, the hallmark event in TSEs seems to be the misfolding, aggregation, and brain accumulation of an otherwise normal protein.¹ The misfolded form of the prion protein (PrP^{Sc}) is not only a typical pathological feature of the disease and a possible triggering event in the pathogenesis, but is also the major (and perhaps the sole) component of the infectious agent.^{2–4}

Over the years, extensive research has been devoted to investigating the controversial nature of the TSE infectious agent and the mechanism of prion replication.^{2–4} Despite impressive accumulation of knowledge about prions, early diagnosis is still not possible and there is no cure or even preventive or palliative treatment for these diseases. Also, little is known about the brain alterations responsible for the disease symptoms and the molecular pathways leading to cerebral damage.

A study by Mallucci and co-workers⁵ provides an important step forward in our understanding of the molecular basis of neurodegeneration in TSEs.⁵ The researchers developed postnatal conditional PrP-null mice that developed normally⁶ and in which prion disease was prevented by knocking down the expression of the PrP gene.⁷ In their most recent study,⁵ they expand these observations to show that the early clinical symptoms and neuropathological alterations induced by prion infection are reversed upon elimination of PrP expression. Mice experimentally inoculated with prions under the conditions used in this study begin to show the first subtle clinical signs around 8 weeks post-infection, correlating with the earliest pathological changes in the brain. The brain damage and clinical condition worsen progressively and animals die at around 13 weeks post-inoculation. By use of the *cre/loxP* system (a tool for tissue-specific knockout of genes), PrP expression can be halted in neurons (but not other cells) at 9–10 weeks of age. Mallucci and colleagues showed that before elimination of PrP expression, inoculated animals developed progressive behavioural deficits in hippocampal-dependent learning and spontaneous burrowing and nesting. These behavioural changes were accompanied by electrophysiological and synaptic alterations as well as histopathological features of spongiosis, gliosis, and PrP^{Sc} deposition. However, neuronal death or extensive PrP^{Sc} aggregation was not observed, indicating that these processes are not responsible for the initiation of the disease. Elimination of PrP expression led to substantial recovery of behavioural, physiological, and histopathological abnormalities.⁵ Conversely, control mice that continued to express PrP progressively worsened, acquiring full-blown clinical signs, and died a few weeks later.

Mallucci's study provides three important messages. First, it shows that the early stages of brain damage and clinical symptoms in TSEs can actually be reversed if the cause of these alterations is efficiently removed. Although this is a very important finding, we have to be cautious in extrapolating the results obtained with young experimental animals to human

patients because the regenerating capabilities in the brains of elderly people are probably substantially reduced. Second, the study suggests that the disease reversibility is probably due to the fact that the pathology (at least its earliest stages) is not caused by massive and irreversible neuronal loss. This conclusion is also lent support by several previous reports from other groups showing that neuronal death occurs only very late in the disease.^{8,9} Third, early clinical and tissue changes occur before extensive accumulation of large PrP^{Sc} deposits and recovery does not parallel a reduction in PrP^{Sc} concentrations.

The implication of these results is that early neurodegeneration is probably not caused by aggregated PrP^{Sc}, but perhaps by a more transient neurotoxic species. Mallucci's findings support a paradigm change that has also been occurring in other neurodegenerative diseases associated with the accumulation of misfolded proteins in the brain. Indeed, recent developments in Alzheimer's disease, Parkinson's disease, amyotrophic lateral sclerosis, and other degenerative disorders of the brain have been pointing to the same conclusions. As a result, neurodegenerative diseases are now seen as problems of neuronal dysfunction (as opposed to neuronal death) and the probable cause of the nerve cells and synaptic alterations seems to be the formation of misfolded proteins arranged in small soluble oligomers.^{10–12} These toxic structures are the precursors of the large protein deposits, which are the pathognomic, but probably inert, markers of neurodegeneration.

The reversibility of neurodegeneration represents a significant change in the view of TSEs and other neurodegenerative diseases as unavoidably fatal diseases that inexorably progress, robbing all human abilities until death. This new concept provides hope for patients because it means that early intervention could lead not only to stopping disease progression, but also to recovery of the cognitive and behavioural problems and healing of the brain damage. Moreover, if a method for early diagnosis is developed and coupled with an efficient treatment, the disease could actually be eradicated. Indeed, there is reason to be hopeful, because substantial progress has been made in recent years in the goal of developing a sensitive, non-invasive, biochemical approach to identify prions and other misfolded proteins in biological fluids of individuals at the presymptomatic stages of the disease.¹³ Whether the degenerative changes if the human brain affected by TSEs can be reversed, as shown by Mallucci and co-workers in experimental rodents, remains to be elucidated. The window of time in which disease recovery is possible also needs to be identified.

Acknowledgments

I have received an NIH grant NS050349.

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