

SEAC 103/2

EFFECT OF AGE ON THE PATHOGENESIS OF TRANSMISSIBLE SPONGIFORM ENCEPHALOPATHIES

ISSUE

1. Most clinical cases of variant CJD (vCJD) have occurred in young adults. The reasons behind this apparent age-related susceptibility are uncertain. A recent paper by Brown *et al* in the Journal of Immunology, (attached at annex A), reports the findings of a study in mice, which suggest that age related decline in the functioning of follicular dendritic cells might impair TSE pathogenesis.

STUDY DESIGN

2. The study used C57BL/Dk mice challenged with ME7 scrapie brain homogenate. The mice were assessed weekly for signs of clinical disease and culled at a standard clinical endpoint. Survival times were recorded for mice that did not develop clinical signs of disease and were culled when they showed signs of intercurrent disease.

FINDINGS

3. This study finds that early TSE agent accumulation in the spleens of aged mice was significantly impaired compared to that in young adults. Furthermore, following peripheral exposure, none of the aged mice developed clinical TSE disease during their lifespans, although most mice displayed histopathological signs of TSE disease in their brains.
4. Comparison of follicular dendritic cell networks (FDCs) in the spleens of aged and young adult mice, showed a highly significant reduction in the total number of PrP^C expressing FDCs in aged mice when compared with those of young adults.
5. The data imply that the reduced status of FDCs in aged mice significantly impairs the early TSE agent accumulation in

lymphoid tissues and subsequent neuroinvasion. Furthermore, the inefficient neuroinvasion in aged individuals may lead to significant levels of subclinical TSE disease in the population.

BACKGROUND

6. Following peripheral exposure, many TSE agents accumulate first in lymphoid tissues before spreading to the Central Nervous System, where they cause neurodegeneration. Early TSE agent accumulation upon FDCs in lymphoid follicles appears to be critical for efficient neuroinvasion.¹

7. Most clinical cases of vCJD have occurred in young adults; the median age at onset of disease was 26 years and the median age at death 28 years (the corresponding ages for sporadic CJD are 67 and 67). The youngest case of vCJD was aged 12 years at onset, while the oldest case of vCJD was aged 74 years.²

ADVICE SOUGHT

8. The committee is invited to note the findings of this study.

**SEAC SECRETARIAT
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¹ Klein, M. A., R. Frigg, A. J. Raeber, E. Flechsig, I. Hegyi, R. M. Zinkernagel, C. Weissmann, and A. Aguzzi. 1998. PrP expression in B lymphocytes is not required for prion neuroinvasion. *Nat. Med.* 4: 1429–1433; Brown, K. L., K. Stewart, D. Ritchie, N. A. Mabbott, A. Williams, H. Fraser, W. I. Morrison, and M. E. Bruce. 1999. Scrapie replication in lymphoid tissues depends on PrP-expressing follicular dendritic cells. *Nat. Med.* 5: 1308–1312.

² National CJD Surveillance Unit, Seventeenth Annual Report, 2008, p.13.

