The intractable puzzle of sporadic Creutzfeldt-Jakob disease in very young people

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In the era of randomised control trials and multicentre observational studies, it is easy for academic neurology to overlook the compelling questions posed by individual patient cases. Sporadic Creutzfeldt-Jakob disease (CJD) in a 21 year-old was the right diagnosis, but hardly a satisfactory explanation for either the doctor or patient and his family [*ref the Neurology paper*]. How can a typically late-onset disorder occur in someone so young?

Confronted with the patient who has an early onset cognitive disorder, thoughts quickly turn to Mendelian genetic forms and rare mimics, but sporadic forms of common dementias are practically unheard of under the age of 30[1]. Familial forms of prion disease can occur in the very young, particularly insertional mutations[2], but all inherited prion diseases are caused by mutations in the gene that encodes the prion protein (*PRNP*), and were excluded in this case.

Prion diseases are special because of the acquired forms, like variant CJD caused by the human transmission of bovine spongiform encephalopathy (BSE) prions, and iatrogenic forms, caused by the use of prion-contaminated cadaveric hormones, surgical instruments, or dura mater. Acquired prion disease can affect children and young adults, but in this case, there was no known history of exposure, or investigation or pathological features of acquired disease. An unrecognised exposure is an important consideration, as the harbinger of each new episode of acquired prion disease has been a sentinel case series, provoking health protection measures that can save future transmissions. The occurrence in the UK of a new variant of CJD in a series of young people instigated a public health crisis, eventually leading to the deaths of over 230 people[3]. Today, chronic wasting disease of cervid species is widespread in N America, and has been observed to a much less prevalent extent in Norway and other Scandinavian countries[4,5]. Whilst this animal prion disease is not currently thought to be zoonotic, the possibility emphasises the importance of accurate diagnosis in cases like this. Vigilance for acquired causes requires long-term funding for surveillance with the tools, including autopsy, to investigate cases thoroughly[6].

Prions are atypical infectious agents comprised of multimeric assemblies of misfolded forms of host prion protein. Prions grow through a process of binding to normal prion protein and templating the disease-associated structure, followed by fission of the assembly to create new prions. There are different types or strains of prion, akin to strains of viruses, thought to be encoded by differences in the pathogenic structure. The “VV1” type of sporadic CJD seen in this case is a rare type but previous reports do have similar clinical features and a predilection for particularly young adults[7]. In the UK too, we have seen young adults with this type of sporadic CJD.

The longstanding and fundamental enigma of sporadic CJD is when and why do the first prions appear in the body? Is this simply a random and extremely rare event of spontaneous protein misfolding, is it provoked by a somatic mutation in *PRNP*, or do prions routinely form in many of us throughout life, only for disease to result when there is a failure of clearance? These are intractable questions, but there are some potential approaches. GWAS has recently identified risk variants in loci unconnected to *PRNP* that might help us understand co-factors involved in the formation of prions in the human body, and maybe are peculiarly enriched in young cases[8]. We might also look for evidence of somatic mutation in a small proportion of brain cells, but even individuals who carry mutations in all cells of the body only uncommonly develop CJD in early adulthood, and genomic somatic mutation studies tell us that we are all likely to carry *PRNP* mutations in many neurons[9]. Perhaps we just have to accept stochasticity and that some fundamental questions are, for now, beyond scientific scrutiny.

There are plenty of other things we can work on. The leading therapeutic hypothesis in prion disease is clear: stabilise, eliminate, or greatly reduce normal prion protein or its genetic code. For the first time, bespoke strategies to do this have either been used in patients, or are planned to be used. We are fortunate in CJD to have MRI and RT-QuIC assays both of which are highly specific and sensitive in the early stages of disease. Whilst in this case the RT-QuIC test was formally indeterminate, the result will have been interpreted as providing support for the diagnosis in the context of an abnormal MRI. Prompt access to and accurate interpretation of investigations, and referral on, will be critical to making early diagnoses of CJD so that patients can be recruited to trials before irreversible neurodegeneration has occurred. Making progress on trials of designed therapeutics is at least a potentially rewarding diversion from our inability to explain the origin of sporadic CJD.

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