Sporadic Creutzfeldt-Jakob disease (sCJD) is relatively rare with an annual mortality rate of 1–2 per million of the population worldwide. It is one of the human prion diseases or transmissible spongiform encephalopathies, which are associated with conversion of normal prion protein (PrP\textsuperscript{C}) to an abnormal form (PrP\textsuperscript{Sc}). Human prion diseases may be genetic or acquired (through iatrogenic transmission or through consumption of BSE-contaminated food). However, about 85% of cases are without known cause, designated as sCJD. The prion hypothesis, put forward by Prusiner [1] in the 1980s, suggests that sCJD results endogenously either from spontaneous misfolding of PrP\textsuperscript{C} into the abnormal form (PrP\textsuperscript{Sc}) or from a somatic mutation of the prion protein gene.

While the majority of the scientific community accepts the prion hypothesis and its explanation of sCJD, some or all of the cases currently classified as sporadic could relate to an environmental exposure, that either predisposes the individual to develop CJD or transmits disease from another individual, such as through surgery involving contaminated surgical instruments. The age-specific mortality data for sCJD show a decline in cases in the very elderly and this argues against theories of spontaneous, chance, events; of course, it could simply reflect case underascertainment in this age group. The possibility of environmental exposure is supported by the fact that CJD has actually been transmitted through neurosurgery, the use of depth electrodes in the brain and corneal transplantation, and that transmissible spongiform encephalopathies can have long incubation periods, up to 40 years in kuru. In addition, sCJD is classified into five clinicomolecular subtypes [2], and a new form was reported recently [3] – this heterogeneity could reflect different aetiologies.

Several previous epidemiological studies have examined possible risk factors, including surgery, for sCJD. Given the rarity of sCJD, case-control studies have been the method of choice, despite recognising their inherent propensity towards bias. Studies that have examined surgery as a risk factor have reported inconsistent results and some have implicated surgery other than that previously recognised as transmitting sCJD (neurosurgery and corneal transplantation) [4–12]. One explanation for the inconsistent results is the differences in the respective methodologies (each producing different biases), particularly the source of the control group and the method of ascertaining surgical histories. As summarised by Barash et al. [13], whether surgery is identified as a risk factor for sCJD depends to some degree on the control group selected, for example, hospital-recruited controls are not representative of the ‘normal’ population with respect to surgery. Previous studies have relied on surrogate informants and/or medical records for surgical histories, sometimes over different time periods, which inevitably has led to bias.

In this journal, Mahillo-Fernandez et al. [14] have attempted to overcome two major problems that may result in bias, by using two control groups (matched and unmatched) sampled randomly from population registries and by ascertaining surgical exposure through the use of hospital discharge data. Sweden and Denmark were used as the source of cases and controls, each country maintaining continuously updated centralised population registries. Surgical histories, independent of case/control status, were obtained from 167 cases of sCJD (definite and probable), 835 age-, sex-, and residence-matched controls and 2,224 unmatched controls. Surgical procedures were categorised into body system groups and windows of time before onset of sCJD (and the equivalent for controls). They showed that a history of any major surgery conducted 20 or more years before onset of sCJD was more frequent in cases than in both sets of controls (OR = 2.44 for matched and OR = 2.25 for unmatched controls). Specifically, surgery of the digestive system and spleen, female genital organs and peripheral vessels* and lymphatic system was associated with a statistically significantly increased risk of sCJD. In addition, there was a dose-response effect observed with a linear increase in risk per surgical discharge, which was observed in a previous Australian study [8].

Why are these results of interest? It is the first published large study that has attempted to reduce the bias inherent in the previous studies by using data from sources recognised for their validity. The results are of potential importance both in relation to the aetiology of sCJD and to public health concerns. These results do not, in themselves, distinguish between surgery directly transmitting disease and surgery as a risk factor in some other sense. Newer, more sensitive techniques have detected PrP\textsuperscript{Sc} in sCJD peripheral tissues, including skeletal muscle and spleen [15, 16]. Unrecognised transmission through surgery is a possibility and a peripheral route of infection would be expected to result in a long incubation period (such as 20 years or more). However, the definitive attribution of cases to infection via surgery requires data that link individuals in space and time, as attempted in previous studies [11, 12]. Conceivably, surgery could be some sort of trigger of later illness or even have an association with another causative factor, although there are no clear biologically plausible mechanisms for these suggestions.

*On request of all authors, the term ‘peripheral nerves’ was changed to ‘peripheral vessels’ to match with the corrected text of Mahillo-Fernandez et al. [14]. October 18, 2008.
sCJD may be a spectrum of diseases with different aetiologies. Some cases may well be due to covert iatrogenic transmission and the authors calculated that 18% of sCJD cases might be attributed to surgery. They thought this was an underestimate because of incomplete surgical data before the mid 1970s. If this were true, it would warrant further investigation, not least in order to reduce the burden of this disease by risk reduction methods, including the further improvement of the decontamination of surgical instruments. Similar studies in countries with equivalent national datasets should be carried out in order to confirm these findings. In addition, a study to investigate possible links between the time and place of surgery of the cases used in this study may be informative.

References

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