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Risks and Biases in Case-Control Studies of Iatrogenic Creutzfeldt-Jakob Disease

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Prion diseases are relentlessly progressive and ultimately fatal illnesses caused by the aggregation and abnormal folding of a host-based cellular prion protein PrP(C) [1]. Creutzfeldt-Jakob disease (CJD) is the commonest form and is characterized pathologically by spongiform changes, micro- and astrogliosis, and loss of neurons [2]. It is of tremendous public health importance due to its incurability and transmissibility, coupled with a generally long lag time between exposure and the expression of symptoms.

CJD occurs in three forms: familial or genetic, sporadic, and acquired, which can be variant or iatrogenic. In view of the latter, European Union-wide guidelines are being drafted for the prevention of the transmission of CJD in medical and health-related environments [3]. In the previous issue of *Neuroepidemiology*, the well-written paper by de Pedro Cuesta et al. [4] provides a timely review of the scientific basis for the EU public health recommendations, specifically of the evidence of the risk of medical procedures and transfusion of blood and blood products, and identifies susceptibility to bias in related publications.

The authors reviewed documents published in MEDLINE or EMBASE between 1 January 1989 and 31 December 2011 related to prion diseases or CJD and procedures or transfusions. From the initial 506 distinct documents, only 20 documents describing 18 case-control studies finally met study criteria. Only papers in English were selected – it is unclear whether papers in other languages would have provided additional information. It should be noted that all studies were conducted in developed countries. Sensitivity to bias in study design was evaluated using the study central birth cohort model.

While data was sparse, exposure to human dura mater grafts was strongly associated with CJD. Conflicting results were found for the association with surgery, while varied results were found for surgery at specific anatomical sites; surgery was even found to be protective in some sites. Significant findings also varied at dif-

ferent time lags. Some studies showed space-time clustering of surgical interventions but no links were found. As for blood transfusion, it was either protective or nonsignificantly associated with sporadic CJD, with conflicting results for long time lags.

The authors found biases in almost all studies, largely related to the source of controls, differences between time periods between case selection and recruitment of controls, source of information on the history of exposure, and the issue of repeated exposures. Types of exposures also varied widely. Not all papers mentioned the use of a classification system for diagnosis and procedures, which may lead to misclassification.

The author's conclusions are that, except for the use of human dura grafts, the results of the case-control studies are inconsistent for an association between medical or surgical/invasive dental or endoscopic procedures, and CJD. This may be due to various biases as well as a lack of control for confounding. It suggests that better study designs need to be employed in subsequent case-control studies. Cohort studies may be a preferred study method, but one with adequate statistical power would require very large sample sizes and prolonged follow-up.

Clearly, more and more accurate data are needed to better inform so that guidelines can be established. Till the evidence is clear, continued vigilance is advised, with careful consideration by the clinician in consultation with the patient and his or her family before the performance of procedures or administration of transfusions. The old adage of 'first, do no harm' is particularly important for diseases with long incubation times, where the symptoms arise years after exposure and associations are not recognized, medical records are missing or destroyed, or the physician has long retired, blissfully unaware of his or her role in the transmission of an uncommon but invariably fatal disease.

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