EDITORIAL

Blood Transfusion and Brain Amyloidosis
Should We Be Worried?

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Is misfolding of the amyloid β peptide—the primary constituent of senile plaques in Alzheimer disease and toxic cerebral vessel wall deposits in cerebral amyloid angiopathy (CAA)[1]—contagious? Data from experimental and clinical sources argue that prion-like transmission of amyloid β misfolding[2] can indeed occur. Experimental studies as early as 1993 reported appearance of cerebral amyloid deposition following intracerebral injection of exogenous amyloid β into marmosets[3] (a nonhuman primate that expresses human-like amyloid β) and subsequently in transgenic mice expressing human amyloid precursor protein.[4] A human correlate for these findings emerged in 2015 with observation of advanced Alzheimer disease and CAA pathology in brains from individuals who had been treated with pituitary-derived human growth hormone.[5] Subsequent clinical reports have identified early onset of the recurrent intracerebral hemorrhages (ICHs) characteristic of CAA decades after neurosurgical procedures such as dural repair with cadaveric grafts.[6,7] The reported number of suspected iatrogenic CAA cases is currently at 49 (mean age at first presentation, 43 [SD, 12] years)[7] and is likely to grow as an echo of an era when cadaveric human tissue grafts were part of the neurosurgical toolbox. This represents a devastating illness for these individuals but nonetheless only a small share of the overall burden of CAA and Alzheimer disease.

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As this cautionary story appeared headed toward a kind of conclusion, a report in the current issue of *JAMA*[8] introduces a new and potentially alarming twist: the possibility of amyloid β transmission via blood transfusion. The authors analyzed national data registries in Sweden and Denmark for ICH in recipients of red blood cell transfusion from donors who themselves had ICH over the years after their blood donations, with the explicit assumption that donors with 2 or more ICHs would likely have CAA. The authors found no increase in posttransfusion ICH risk among the approximately 1% of recipients whose donors had a single post-blood donation ICH (hazard ratios of approximately 1), but found greater than a doubling of the hazard for the 0.1% of recipients whose donors had multiple post-blood donation ICHs (multivariable-adjusted hazard ratios, 2.73 [95% CI, 1.72-4.35] for the Swedish registry and 2.32 [95% CI, 1.04-5.19] for the Danish registry). Although dementia was not analyzed as an outcome (in part because the sensitivity of detecting dementia in national registries is low[9]), the authors did observe a similar increase for hazard of posttransfusion ICH (2.44 [95% CI, 1.52-3.94]) among recipients of blood from donors with a single posttransfusion ICH plus dementia. A control analysis of posttransfusion ischemic stroke instead of ICH found no increased hazard among recipients of blood from donors who had single or multiple ICHs.

There are good reasons to treat the possibility of CAA transmission via blood transfusion seriously—and good reasons to remain skeptical at least for the present. A powerful argument in support of the findings is the robust study methodology. Because the multiple ICHs that determine whether a donor's blood represents an "exposure" are entirely unknown at the time of transfusion, there should be little possibility of bias or confounding that predispose a particular group of recipients to receive that blood. Other particularly supportive features of the analysis are the striking similarity in results from the 2 independent national registries (arguing against a chance finding) and the negative control with ischemic stroke as the outcome (arguing against unsuspected confounding causing associations with all types of stroke). A major limitation of registry-based studies is the lack of detailed clinical or neuroimaging information about the analyzed individuals, and in this study it is likely that some donors with multiple post-blood donation ICHs and many recipients with posttransfusion ICH did not in fact have CAA, the amyloid β-driven disease that forms this study's biological premise. Even this important limitation can be seen as an argument in favor of a true association between donor and disease, however, as misdiagnoses of CAA would be predicted to bias the findings toward a null result rather than a false finding.

The arguments for remaining unconvinced of the association center on the weakness of evidence for a plausible biological mechanism for blood from a donor with future CAA to rapidly transmit CAA-related hemorrhage. The short-time course is quite challenging to explain: Nearly half of the ICHs among blood recipients occurred within 5 years of transfusion,[8] dramatically faster than the 30- to 40-year interval reported between neurosurgical exposure to cadaveric tissue and first ICH.[6,7] A similar multidecade time course has emerged from biomarker-based studies of autosomal dominant forms of CAA, which support a framework in which ICH is the culminating step in a lengthy path that travels from initial amyloid deposition to impairments in vascular physiology, nonhemorrhagic brain injury, and only then to first appearance of hemorrhagic lesions.[10] It is thus unclear whether exposure to transmissible agents, even for relatively older recipients (median ages of 65 and 64 years in the Swedish and Danish cohorts, respectively), could accelerate this pathway sufficiently to account for the observed transfusion-to-ICH timeline. A second related mechanistic reservation is the plausibility

that a transmissible species of amyloid β could travel from blood to brain in sufficient quantities to trigger advanced CAA or Alzheimer disease pathology. Transmission from blood is substantially harder to explain than from amyloid β-containing neurosurgical tissue placed directly within the central nervous system, where the triggering agent can likely circulate within the cerebrospinal fluid and glymphatic system[11] without needing to cross the blood-brain barrier. Abnormal concentrations or ratios of amyloid β species can indeed be detected in the blood of individuals with increased brain amyloid burden,[12] but the blood findings are generally interpreted as markers rather than causes of brain amyloid β deposition. A head-to-head experimental comparison of intraperitoneal and intracerebral amyloid β injection estimated that the former required 1000 times more injected peptide and 2 to 5 months longer to produce equivalent cerebral amyloid β deposition.[13]

The current study leaves at least this writer squarely at the corner of anxiety and skepticism. More than 10 million units of blood are transfused in the US per year,[14] suggesting that even a modest increase in hazard of future brain hemorrhages or dementia conferred by an uncommon—but as of now undetectable—donor trait would represent a substantial public health concern. From the standpoint of scientific plausibility, however, even this well-conducted analysis is at risk of representing a false alarm. How then to proceed? One clear direction is further independent replication, ideally with datasets in which donor and recipient dementia can be reliably ascertained to assess the possibility of Alzheimer disease as well as CAA transmissibility. The other challenge is for experimental biologists to consider the alternative possibility of transfusion-related acceleration of downstream steps in the CAA-ICH pathway, such as the vessel remodeling by which amyloid β-laden vessels proceed to rupture and bleed.[15] The current study is not yet a reason for alarm, certainly not a reason to avoid otherwise indicated blood transfusion, but it is a strong call for more scientific digging.

ARTICLE INFORMATION

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Conflict of Interest Disclosures: None reported.

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