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Amyotrophic Lateral Sclerosis and Organ Donation: Is There Risk of Disease Transmission?

Brandon B. Holmes, BA and **Marc I. Diamond, MD**
Department of Neurology, Hope Center for Neurological Disorders, Washington University in St Louis, School of Medicine, St Louis, MO

Abstract

A new protocol suggests that patients with amyotrophic lateral sclerosis (ALS) are a viable source of tissue for organ transplantation. However, multiple lines of evidence suggest that many neurodegenerative diseases, including ALS, might progress due to transcellular propagation of protein aggregation among neurons. Transmission of the disease state from donor to host thus may be possible under the permissive circumstances of graft transplantation. We argue for careful patient selection and close longitudinal follow-up of recipients when harvesting organs from individuals with neurodegenerative disease, especially dominantly inherited forms.

A report in the *Annals of Neurology*[1] indicates that patients with amyotrophic lateral sclerosis (ALS) are a potential source of tissue for organ transplantation. We question the wisdom of this strategy. Recent developments in our understanding of the pathogenesis of neurodegenerative diseases suggest that there may be risks to the recipients of organs from such patients due to prion-like propagation of protein misfolding from affected donor to unaffected host. The idea that sporadic neurodegenerative diseases such as Alzheimer disease (AD) might have connections to prionopathies is not new. Based on the slow virus hypothesis, prior studies attempted to induce pathology in primate hosts via injection of AD-derived brain material, with variable results.[2,3] With the recognition that prions form fibrillar structures similar to those observed in AD, Prusiner originally hypothesized that a mechanistic connection might exist between the 2 diseases.[4,5] Despite decades of exposures, however, there are no proven examples of donor-to-host transmission of sporadic neurodegenerative diseases in humans, and there is a clear and immediate need for lifesaving organ transplants. Nonetheless, we argue for caution in harvesting tissues from patients with autosomal dominant forms of neurodegenerative diseases such as ALS, and careful longitudinal observation of all recipients.

We believe that our understanding of neurodegenerative disease is in the midst of a paradigm shift. An emerging consensus suggests that the mechanisms associated with infectivity and propagation of the prion protein may apply more generally to other fibril-forming proteins associated with common neurodegenerative diseases. Prions propagate a misfolded form of PrP from cell to cell, and from donor to host. Aggregated PrP recruits native forms, amplifying the misfolding phenomenon in a process termed *templated conformational change.* Accumulations of misfolded protein eventually cause cell toxicity.

Address correspondence to Dr Diamond, Department of Neurology, Hope Center for Neurological Disorders, Washington University in St Louis, School of Medicine, Biotechnology Building, Room 111, 4559 Scott Ave, St Louis, MO 63110. diamondm@neuro.wustl.edu.

Potential Conflicts of Interest
Nothing to report.

Until recently, it has not been clear whether this mechanism could play a role in the cellular pathogenesis of more common neurodegenerative disorders. However, recent experiments now strongly suggest that a variety of disease-associated proteins can propagate misfolding between cells in vitro, and in vivo after intra-cerebral injection and systemic exposure as described below. We posit that these mechanisms could place recipients of organs derived from ALS patients at risk of acquiring the disease.

Just as the creation of mice transgenic for PrP facilitated the study of prion infectivity, development of mice that overproduce human Aβ, tau, and synuclein has facilitated studies of infectivity of these proteins. Injection of Aβ mouse models with extracts from human AD brains produced distinct patterns of pathology reminiscent of prion strains, and was dependent on Aβ within the extracts.[6] The transmission of amyloid pathology has now also been demonstrated after inoculation with contaminated surgical wire and intraperitoneal inoculation of Aβ-containing brain extracts.[7,8] Yet because Aβ accumulates predominantly in the extracellular space, these effects are not necessarily unexpected; Aβ fibrils present in brain lysates might be predicted to effectively seed accumulation of more Aβ fibrils by contact with existing Aβ in the extracellular space.

Two publications in 2008, however, reported Lewy body pathology in fetal dopaminergic neuron transplants in Parkinson disease (PD) patients.[9,10] This suggested for the first time that transfer of intracellular aggregated synuclein might have occurred from host to donor tissue. Subsequent studies soon indicated that synuclein is secreted from cells; that it can accumulate in cocultured cells; and that it can transfer from cell to cell in mice.[11,12] Transcellular transmission in vivo has been documented, with the finding of human synuclein pathology in wild-type (WT) neurons transplanted into mice transgenic for human synuclein.[12,13] Most recently, acceleration of both aggregation and pathological phenotype was demonstrated in human mutant α-synuclein transgenic mice after intracerebral injection of brain extracts derived from aged mice of the same transgenic line.[14,15]

In 2009, Tolnay and colleagues demonstrated that it is possible to induce local, endogenous tau pathology in mice by the injection of transgenic mouse brain extract containing tau aggregates, and that this can be blocked by immunodepletion of tau.[16] Concurrently, our lab identified key biophysical aspects of tau protein aggregation that highlighted its similarity to prion protein, and described cellular events that could explain a propagation mechanism. First, tau fibrils exhibit conformational diversity and stable propagation of these conformations in vitro.[17] Second, recombinant tau fibrils are directly taken up into cultured cells, where they colocalize with endogenous tau protein, and convert it to a fibrillar form.[18] Furthermore, we recently demonstrated that tau protein fibrils are released directly into the extracellular space, re-enter neighboring cells, and physically interact with the tau in these recipient cells to propagate misfolding.[19] Finally, human studies have suggested an orderly progression of pathology between connected brain regions in AD and PD[20–22] that may depend on neural networks.[23–25]

Insights from prion biology also influence our understanding of the pathophysiology of ALS. ALS exhibits clear evidence of focal motor neuron degeneration that later spreads to contiguous regions as the disease progresses.[26–28] This is consistent with a model in which pathogenic proteins aggregate initially in a subset of cells and then propagate to connected neurons. Both TDP-43 and SOD1 exhibit the potential for seeded aggregation in vitro. In sporadic and familial ALS patients, TDP-43 forms inclusions in the cytosol.[29,30] In cultured cells, TDP-43 fibrils applied to the cell medium induce the intracellular aggregation of otherwise soluble protein.[31,32] Similarly, in cell culture, SOD1 aggregates enter cells and gain access to the cytosol, where they can seed aggregation of normally folded SOD1 protein. Last, the SOD1 misfolding induced by the exogenous seeds is self-propagating in

that it can stably induce the mis-folded state over many cell generations long after the disappearance of the progenitor seed.[33] Thus, SOD1 exhibits both seeded aggregation and self-propagation in culture, 2 critical properties of prions.

In summary, clear experimental evidence exists for cell-to-cell propagation of multiple types of protein aggregates associated with noninfectious neurodegenerative diseases based on templated conformational change. Protein aggregates formed in 1 cell can escape that cell to seed further aggregation in recipient cells, and exogenous application of fibrillar species in vivo and in vitro will induce intracellular misfolding. No in vivo studies have directly tested putative cellular mechanisms of aggregate propagation, although vaccine-based therapies have worked in models of synucleinopathy, tauopathy, and SOD1 pathology,[34–38] consistent with a role for extracellular aggregates. Thus, it is unknown whether cell-to-cell propagation could underlie progression of disease within an individual. Furthermore, no evidence exists for person-to-person transmission of neurodegenerative disease, and it is extremely unlikely that normal environmental exposures to disease-afflicted individuals could result in acquired disease. Yet could organ transplantation provide permissive circumstances?

Iatrogenic transmission of prion disease was first described in 1974, when a 56-year-old woman died of autopsy-confirmed Creutzfeldt–Jakob disease (CJD) after receiving a contaminated corneal graft from an unsuspected CJD patient.[39] More than 400 documented cases of iatrogenic CJD caused by exposure to contaminated medical equipment or human transplant materials have now occurred.[40] In the mid-1980s, 2 CJD outbreaks resulted from contaminated human growth hormone and dura mater grafts, accounting for >95% of iatrogenic CJD.[41] In virtually all known cases, tissues closely associated with the brain served as the inoculum.[42] It has thus been assumed that transmission of neurodegeneration probably requires brain-derived tissue. However, transmission of variant CJD (vCJD) prions via red blood cell transfusions has surfaced in at least 3 independent cases since 2002.[43] Of the 222 documented cases of vCJD, 18 preclinical patients donated blood. Of the 66 recipients of these blood components, 3 individuals acquired vCJD.[43,44] Thus, peripheral blood harbors vCJD infectivity even at presymptomatic stages.

Familial amyloid polyneuropathy (FAP) can also be transmitted between individuals. This autosomal dominant, progressive peripheral sensorimotor and autonomic neuropathy is caused by the extracellular deposition of mutated transthyretin (TTR) amyloid fibrils.[45] The liver produces pathogenic TTR, and only liver transplantation can arrest disease progression. The livers of FAP patients are otherwise functionally normal, and organ shortages have motivated their use as grafts in those with hepatic failure, a procedure known as domino liver transplantation (DLT). Because FAP requires ~20 years to manifest in patients, it was assumed that elderly patients undergoing DLT would incur only minimal risk of acquired disease. However, cross-sectional and prospective studies to assess the risk of FAP transmission after DLT demonstrated several systemic amyloidosis cases in recipients. In 2 independent studies, 37 and 48% of DLT recipients had TTR-amyloid deposits on tissue biopsy; 5 and 23% of patients developed amyloid polyneuropathy. Furthermore, mean disease onset was only 5.75 years after DLT.[46,47] Thus, transplantation of a mutant TTR-producing graft is sufficient to transmit a dominantly inherited amyloidosis to a normal host, with greatly accelerated disease onset. Despite this risk of transmission, the shortage of organs and the overall benefit experienced by recipients continues to inspire DLT.

Toossi et al provide a thoughtful protocol for organ donation after cardiac death for patients suffering from ALS.[1] Sulmasy's accompanying editorial states: "allowing patients with ALS greater opportunities to give consent to donate their own organs after electing to discontinue ventilator support represents moral progress," and "there is no reasonable basis for fearing that the organs of patients with ALS could harm recipients." [48] However, we question

whether organs derived from ALS patients, especially those with autosomal dominant disease, are in fact benign.

Several critical features of ALS must be considered. Although the pathological hallmarks of ALS are ostensibly restricted to the central nervous system,[49] a number of case studies from ALS patients with *SOD1* mutations demonstrate the presence of SOD1 inclusions in the liver and kidney.[50,51] Jonsson et al described a patient harboring the G127X *SOD1* mutation with widespread mutant SOD1 pathology in hepatocytes and kidney tubular epithelium.[51] Guareschi et al discovered that sporadic ALS (sALS) patients with bulbar onset contained abnormal WT SOD1 in their lymphocytes; 94% of the lymphocytes from the bulbar sALS cases displayed SOD1-positive inclusions.[52] Thus, SOD1 pathology is probably not restricted to the nervous system, and pathogenic SOD1 aggregates may form in other organs. Furthermore, the presence of macroscopic SOD1 inclusions in an organ does not necessarily correlate with that organ's potential for pathogenic seeding, because SOD1 seeds too small to be visible by light microscopy may be the most efficient at propagating misfolding.[33] Finally, non–cell-autonomous SOD1 toxicity has been described in vitro, as transplanted mouse astrocytes harboring the *SOD1* G93A mutation induced motor neuron death and ubiquitinated inclusions in the spinal cord of nontransgenic mice.[53] In another study, stem cell-derived astrocytes from sporadic and familial ALS patients were toxic to cocultured mouse motor neurons. RNA interference knockdown of human SOD1 attenuated this astrocyte-mediated neuronal toxicity, even in cells from sporadic cases.[54] A toxic secreted factor, possibly SOD1 itself, could thus be playing a role. For further discussion of ALS progression and protein misfolding, we direct the reader to a comprehensive and insightful review by Polymenidou and Cleveland.[55]

In light of the community's organ shortage and net benefit of organ transplants, donation of organs from ALS patients may well remain practical. In instances of emergent need for organs (eg, acute liver failure), ALS patient grafts may serve as the sole lifesaving materials available, making moot a discussion of ALS transmission risk. In other nonurgent scenarios for tissue transplantation, however, we recommend careful calculation of potential risks and benefits. At this point, given the experience with FAP, we cannot assume that aged organ recipients have no risk of acquiring disease from donor tissue: FAP organs induced amyloidosis after DLT in as little as 3.5 years. Although we hope that our concerns are unfounded, until we know more about risks, we recommend a conservative transplantation strategy. Specifically, patients suffering from dominantly inherited forms of ALS in which mutated proteins are produced should not initially be considered as organ donors in nonacute cases. SOD1, TDP-43, and possibly FUS possess prion-like properties that might be potentiated by disease-causing mutations. In parallel, candidate organ recipients should be screened for possible ALS risk factors, such as have been described recently.[56–58] Finally, we strongly encourage careful and comprehensive prospective follow-up for all recipients of organs derived from ALS patients for any signs of neurodegeneration, especially motor neuron disease and dementia. We hope that, as we expand our knowledge of pathogenic mechanisms, it will be more feasible to minimize exposure of patients to prion-like proteins.

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