Commentary

Is cardiovascular fitness a risk factor for ALS?

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The association between ALS and reduced cardiovascular disease is hypothesis-generating, driving pathway discovery, rather than necessarily simple cause and effect.

Those living with the adult neurodegenerative syndrome of amyotrophic lateral sclerosis (ALS) naturally want to understand why. A monogenetic association may be identified in approximately 10% of cases. For the majority, ALS has a polygenetic and environmental 'multiple hit' model of pathogenesis, like many cancers, and supported indirectly through analysis of the incidence of ALS in relation to age (1). Neurologists who regularly diagnose those with ALS observe a characteristic syndrome of progressive weakness with strikingly focal symptom onset, but recognise an increasingly complicated phenotypic taxonomy and molecular heterogeneity (2). The causes of ALS may be diverse, and none are yet certain at a cellular level. There is also likely to be a significant pre-symptomatic period (3).

A frequent perception concerning the premorbid lifestyle of those with ALS involves athleticism, typified by the eponymous "Iron Horse" Lou Gehrig (4). Premorbid physical activity has been shown to be increased in those who develop ALS, in multiple studies spanning more than a decade, though with important exceptions (reviewed in (5)). A reduced incidence of premorbid cardiovascular disease has been separately noted (6, 7). Visser and colleagues now probe the 'fitness hypothesis' further. Specifically, they explore the cause of death in the parents of those with ALS (8).

Their headline result is that death from cardiovascular disease is significantly lower in the parents of the sporadic ALS group compared to the control parent group,

though with no difference in overall survival and no influence of parental gender apparent. This analysis was adjusted for potential confounds, including for some previously identified premorbid associations with the development of ALS including diabetes (9), and lower body mass index (6), though not smoking. In a non-adjusted analysis, the parents of the much smaller sub-group with familial ALS (n=86, defined as having first, second or third degree relative with ALS or known *C9orf72* expansion), were more likely to die from causes listed as neurodegenerative (approximately two thirds of whom were labelled as a dementia, with one third as Parkinson's disease). The reduced incidence of premorbid cardiovascular disease in ALS patients might be assumed to be a corollary of physical activity. However, no firm conclusions can be drawn from this study's finding of a lack of association between the ALS patient levels of physical activity in leisure time and the rates of cardiovascular disease or survival of their parents, given that parental levels of activity were not captured.

The axiom that association is not causation cannot be overstated. Being fit does not necessarily drive someone to develop ALS, though cellular stress and injury response pathways appear superficially appealing and have biological plausibility (10). There is no basis to suggest that clinicians should advise asymptomatic carriers of ALS-causing genes to limit their physical activities, or deviate from standard medical practice in promoting measures to reduce cardiovascular risk. Rather, Visser and colleagues' study reinforces the broader hypothesis of a shared genetic profile between cardiovascular fitness and ALS. The authors offer altered premorbid metabolism as a source for potential common pathways. Equally one might envisage a structural and functional configuration of the human motor system conducive to physical activity, with an associated reduced cardiovascular risk for some.

Alternatively, a ‘high performance’ motor system might be a more permissive environment for the propagation of ALS pathology, the latter arising due to an entirely independent molecular chain of events.

Can anyone develop ALS? If not, what is the basis for any resistance? These remain fundamental questions to pursue. Studying premorbid disease associations represents an important way to generate novel hypotheses, as well as test existing concepts and shared molecular pathways, with the aim that therapeutic interventions may be more effectively targeted.

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