SCIENTIFIC COMMENTARY

Familial versus sporadic amyotrophic lateral sclerosis—a false dichotomy?

Historically, there has been a surprising level of uncertainty about whether amyotrophic lateral sclerosis (ALS), in its typical form, has a genetic basis. No less a figure than Jean-Martin Charcot (1825–93), at least initially, held the view that the disease he first named was never familial (Charcot and Joffroy, 1869). Some years earlier, in fact, familial cases of progressive muscular atrophy, a disorder that is now generally considered to be part of the same clinicopathological spectrum as ALS, were clearly described (Aran, 1850). Twenty years after Charcot, William Osler (1849–1919) reported typical ALS with autosomal dominant inheritance in a family from Vermont, which in the modern era, has been shown to have a mutation in SOD1 (Osler, 1880; Rouleau and Meijer, 2007). The view that the genetic contribution to ALS as a whole is relatively insignificant prevailed in the first half of the 20th century, but the development of modern molecular biology was a major impetus to the collection of familial kindreds with ALS in the 1980s and 1990s, leading ultimately to the identification in 1993 of mutations in SOD1 (Osler, 1880; Rouleau and Meijer, 2007). In the view of the last 2 years a further five genes have been associated with classical ALS (FUS, OPTN, ANG, VCP and most recently UBQL2: Greenway et al., 2006; Vance et al., 2009; Johnson et al., 2010; Maruyama et al., 2010; Deng et al., 2011). The result is only a partial clearing of the fog surrounding the causes of motor neuron degeneration in ALS. Diverse pathways including RNA processing, protein turnover and mitochondrial function have been implicated but a unifying model of how ALS is initiated and propagated remains elusive. However, with increased knowledge the concept of ALS as a pure motor system disease having a single cause, and ultimately a common treatment, has to be abandoned in favour of a model where complex multisystem degeneration results from multiple genetic and other causes, producing a continuous clinical and pathological spectrum between pure ALS and FTD.

The majority (95%) of patients with ALS have no affected first degree relatives (Byrne et al., 2011). The apparently sporadic occurrence of their condition has generally been interpreted by ALS specialists as grounds for reassuring such patients that the risk to their children is negligible. But increasingly this approach sits uncomfortably with the large-scale efforts devoted to genome-wide association studies, based on the theory that even sporadic ALS has a significant, but complex, genetic contribution from common variants each exerting individually a small effect. It is a striking fact that the discovery of each new gene in which mutations cause familial ALS has been followed almost immediately by the identification of mutations in patients without a family history, indicating that rare variants can act as low penetrance dominant alleles (Talbot, 2009). The contribution of such rare variants to the causation of ALS as a whole is currently unknown, but could be considerable, and will be revealed by the whole exome studies that are now underway.

Patients are increasingly well informed. Although they come to a specialist clinic with varying levels of understanding, most are aware that genetics plays a role in ALS at some level. The standard response to questions about genetic risk is to make a concrete distinction between familial and sporadic disease, offering general reassurance that the relatives of patients with sporadic ALS have the same risk as the background population (estimated to be 1:400 over a lifetime; Johnston et al., 2006). However, does ALS in a family member confer an increased relative risk, as is well understood for multiple sclerosis and many other diseases (Sawcer et al., 2010)? Until now we have had no adequate data to begin to answer this question and there has been an understandable tendency to avoid the issue. Hanby and colleagues, in this issue of Brain, provide a very useful initial answer by studying a large clinic-based series from a specialist ALS centre in London, UK. Over a 16-year period 0.5% of siblings of patients with ALS developed ALS, indicating that the age-adjusted risk of remaining free of disease by the age of 85 years fell from 99.7% (the figure for the general population) to 97.6%. Reassuringly, perhaps, this means that a first degree relative of a patient with ALS is overwhelmingly likely to die of something else. Tertiary referral clinics are well recognized to contain biases, with larger numbers of younger patients and those with prolonged survival. The ideal methodology to determine the risk to first degree relatives is a...
prospective population-based study carried out over many decades, which is not currently practicable. Therefore a carefully conducted clinic-based study, such as the one now reported, with proper acknowledgement of the inherent biases, provides a reasonable ‘real world’ estimate from a setting in which, pragmatically, most discussions about ALS inheritance are usually held.

Until very recently only 30% of familial cases had been accounted for by known genetic mutations. Two recent landmark papers in Neuron have produced a step change in our understanding of ALS genetics (Dejesus-Hernandez et al., 2011; Renton et al., 2011). A large expansion of a hexanucleotide repeat in an intron of a previously anonymous gene, C9orf72, on chromosome 9p21 appears to be responsible for between 30% and 60% of familial ALS cases, depending on the population studied. Astonishingly, ~8% of apparently sporadic cases also carry the mutant expansion. Therefore, although the penetrance of this mutation is presumably low, it is likely to be variable. Rather than a simplistic division between familial and sporadic ALS, a more appropriate model of ALS genetic risk in this context is therefore a continuum in which the same genetic variants can serve as either mutations with Mendelian segregation or low-penetrance risk alleles, depending on the genetic background. Therefore, a more complex picture is likely hidden within the findings from Hanby and colleagues’ study, that the risk to relatives of patients with sporadic ALS is low overall. It is possible that the small increase to first degree relatives can be generalized to all patients with sporadic ALS. However, an alternative explanation is that the effect is accounted for by subpopulations of patients who might transmit this risk with a much higher likelihood of disease to the next generation, despite the lack of family history. Combining a study such as this clinic-based enquiry with large-scale analysis of the recently identified hexanucleotide repeats may give a more complete answer. However, individualizing risk will continue to remain challenging. It is becoming increasingly difficult to offer global reassurance to patients with ALS that their offspring are at negligible risk of the disease, although it remains critical for specialists to approach these new findings with caution in order to avoid increasing anxiety among members of families currently living with the example of ALS. Familial and sporadic ALS cases are clinically indistinguishable and it is now clear that the two forms of ALS have common determinants. The old dichotomy of sporadic versus familial is breaking down. Sporadic ALS is likely to arise from the combinatorial effect of rare variants in familial ALS genes and common variants of small overall biological effect. Given that most of our current insights into ALS pathogenesis are based on genetic discoveries, this provides a new opportunity to explore the earliest pathological steps in ALS and FTD. The recent identification of the C9orf72 hexanucleotide repeat might, in combination with other genes, explain the majority of familial, and a surprisingly high number of sporadic, ALS cases. For the first time large numbers of pre-symptomatic mutation carriers will be potentially available for study in longitudinal biomarker studies. While this must be handled extremely carefully, so as not to raise undue anxieties in offspring of patients with sporadic ALS, a concerted multimodal, multicentre study of the earliest phase of ALS pathogenesis has a significant chance of producing insights that will translate into genuine therapeutic targets.

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