PERSPECTIVE

Don't keep it in the family

Let's start describing ALS on the basis of its cause, not on whether someone obtained a relevant family history, says **Ammar Al-Chalabi**.

The terms familial ALS and sporadic ALS are outdated and illogical. They impede research, confuse patients and cloud our thinking. It's time to ditch them.

A major goal of research into amyotrophic lateral sclerosis (ALS) is the discovery of its causes. The idea is that understanding the genetic (often equated with familial) and environmental (often equated with sporadic) factors leading to ALS will give insights that will help to design new treatments. If we discard for a moment the implicit assumption that the causes of ALS are the same as the processes that perpetuate it, there remains a major flaw in this way of thinking. We are taught that 5–10% of ALS is familial and the remainder sporadic. This false distinction affects the design and interpretation of research. For example, sporadic ALS is considered synonymous with ALS not associated with a Mendelian disease gene, whereas this is not necessarily the case. Or a mutation may be described as causing familial ALS, even though mutations in every gene that's been linked to the condition have also been found in people with apparently sporadic ALS¹. The muddy nomenclature affects the way the disease is managed in the clinic and the information given to patients; genetic counselling, for example, is usually reserved for those with a family history.

The terms familial and sporadic are not useful for several reasons. First, neurologists have wildly varying definitions of familiarity. Take a situation in which a woman, her father and uncle all have ALS. That would strike many people as a textbook example of familial ALS, but not everyone would agree with that classification. On the other hand, there are experts who consider that a situation in which the only affected individuals of a family are fourth cousins is familial ALS².

Even if a consistent and agreed definition of familial disease were in place, we would not know what to regard as a positive family history. For example, until the past decade or so, a family history of frontotemporal dementia would not have been thought relevant, but we now know that several ALS genes may also cause that disorder. What other related conditions might be dismissed inappropriately? If we truly think that only the existence of affected family members should guide whether we perform genetic tests, or influences the risk to offspring, then we risk giving inappropriate reassurance to those with sporadic ALS. In fact, first-degree relatives of someone with apparently sporadic ALS have about eight times greater risk of developing ALS than those whose family is unaffected³.

We also need to bear in mind that statistical effects can influence the relevance of a family history. The lifetime risk of ALS is 1 in 300 by the age of 80 (ref. 4), and so we can reasonably estimate that 1 in 1 million families will have 2 affected people by chance, not because they share a common cause. This corresponds to about 120 such families in the United States, and about 35 in the United Kingdom. On the other hand, in a family in which a parent definitely carries a high-risk

disease-gene variant, the pattern of inheritance will frequently be classified as sporadic⁵. This is due to two factors. First, not every person who inherits a disease-causing mutation will manifest the disease. Second, the probability of transmission is 50% per child, so in smaller families there are fewer opportunities for a mutation to be transmitted. Therefore, it is arbitrary to say that a family with one affected person should be regarded as meaningfully different from a family with more than one.

Evidence has emerged suggesting that the development of ALS may be a multistep process in which, on average, six molecular steps must occur, similar to some types of cancer⁶. In this situation, a genetic variant conferring a large risk would be expected to account for several of the steps, explaining the higher probability of disease in a mutation carrier. That means that it makes sense to search for environmental

risk factors in those with a clear genetic basis to their ALS, because there will be only one or two factors left to identify. This is true regardless of family history.

It is easy to demonstrate the harmful consequences of the archaic familial/sporadic division. Let us take the most frequent cause of ALS: expansion mutation in the gene *C9ORF72*. This is present in about 45% of people with a family history, making it by far the most important cause of 'familial' ALS. But this mutation is also present in up to 10% of the much larger number of people with apparently no relevant family history, so it is the most important cause of 'sporadic' ALS as well. In fact, these mutations account for about 14% of all ALS, and in most cases there will be no family history. How can it make sense to treat people differently on the basis of their family history in this context?

What matters is the underlying cause. In these

cases, we should be using the term *C9ORF72*-mediated ALS, not familial or sporadic ALS. Whether there is a family history of the disease is irrelevant to the patient, to the family, to the research team and to our understanding of the mechanism.

Now that gene sequencing is cheap and easy, we need to move away from the outdated, unhelpful familial/sporadic dichotomy and instead use terms that describe what is known about the causes of ALS in each person. Only then can we think clearly, identify risk factors, and counsel patients correctly. ■

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