Appendix e-2. Translating evidence implicating an alleged risk factor for ALS into conclusions.

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Level A rating: This is an established risk factor ("Overwhelming evidence")

Two class I studies, or one class I and 2 class II studies, or three class II studies, with no contradictory evidence of equal or higher quality ranking, and which lend themselves to the application of the criteria for inferring causation from association*.

Level B rating: This is a probable risk factor ("More likely than not")

1. One class I study or 2 class II studies, with no contradictory evidence of equal or higher quality ranking, and which lend themselves to the application of the criteria for inferring causation from association*.

2. Two class I studies, or one class I and 2 class II studies, or three class II studies, with some contradictory evidence of equal quality ranking. The evidence in favor of inferring risk factor status preponderates, through the application of the criteria for inferring causation from association*.

Level C rating: This is a possible risk factor. (Does not attain a "more likely than not" status). Better designed studies may be warranted with regards to this risk factor.

One class II study or several class III studies, with or without contradictory evidence of equal or lesser quality. If there is contradictory evidence of equal quality ranking, there must be less such evidence than there is evidence favoring risk factor status. The inconsistencies in the evidence do not permit consideration of inferences about causation.
Biologic plausibility is not necessary for assignment to this category.

Level U rating: It is unknown whether this is a risk factor

Evidence with regards to this risk factor is from conflicting or an insufficient number of class I-III studies, without a preponderance of evidence one way or another; or is from class IV-V studies; or there is no evidence.

If evidence that this is not a risk factor outweighs the evidence in support of this being a risk factor, assignment should be to a level A or B rating, as outlined in the comments below.

Comments:

1. This table is designed to permit moving from the default position, that it is not known if a putative risk factor is a risk factor (level U), to a position that a risk factor has been identified. Consistent evidence in the form of class I-III studies that permit inferring lack of association from failure to find an association (see comment for Table 1) should also result in a shift away from level U. However, assignment to level C ("possibly not a risk factor") is meaningless in this setting. Hence, to translate evidence that there is a no association, a simpler system is proposed, whereby a level B rating ("probably not a risk factor") is assigned if there is stronger quality of evidence that there is no association than that there is an association, and a level A rating ("definitely not a risk factor") is assigned if there is a preponderance of evidence for lack of association. Further, it should be recognized that, realistically, there will be very little impetus for the scientific and funding communities to replicate even one class II study that establishes that there is no association for a particular presumptive risk factor; hence, one class II study unopposed by equal or higher class evidence is a realistic minimal requirement for assignment of a level B rating for absence of association. This is a small relaxation of the requirements to establish level B rating in support of presence of association.

2. Biologic onset of ALS precedes clinical onset, but it is not known by how many years. In all likelihood, the slower the disease progression, the longer it is reasonable to assume its preclinical course has been. Exposures or events which happened within the 1-3 years before clinical onset of ALS most likely happened after its biological onset, thus cannot have caused the disease, and constitute class V evidence for risk factor status. Studies may choose to exclude from consideration exposures or events within 5 or even 10 years of clinical onset, to avoid this limitation.

3. Invoking Hill's criteria of inferring causation from association* to the process of assignment of risk factor level is done intentionally, recognizing that "risk factor" and "cause" are not synonymous. The purpose is that those risk factors that are assigned higher levels will be further along the road towards potential causal status than if they were mere associations.

4. Biologic plausibility. In general, a critical link between a well-established risk factor and causation is biologic plausibility. Biologic plausibility is proved either by producing the disease in excess in an appropriate animal model exposed to the risk factor or by knowing with certainty how the risk factor would interact with the established biological mechanism of disease causation. In the case of ALS, the biologic mechanisms underlying disease causation are not known, animal models of sporadic ALS are lacking, and the animal models of familial ALS may or may not be relevant to the pathogenesis of sporadic ALS. Thus, biological plausibility cannot be proved for most risk factors for ALS under consideration. However, biologic plausibility may be considered within the framework of existing hypotheses regarding the pathogenesis of ALS, recognizing the speculative or hypothetical nature of this process, for the time being. This is required for levels A and B.

REFERENCE

* Hill AB. The environment and disease: association or causation? Proc R Soc Med 1965;58:295–300.