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Purkinje Cell Loss in Essential Tremor

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The recent study published by Symanski et al.[1] reports similar Purkinje cell counts in a group of "essential tremor" cases compared to a group of controls. There are a number of major methodological problems with the design of the study and these problems cast doubt on the validity of the results that are reported.

The first problem is that of case definition. ET was defined simply as "action tremor of the hand, voice, or isolated head tremor." This loose definition does little to exclude enhanced physiological tremor, which is an action tremor of the hands, and is very common in the elderly. While the authors note that tremor had to have a rating of 2 or higher, for their cases who had had tremor for 3 or more years (i.e., the vast majority of their cases), a low amplitude tremor was deemed acceptable. Indeed, there is no specified lower limit of tremor severity for the bulk of their "ET" cases. This is very problematic and, as a methodological flaw, could by itself account for their null finding. In some of the allied studies from this cohort, these authors are reporting extremely high prevalence values for "ET", furthering these concerns that there is a problem with their case definition.

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The second issue is that the disease duration was very short and this too could account for their results. They try to dismiss this point, writing that there was no association between duration and Purkinje cell linear density. The problem with their argument is that there were so few cases with longer duration, and the range of durations was so narrow, that it would be mathematically challenging, with a correlation coefficient, to detect an association. So, their argument is not valid.

In discussing the results of the Canadian group, they correctly note the small sample size, but do not pay heed to the issue of Type II statistical error, which is a real problem with those results.[2]

In many places, they overstep their results. For example, they write: “it seems clear that ET is unlikely a primary Purkinje cell degeneration”. This study does not show that. It merely demonstrates that, using a sample of elderly people with loosely defined tremor of short duration, they were unable to replicate another group’s results.

They indicate that our group has not adjusted for alcohol intake or anticonvulsant use, but this is not the case in more recent papers.[3, 4] A more thorough reading of those papers is called for.

Their statement that Purkinje cell loss should be present even before the development of tremor is not a sophisticated argument. For example, if Purkinje cell loss were a by-product of longstanding pathological molecular/cellular processes occurring in ET, it might not be the earliest finding. Rather, it could be a relatively late finding and might long-follow the onset of tremor. More recent papers emphasize an array of pathological findings involving Purkinje and neighboring cells in ET, and portray Purkinje cell loss in ET as a relatively late event.[4, 5]

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