Concordance between site of onset and limb dominance in amyotrophic lateral sclerosis

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ABSTRACT
Background Focality of onset of amyotrophic lateral sclerosis (ALS) is not understood. Attempts to implicate physical exercise in the aetiology of ALS have provided inconsistent results. If physical use of a limb were important in defining the site of onset, then handedness might be expected to influence the side of upper limb-onset disease and footedness likewise in lower limb-onset ALS.

Methods ALS patients registered with an internet-based support site were invited to complete an online questionnaire concerning site of onset of symptoms and their dominant hand and foot. A binomial test of proportions was used to investigate the null hypothesis that handedness and footedness do not influence side of onset in upper and lower limb-onset ALS, respectively.

Results 343 ALS patients with limb-onset disease were studied. For upper limb-onset patients, there was concordance for side of onset and handedness (64%; p<0.0006). For lower limb-onset patients, concordance for side of onset and footedness was absent. The frequency of left handedness was commensurate with that found in the general population.

Interpretation These results are potentially consistent with the hypothesis that exercise influences pathogenesis in ALS since routine physical demands on the upper limb are heavily influenced by limb dominance, whereas in the lower limbs the commonest function is standing or locomotion, which uses both legs equally. However, there may also be an inherent cortical vulnerability underlying upper limb-onset laterality, possibly influenced by changes in neuronal connectivity and cortical excitability in relation to handedness and reflected by the "split hand" phenomenon consistently observed in ALS.

RESULTS
Overall group
A total of 502 patients responded (estimated to be 75% of the total possible). Seventy-two patients were either unable to specify the site of symptom onset (n=43) or entered more than one site for initial symptoms (n=59) and were removed from the subsequent analysis. Of the remaining 400 patients, 55% were male. The mean age of respondents was 56 years (SD 10, 26–82); there were no significant differences in age with respect to sex. The site of initial symptoms was bulbar in 18%, UL 37% (right 25%, left 14%), LL 43% (right 24%, left 19%) and respiratory 2%. There was no significant difference in the proportion of left-handedness or left-footedness for males versus females, nor for bulbar versus limb-onset patients. The male:female ratio was significantly reversed for bulbar (0.7:1) versus limb-onset patients (1.5:1; p=0.006) but with no significant difference in mean age.
Limb-onset sub-group
A total of 343 limb-onset patients were available for analysis. For handedness, 87% reported right dominance, 10% left and 3% equal. For footedness, 86% reported right dominance, 10% left and 4% equal. Ten patients (3%) reported discordance for upper and lower limb dominance.

Concordance of handedness to side of UL onset
Excluding those reporting equal dominance for handedness (n=11), for upper limb-onset patients, there was concordance for side of onset and handedness: 97 of 151 (64%) overall (right 90 of 159 and left 7 of 12); p<0.0006.

Concordance of footedness to side of LL onset
Excluding those reporting equal dominance for footedness (n=15), for the lower limb-onset patients, concordance for side of onset and footedness was absent: 99 of 181 (55%) overall (right 91 of 162 and left 8 of 19); p=0.234.

DISCUSSION
This study demonstrated high concordance for handedness and side of upper limb-onset ALS but no similar relationship in relation to footedness and side of lower limb onset.

For the upper limb-onset patients, our finding is potentially consistent with the hypothesis that exercise influences pathogenesis in ALS, since routine physical demands on the upper limb are highly influenced by limb dominance. For the lower limb-onset patients, the lack of an effect of footedness is also consistent with this hypothesis since the commonest function is standing or locomotion, which uses both legs equally.

However, another potential reason for a difference in the result between upper and lower limb onset is some inherent vulnerability in upper limb motor neuronal organisation and laterality. There is evidence for greater connectivity in the dominant motor cortex with respect to handedness, specifically, it has been noted that the production of movements in dominant and non-dominant hands involves distinct cerebral networks.

Evolutionary aspects of neocortical function might have relevance to ALS pathogenesis, in that humans have evolved uniquely complex aspects of neocortical function that may have conditioned the results in relation to this.

Prospective, clinic-based studies of handedness in relation to upper limb-onset ALS are needed to confirm our findings, and further research aimed specifically at understanding more about corticomotorneuronal connectivity might be revealing.

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