PROGRESSION OF SPORADIC ALS: AXONAL VS CSF SPREAD?

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Background: It is proposed that the onset of ALS is local and that progression is regional [1,2]. However, exceptions to this are notable: 15% of patients with lower limb onset subsequently develop bulbar symptoms [3,4]. An even larger percentage of patients with bulbar onset next develop lower limb symptoms.

Discussion: To account for these exceptions, we propose that propagation may occur via the CSF, suggesting ALS may represent a spinal fluid pathway disorder. This would account for the predilection of ALS to involve brainstem and spinal cord which are in close anatomic proximity to the spinal fluid pathway. Also, once established locally, contiguous spread could proceed as chronicled by numerous investigators [1,3,4,5].

Several disparate clues are compatible with the assumption. Firstly, absorption of CSF from the arachnoid villi decreases with age [6]. This offers a possible explanation for the increased incidence of ALS in older persons. Secondly, a number of molecules, including proteins and oligonucleotides, are robustly taken up by motor neurons and non-neuronal cells from the CSF [7]. Finally, CSF from ALS patients is toxic to motor neurons in in-vitro models [8].

Conclusions: Emphasis on the means of progression of ALS may provide clues as to the origins of the disease. If the clue resides in the spinal fluid, an effort to study the sources of potentially toxic molecules that find their way into the CSF may shed further light on the origins and spread of the disease.