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Editorial

ALS-Plus — Where does it begin, where does it end?

Nothing vexes and delights the neurologist more than the patient in whom the borders are blurred between diagnostic entities. The era of 'big data' nearly a half-century ago enabled Arthur Hudson [1] to state that "…an extensive review has been made of dementia, parkinsonism and other neurological features that have been described in the literature as accompanying ALS." Culling a new vision from the individual case reports, autopsy studies and small case series in the literature at that time, Hudson set the stage for the epoch that followed. That same year, McGlone and Hudson [2] quietly confirmed Jacobs's finding of eye movement abnormalities in some ALS patients [3]. It is McCluskey and colleagues [4] who redefined 'big data' to permit sculpturing a masterful clinical study of a modern series of cases of ALS-Plus from a single center. The strengths of this presentation include the patients studied with and without the ALS-Plus syndrome, the careful clinical evaluation of patients in each group, the genetic studies and the correlation with neuroimaging. But what makes this step forward so special?

Hudson opened a dialog regarding the diagnostic fault lines associated with overlap syndromes embracing amyotrophic lateral sclerosis. Within the succeeding decade, the ALS mimic, multifocal motor neuropathy, identified by Pestronk and colleagues [5] accelerated the need for a consensus workshop to define the "clinical limits of amyotrophic lateral sclerosis" sponsored by the Subcommittee on Motor Neuron Diseases/Amyotrophic Lateral Sclerosis of the World Federation of Neurology Research Group on Neuromuscular Diseases [6]. The term 'ALS variant' was introduced at the El Escorial workshop to describe syndromes that met the clinical, electrophysiological and neuroimaging criteria for possible, probable or definite ALS as the predominant presentation as that seen in sporadic ALS, but that included one or more features such as: familial pattern of inheritance, geographical clustering, extrapyramidal signs, cerebellar degeneration, dementia, autonomic nervous system involvement and objective sensory abnormalities.

The discovery of the SOD1 gene causing one form of familial ALS by Siddique and Brown [7] sharpened the focus on the familial pattern of inheritance in ALS leading to the partitioning of genetically determined (familial, hereditable) ALS as a separate entity from sporadic ALS at the World Federation of Neurology Research Group on Motor Neuron Diseases three-day workshop, convened at Airlie Conference Center, Warrenton, Virginia on 2–4 April, 1998 [8]. The term ALS variants was removed and specific delineation of [1] ALS with clinical features of other neurological diseases (ALS-Plus) including geographical clustering (Western Pacific, Guam, Kii, North Africa, Madras), extrapyramidal signs, cerebellar degeneration, dementia, autonomic nervous system involvement, objective sensory abnormalities, oculomotor abnormalities from [2] ALS mimics (multifocal motor neuropathy with and without conduction block, etc.) and [3] ALS with Laboratory Abnormalities of Unknown Significance (ALS-LAUS) was established.

It has taken nearly two decades for the information structure inherent in ALS registries to permit the clinic-based assessment of the position of those ALS-Plus patients in the context of other sporadic and familial ALS patients at a major academic center. McCluskey and colleagues provide the first documented prevalence of atypical clinical multi-system manifestations in slightly over one in seven of 550 ALS patients diagnosed at their center. The array of conditions included nearly one in nine ALS patients with oculomotor abnormalities [gaze abnormalities, horizontal, up-gaze, down-gaze, impersistence, and/or head movements], one in thirty-two patients with extrapyramidal features [resting tremor, masked face, startled appearance, bradykinesia, rigidity, dystonia, retropulsion, apraxia of eye closure and/or gait apraxia], one in one hundred thirty-eight ALS patients with cerebellar features [ataxia and/or limb dysmetria] and one in five hundred fifty ALS patients with autonomic features [excessive sweating, special sensory, and/or loss of taste and smell]. Their careful assessment of this clinic population will provide a model for other ALS centers to emulate as the precision in asking focused questions in clinic-based registries becomes more wide-spread.

The authors identified important algorithms to evaluate their patient populations. ALS-Plus features were clustered into deficits of one of four systems: ocular motility abnormalities, cerebellar features, extrapyramidal features and autonomic dysfunction (excessive sweating, special sensory, and/or loss of taste and smell). ALS-Plus patients underwent co-examination of patients with an ALS-Plus feature until 100% agreement was consistently achieved. Examiners were blinded to genetic status. ALS-Plus patients were characterized by 1–11 multisystem features with a median of 4 features per ALS-Plus patient. They differentiated the onset of ALS syndromes from onset of the multisystem symptoms that characterized the ALS-Plus syndrome allowing for future resolution as to whether particular multi-system symptoms appeared differently. Subgroup analysis of such features will come as more centers structure ALS-Plus data sets that may be shared for such analyses.

One important confirmed observation was that pseudobulbar affect was seen in nearly one in two ALS-Plus patients compared with one in four non-ALS-Plus patients and cognitive dysfunction which was labeled as consistent with dementia was seen in slightly over one in thirteen ALS-Plus patients compared with one in thirty-four non-ALS-Plus patients. Dementia in ALS patients characterized clinically has been categorized according to the El Escorial criteria (variant) and the Revised-El Escorial criteria (ALS-Plus). As it has become evident that cognitive and behavioral changes, short of dementia, may be common in ALS patients and that there is a significant appearance of frank dementia by various criteria in both sporadic and familial amyotrophic lateral sclerosis, the concatenation of cognitive dysfunction that was labeled as

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consistent with dementia alongside the other presentations of ALS-Plus provides an estimate for these conditions at nearly one in six ALS patients.

Could this be a function of burden of disease, namely the addition of clinical features might be a surrogate for the wide-spread pathophysiological impact of the underlying disease process in ALS for which there is now new pathological evidence of TDP-43 involvement in the midbrain oculomotor nuclei [9]. The authors suggest in this latest paper that the oculomotor features of ALS-Plus may constitute a pathological stage 5 in their proposed staging system for ALS pathology [10]. If this is the case, then the authors are positing that ALS-Plus exists as a manifestation of early wide-spread dissemination of an underlying ALS disease process that might occur later in those ALS patients who proceed to have prolonged disease mediated by respiratory support, commonly referred to as total ALS [11]. These nuances will have to be carefully addressed in confirmatory studies.

The detailed stipulation of the ALS-Plus clinical syndromes by McCluskey and colleagues has shown a pathway to the future. Just as identification of specific genes associated with familial amyotrophic lateral sclerosis and neuroimaging advances have permitted further categorization of patients with amyotrophic lateral sclerosis, careful critical analyses of clinic-based ALS populations will provide a tool for the proper categorization of clinical presentations of amyotrophic lateral sclerosis.

The learning points provided by this important first step in analyzing those ALS patients with atypical clinical multi-system manifestations include distinctions regarding the potential genetic assortment in ALS-Plus cases that might lend credence to the developing hypothesis of oligogenic clustering in some patients with ALS and whether this might be more common in the ALS-Plus presenting patients [12]. In addition, the distinguishing neuroimaging markers regarding gray matter atrophy are already emerging in studies by others [13] that indicate that those ALS patients with dementia and other atypical clinical multi-system manifestations have demonstrable gray matter atrophy that could constitute a recognizable categorization of ALS patients important for understanding the natural history of such patients. More importantly, however, is the possibility that such overlap syndromes might provide insights to the causation of the disease process in ALS-Plus patients who might have early wide-spread atypical clinical multi-system manifestations [14]. Recent papers are already expanding the presentation of the possible atypical clinical multi-system manifestations of ALS-Plus that imply the work is not quite over [15,16].

McCluskey and colleagues have provided a clinical-based framework to better understand the position of ALS-Plus in the firmament of sporadic and familial motor neuron diseases. I anticipate that their approach will embolden others to look more carefully at the position of ALS-FTD (ALS with Frontotemporal Dementia) and ALS-LAUS (ALS with Laboratory Abnormalities of Unknown Significance) in the future. As Winston Churchill opined in 1942, "*Now this is not the end. It is not even the beginning of the end. But it is, perhaps, the end of the beginning.*" [17]

Conflict of interest

Professor Brooks has no conflicts of interest.

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