Upper motor and extra-motor neuron involvement in recent-onset motor neuron disease

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Upper motor neuron and extra-motor neuron involvement in amyotrophic lateral sclerosis: a clinical and brain imaging review

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ABSTRACT

Background

There is an ongoing discussion whether ALS is primarily a disease of upper motor neurons or lower motor neurons.

Methods

We undertook a review to assess how new insights have contributed to solve this controversy. For this purpose we selected relevant publications from 1995 onwards focussing on (1) primary targets and disease progression in ALS and variants of ALS, (2) brain imaging markers for upper motor neuron lesion, and (3) evidence for ALS being a multisystem disorder.

Results

Clinically, upper motor and lower motor neuron symptoms can occur in any order over time. Brain imaging markers show upper motor neuron involvement in early disease. Overlap syndromes of ALS and dementia, and involvement of autonomic and sensory nerves occur frequently. PET/SPECT scans, functional MRI and voxel based morphometry studies clearly show abnormalities in extra-motor areas of the brain. Pathologically, the 43 kDa TAR DNA-binding protein (TDP-43) provides a clue to these overlapping disorders.

Conclusion

Evidence accumulates that ALS is a multisystem disorder rather than a pure lower and/or upper motor neuron disorder.

INTRODUCTION

Amyotrophic lateral sclerosis (ALS) is a neurodegenerative disease characterized by features indicative of both upper and lower motor neuron lesion. Criteria for the diagnosis were defined at a meeting in El Escorial in 1994 and were further refined at the Airlie House meeting in 1998.[1, 2] More than a decade ago, between 1993 and 1995, there was a revival of the discussion whether ALS was primarily a disease of the upper motor neurons (UMNs) or of the lower motor neurons (LMNs).

Chou and Norris postulated that ALS is primarily a lower motor neuron disease spreading to upper motor neurons ("dying back").[3] Primary target was thought to be the proximal axonal segment of the lower motor neuron. They argued that: (1) characteristic proximal axonal swellings and ubiquitinated inclusions are seen more commonly in anterior horn cells compared to the corticomotoneurons, (2) loss of upper motor neurons is relatively inconspicuous in fully developed ALS, (3) absence of upper motor neuron lesion can be found in a variant of ALS known as progressive muscular atrophy (PMA), (4) the segmental pattern of spread of the disease suggests LMN degeneration, and (5) previous poliomyelitis infection or infection with other viruses may be implicated in the aetiology of ALS.

However, Eisen et al. stated that these "characteristic" pathological findings are secondary findings, as they can also be found in a number of other neurodegenerative diseases.[4] In addition, they questioned the assumption that PMA is an entity in itself, as it is rare and often either identifiable as a motor neuropathy or as ALS with subtle UMN deficits. Lastly, they refuted that poliomyelitis might be implicated in the development of ALS since cases of ALS following poliomyelitis are anecdotal. Instead, they proposed an anterograde ("dying forward") transneuronal degeneration of the anterior horn cells, which is in keeping with Charcot's opinion on this matter in his days.[5-7]

Two other research groups took a more neutral position based on their pathological studies showing that upper and lower motor neurons in ALS degenerate at different rates implying a parallel process of degeneration in LMNs and UMNs.[8, 9] In his time, Gowers also favoured the concept of a simultaneous and independent degeneration of LMNs and UMNs.[10]

Since then, more studies supporting either the LMN or UMN hypothesis were published. There is also growing evidence that ALS, at least in a proportion of the patients, affects

other structures of the central nervous system (CNS), which is illustrated for example by the prevalence of cognitive impairment in ALS.[11, 12] Therefore, a concept of ALS being a multisystem disease is evolving. Although it was already known in the first half of the 20th century that ALS was sometime accompanied or preceded by mental symptoms, not much attention was paid to this until quite recently.[13, 14]

From a clinical perspective, the possibility that ALS encompasses phenotypes which have different aetiologies or at least different modifying factors was stressed recently.[15, 16] Even in familial ALS patients carrying the same superoxide dismutase 1 (SOD1) mutation a striking phenotypic variability was found.[17] Unfortunately, despite an intensive search for biomarkers none of those currently known can be used for individual sporadic patients.

Understanding the primary targets of the disease and the subsequent extension of the pathological process over time, which may differ between the ALS/MND variants, is highly relevant. It may guide the development of new therapeutic strategies, and might explain why effects of therapeutic interventions vary among patients.

The purpose of this article is to review whether new insights since 1995 have clarified the role of upper motor neurons and extra-motor neurons in ALS and its variants. The review focuses on:

- disease progression in ALS and variants (I),
- brain imaging studies of upper motor neurons (II),
- evidence for ALS being a multisystem disorder (III).

Search terms in Pubmed included (number of references between brackets):

- clinical entities: ALS/MND (10), PMA (2), PLS (6), SOD1 (4) in combination with the search terms below:
- disease course: spatiotemporal (3), cognitive impairment/dementia (8) , autonomous nervous system (4), sensory nerves (2),
- brain imaging: magnetic resonance imaging (MRI) (3), magnetic resonance spectroscopy (MRS) (8), diffusion tensor imaging (DTI) (10), voxel based morphometry (VBM) (3), functional MRI (f-MRI) (2), positron emission tomography (PET) (3), single-photon-emission CT (SPECT) (2),
- underlying mechanisms in disease progression: microglia/astrocytes (4), and in ALS with dementia: TDP-43 (15).

Publications from 1995 on were included. Relevant references in publications were hand-searched. Studies focussed on findings at an early stage of disease and on subsequent disease progression were, when available, used as these studies reflect more of the initial disease process than studies focussed on late stages of disease. Brain imaging techniques providing information on extra-motor neuron involvement are discussed in Section 3 and not in Section 2.

DISEASE PROGRESSION IN ALS AND VARIANTS OF ALS

Amyotrophic lateral sclerosis

Careful studies of disease progression in early ALS and its variants on the MND spectrum such as progressive muscular atrophy (PMA) and primary lateral sclerosis (PLS) are rare. However, they may elucidate the sequential pattern of motor neuron death at the UMN and LMN level.

An elegant, albeit retrospective, clinical spatiotemporal analysis of disease progression in 100 patients with early ALS revealed that, although UMN and LMN signs were both most conspicuous in the region of onset, further progress and extension to other body regions were essentially independent of each other, supporting a simultaneous and independent process of degeneration in UMNs and LMNs.[18] This was also found in a longitudinal study monitoring the LMN by studying functional characteristics of motor units and the UMN by analysing excitatory responses to transcranial magnetic stimulation in ALS patients over time. In this study, LMN and UMN degeneration also seemed to occur independently.[19] A post mortem study in 19 deceased ALS patients in search of the distribution of LMN loss in relation to the site of onset found that LMN degeneration is a focal process that advances contiguously.[20] A very relevant finding in this context is the active involvement of microglia and astrocytes in disease progression. Boillee and Yamanaka et al. showed that by reducing the expression of pathogenic mutant superoxide dismutase I (SOD1) in *motor neurons* in ALS mice, disease onset and progression at an early stage of disease could be delayed. However, reduced expression of pathogenic mutant SOD1 both in *microglia* and in *astrocytes* markedly slowed disease progression in later stages of disease.[21-23] This could explain why ALS often starts focally, reflecting damage to a localized group of neurons, then spreading “like a brush fire” through activated microglia and/or astrocytes to contiguous groups of motor neurons.[24] If more evidence arises to confirm this finding, it puts disease progression in a new perspective, and may leave the dying back/dying forward hypothesis behind.

Progressive spinal muscular atrophy

In the 1994 El Escorial criteria PMA was defined by progressive LMN signs in one or more of four regions (bulbar, cervical, thoracic, lumbosacral), with the (electromyographic) exclusion of other LMN syndromes such as multifocal motor neuropathy, and classified as suspected ALS.[1] However, in the 1998 revised El Escorial criteria, this subgroup was omitted because a pure LMN syndrome was not regarded sufficiently certain for the diagnosis of ALS.[25] The exact relationship between PMA and ALS is unresolved. The fact that criteria for a diagnosis of PMA are not clear-cut explains why studies on PMA may yield varying results. This can be illustrated with two MR studies using diffusion tensor imaging in ALS and PMA. The first used strict criteria for PMA, such as the presence of areflexia and presence of the pure lower motor syndrome for at least 2 years after diagnosis, the second included patients with hyporeflexia with no fixed disease duration.[26, 27] The first study found no changes along the corticospinal tract in PMA patients. The second study did, and also showed that clinically the lower motor neuron syndrome evolved into ALS at follow up. An autopsy study found clinically undetected degeneration of the corticospinal tract in half of the patients with PMA.[28]

In an 18 months clinical follow up study of 37 patients with PMA 12 patients developed either possible or probable ALS.[25] Included patients had clinical and electrophysiological evidence of progressive LMN involvement in one or more of four regions and a disease duration of less than 4 years at inclusion. Prognosis, whether evolving into ALS or not, was as poor as in ALS. Decreasing vital capacity was a strong prognostic factor in relation to death. The authors conclude that PMA and ALS are variants of a clinical spectrum but not separate entities. They recommend that PMA patients with declining vital capacity should also be included in ALS drug studies. A strong argument in favor of this view is provided by several studies that demonstrated SOD1 mutations in pure lower motor neuron syndromes.[29-31] Others however, advocate to categorize variants of MND as precisely as possible, “splitting” patients instead of “lumping” patients, as they consider it unlikely and optimistic to expect one single effective drug treatment for all types of MND.[15]

Primary lateral sclerosis

PLS is a pure UMN syndrome which was described by Charcot, more than 100 years ago.[32] Survival is generally longer than that of ALS. PLS remains a clinical diagnosis after excluding an extensive list of other disorders. It has not been settled whether PLS is an entity separate from ALS. Gordon et al. defined pure PLS as a syndrome with isolated

UMN signs 4 years after symptom onset, and UMN dominant ALS as a syndrome with prominent UMN disease and minor LMN signs.[16] The latter group had disability similar to ALS, but slower progression. The description of 2 patients with PLS and a positive (SOD1-negative) family history of ALS provided evidence that PLS can be linked pathophysiologically to ALS.[33] In a clinical and electrophysiological study it was shown that degeneration was not restricted to the UMN.[34] The authors state that the distinction between ALS and PLS is related to the degree of LMN involvement and consider PLS to be a slowly progressive syndrome closely related to ALS.

In a review, Strong et al. state that modern neuroimaging, neuropsychological testing, neurochemistry and immunohistochemistry indicate that, in most instances, the similarity between the two disorders outweighs their differences.[35] They advocate to recognize a pure phenotype of PLS, and a "complicated" phenotype, i.e. PLS in combination with for example lower motor neuron features or cognitive dysfunction.

In summary, interpretation of clinical studies on PMA and PLS is hampered by absence of well-delineated consensus diagnostic criteria. ALS, PMA and PLS seem to be at least closely related syndromes with a varying mixture of UMN and LMN signs and symptoms. Certain clinical conditions (e.g. decreasing vital capacity, predominantly UMN phenotype) determine prognosis rather than the diagnostic label itself. The role of microglia in propagating disease progression is unclear, but possibly very important. The perspective of disease progression due to spread from motor neuron to motor neuron (whether it is dying back or dying forward) could change into a perspective where activated microglia is responsible for disease progression. The latter hypothesis is known as "non-cell autonomous" cell death.

BRAIN IMAGING STUDIES OF UPPER MOTOR NEURONS

Magnetic resonance imaging

Conventional MRI findings such as corticospinal tract hyperintensities on Flair, T2-weighted and Proton Density (PD) images or a hypointense rim at the margin of the precentral gyrus in T2-weighted images are frequently found in ALS patients, but also in healthy controls, and are thus considered non-specific.[36-38]

Diffusion tensor imaging (DTI) of the cortical spinal tract

DTI is a MR technique to study the integrity of white matter fiber tracts by measuring water diffusion (anisotropy) changes along a tract, e.g. the corticospinal tract. Anisotropy is high along an intact tract. Decreased anisotropy was found to be related to clinical and electrophysiological measures of UMN degeneration in ALS patients, therefore suggesting that DTI can be used for objective evaluation of the UMN.[39] DTI also allows for the *in vivo* investigation of white matter tracts by diffusion tensor tractography (DTT).[40] The combination of DTI voxel analysis and DTT is a unique tool to detect intracranial pathological changes in ALS non-invasively.[41, 42] With this tool it is feasible to monitor changes along the CST over time and evidence for either a “dying back” or “dying forward” process may be found. So far, results from DTI/DTT studies in ALS patients have been contradictory. One controlled study showed a significantly reduced anisotropy in ALS patients along the CST in the cerebral peduncle but not more caudally, suggesting a “dying forward” phenomenon.[43] Another study detected significant abnormalities in the pons but not in the internal capsule or corona radiata when compared to controls, suggesting a “dying back” phenomenon.[44] A third study showed significantly increased diffusion more caudally in patients but also in controls.[45]

Studies focussed at an early stage of disease are scarce. Only one controlled study in early MND has been done including patients with ALS and PMA.[27] In both groups decreased anisotropy along the CST was observed. All patients with PMA later developed ALS, suggesting that DTI can be a marker for UMN involvement in early disease. In contrast, another controlled study comparing patients with ALS and PMA found no anisotropy changes in the CST of PMA patients. However, this study used stricter criteria for a diagnosis of PMA namely the presence of a pure lower motor syndrome and areflexia for at least two years after diagnosis whereas the first study included patients with hyporeflexia without a criterion for disease duration.[26]

In conclusion, DTI/DTT is a promising tool to study early involvement of the UMN in ALS and its variants, but results so far have been conflicting when it comes to the dying back/ dying forward hypothesis. This may be due to the small numbers and varying disease duration in some studies, and different criteria for the diagnosis of the various MND phenotypes. Finally fiber tracking is known to be a user-dependent process, which may have hampered interpretation of findings.[46]

MR spectroscopy

N-acetyl aspartate (NAA) is present primarily in (motor) neurons and decreased levels reflect a loss or dysfunction of neurons. Therefore, reduced NAA levels are used as a spectroscopic marker for UMN degeneration.[46] MRS of the motor cortex showed abnormally low NAA levels in patients with advanced ALS in several studies.[47-49] Studies at an early stage of disease and with an adequate follow up time are scarce. One controlled longitudinal study investigated the least symptomatic of the two sides of the motor cortex of 28 ALS patients, as a model for pre-symptomatic or early symptomatic stages. Repeat measurement after three months in a subgroup of 9 patients showed significantly decreased NAA levels suggesting an early and active neurodegenerative process in the motor cortex.[50] Two other follow up studies showed similar results.[51, 52] Two studies in patients with PMA found normal NAA levels.[48, 49]

Myo-inositol (MI) is a spectroscopic marker for glial activity. MI levels were increased in the motor cortex of ALS patients.[47, 53] NAA *and* MI combined in a ratio (NAA/MI) may provide better sensitivity and specificity for detecting disease than the individual metabolites, as was shown in a cross sectional study among ALS patients.[54] Therefore, this ratio may provide a meaningful biomarker in the future, but its use in early ALS is as yet unknown.

In conclusion, MRS findings suggest an active degenerative process in motor neurons of the primary motor cortex at the early stage of ALS. Furthermore, myo-inositol levels may be of use to monitor glial hyperactivity.

EVIDENCE FOR ALS BEING A MULTISYSTEM DISORDER

For a long time ALS was considered to be a disease exclusively affecting motor neurons. However, there is accumulating evidence that ALS affects other parts of the nervous system as well.

Cognitive impairment in ALS

In sporadic ALS cognitive impairment, usually of a frontotemporal/behavioural type, was found in 30-50% of the patients.[12, 55-57] In approximately 15% of the patients criteria for frontotemporal lobar dementia (FTD) were fulfilled, the others had mild cognitive

impairment. A prospective study observed executive dysfunction relatively early in the course of ALS.[11] Several studies recognized that ALS and FTD show significant pathological overlap with neuronal ubiquitinated inclusions, not immunoreactive for tau, as a hallmark feature.[58, 59] A Scandinavian study strongly supported a shared pathogenesis with the identification of a FTD-ALS locus on chromosome 9p in a family with five members dying of ALS and nine suffering from FTD.[60]

A major breakthrough in this context was the discovery that a TAR DNA-binding protein of 43 kDa (TDP-43) seemed to play a role in the pathology of ALS *and* FTD.[61] The exact biological role of TDP-43 is as yet unknown. Pathologic hyperphosphorylated ubiquitinated TDP-43 was found in cytoplasmatic inclusions in the central nervous system, including hippocampus, neocortex and spinal cord, of patients with sporadic ALS *and* patients with FTD.[61, 62] In ALS patients neuronal and glial TDP-43 pathology was also found in the nigrostriatal system and cerebellum, in lower motor neurons and in glial cells of the brainstem.[63-65] In addition to this, it was shown that TDP-43 immunoreactive inclusions were found in 20% of patients with Alzheimer's disease and in 70% of patients with hippocampal sclerosis.[66] These findings were confirmed by other studies.[67, 68] Therefore a clinicopathologic spectrum of TDP-43 proteinopathies seems to be emerging with ALS, FTD, Alzheimer's disease and possibly other neurodegenerative diseases such as corticobasal degeneration being representatives.[69-71] Two studies found abnormal TDP-43 in SOD1-negative familial ALS patients, but *not* in patients with SOD1 mutations, suggesting that motor neuron degeneration in the latter group may result from a different mechanism.[64, 72] However, a third study demonstrated abnormal TDP-43 also in SOD1- positive ALS patients.[73] The same study found no TDP-43 abnormalities in mutant SOD1 transgenic mice thus calling for caution in the interpretation of SOD1 transgenic mice studies.[73] Very recently TDP-43 gene mutations were demonstrated in sporadic and in SOD1-negative familial ALS patients.[74, 75]

Brain imaging studies

PET studies found cerebral dysfunction not only the motor and premotor areas, but also in the prefrontal/frontal regions and parietal and occipital cortex, when compared to controls.[76-78] Serial SPECT scanning in a sporadic ALS patient detected hypoperfusion confined to the motor cortex, later extending to the fronto-parietal area with progression of the disease.[79] SPECT scanning also provided evidence for subclinical involvement of nigrostriatal dopaminergic neurons in a subset of sporadic ALS patients.[80] Functional MRI studies found patterns of reduced activation in prefrontal/frontal areas.[81, 82] Voxel

based morphometry (VBM) MRI studies found regional grey matter reductions extending beyond the motor cortex, but also regional white matter alterations not only in the CST but also in the corpus callosum, cerebellum and in the frontal and occipital regions.[83-85]

Sensory and autonomic nervous system

Evidence for ALS being a multisystem disorder also comes from other directions. For example, autonomic disturbances such as dysregulation of blood pressure and possibly an increased risk of sudden cardiac arrest in association with prolonged QT intervals at electrocardiography were found in ALS patients.[86, 87] Histologically, numbers of neurons in the intermediolateral nucleus in the upper thoracic cord were significantly lower in sporadic ALS patients than in controls, comparable to findings in multiple system atrophy.[88] A case report presenting a patient with a (V118L) SOD1 mutation who died after a sudden cardiac arrest found widespread multisystem degeneration, not only in the intermediolateral nucleus in the upper thoracic cord but also in the globus pallidus, subthalamic nucleus, substantia nigra and locus ceruleus.[89] Two recent studies presented evidence for involvement of sensory nerves in about 20-30% of the ALS patients after a mean duration of symptoms of 10-14 months.[90, 91]

In conclusion, there is fast growing evidence that ALS exceeds the motor system in at least a proportion of the patients.

CONCLUSION AND FUTURE PROSPECTS

Studies on disease progression in PMA and ALS reveal that delineation of the clinical entities is still under debate. Clinically, UMN and LMN symptoms can occur in any order over time, therefore supporting neither the UMN nor the LMN hypothesis. The majority of brain imaging studies in search of biomarkers for UMN degeneration did not focus on early stage ALS, but it is clear that abnormalities of the UMNs are found too early to be due to a “dying back” phenomenon. Possibly activated astrocytes and microglia are a key factor in disease progression, rather than transsynaptic “dying back” or “dying forward” of motor neurons.

The association of ALS with cognitive impairment and dementia suggests that ALS is a multisystem disorder rather than a pure motor neuron disease system in at least a proportion of the patients. The protein TDP-43 may play a key role in the understanding

of these overlap syndromes. A clinicopathologic spectrum of TDP-43 proteinopathies seems to be emerging with ALS, FTD, Alzheimer's disease and possibly other neurodegenerative diseases being representatives. PET/SPECT scan studies, voxel based morphometry and functional MRI provide evidence for involvement of extra-motor areas in ALS. Abnormalities of the autonomic nervous system and sensory nerves in a significant proportion of ALS patients further underline the concept of ALS being a multisystem disorder.

Further research focussed on the primary targets of the disease and the pathogenic process over time in ALS and its variants is important. It may offer a new perspective on the development of therapeutic strategies, and might explain why effects of therapeutic interventions vary among patients.

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