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Phenotypic variability in Amyotrophic Lateral Sclerosis

Philippe COURATIER[1,2,3,*], Géraldine LAUTRETTE[1,3], Jaime Andres LUNA[2], Philippe CORCIA [3,4]

Philippe COURATIER[1,2,3,*]

[1] Centre de Référence Maladies rares SLA et autres maladies du neurone moteur
Service de Neurologie, CHU de Limoges, France

[2] INSERM, Univ Limoges, CHU Limoges, IRD, U1094 Tropical Neuroepidemiology, Institute of Epidemiology and Tropical Neurology, GEIST, Limoges, France

[3] Fédération des Centres SLA de Limoges et Tours, LITORALS

Géraldine LAUTRETTE[1,3]

[1] Centre de Référence Maladies rares SLA et autres maladies du neurone moteur
Service de Neurologie, CHU de Limoges, France

[3] Fédération des Centres SLA de Limoges et Tours, LITORALS

Jaime Andres LUNA[2]

[2] INSERM, Univ Limoges, CHU Limoges, IRD, U1094 Tropical Neuroepidemiology, Institute of Epidemiology and Tropical Neurology, GEIST, Limoges, France

Philippe CORCIA[4]

[3] Fédération des Centres SLA de Limoges et Tours, LITORALS

[4] Centre de Référence Maladies rares SLA et autres maladies du neurone moteur, CHU Bretonneau Tours, France

Philippe COURATIER[1,2,3,*]

*To whom correspondence should be addressed

[1] Centre de Référence Maladies rares SLA et autres maladies du neurone moteur

Service de Neurologie, CHU de Limoges, 2 Avenue martin Luther King, 87000 Limoges, France

Phone number: 33555056561

e-mail: philippe.couratier@unilim.fr

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Abstract

Clinically, ALS phenotypes depend on the areas of the body that are affected, the different degrees of involvement of upper and lower motor neurons, the degrees of involvement of other systems, particularly cognition and behavior, and rates of progression. Phenotypic variability of ALS is characteristic and can be declined on the distribution of motor manifestations but also on the presence of extra-motor signs present in a variable manner in ALS patients. Neuropathologically, ALS is defined by the loss of UMN and LMN and the presence of two representative motor neuronal cytoplasmic inclusions, Bunina bodies and 43 kDa Transactivation Response DNA Binding Protein (TDP-43) - positive cytoplasmic inclusions. The distribution of cytopathology and neuronal loss in patients is variable and this variability is directly related to phenotypic variability. Key regulators of phenotypic variability in ALS have not been determined. The functional decrement of TDP-43, and region-specific neuronal susceptibility to ALS, may be involved. Due to the selective vulnerability among different neuronal systems, lesions are multicentric, region-oriented, and progress at different rates. They may vary from patient to patient, which may be linked to the clinicopathological variability across patients.

Key words

Amyotrophic Lateral Sclerosis, phenotype, upper motor neuron, lower motor neuron, Transactivation Response DNA Binding Protein

1. Introduction

The concept of amyotrophic lateral sclerosis (ALS) was first established by Jean-Martin Charcot of the Salpêtrière Hospital. The name ALS was speculatively derived by Charcot who assumed that spinal cord degeneration would be a primary lesion and that the amyotrophy associated with anterior horn motor neuron degeneration could be secondary to spinal cord degeneration [1]. However, regardless of this hypothesis, the name "ALS" with only three words with the implication that amyotrophy and spinal cord degeneration coexisted was accepted and persists to this day [2]. The main defining characteristic of ALS is progressive weakness due to neurodegeneration of the upper motor neuron (UMN) and lower motor neuron (LMN). Clinically, ALS is defined by a history of weakness over time and space, and by an examination showing evidence of upper and lower motor neuron dysfunction in one or more areas of the body. Neuropathologically, ALS is defined by the loss of UMN and LMN and the presence of two representative motor neuronal cytoplasmic inclusions, Bunina bodies and 43 kDa Transactivation Response DNA Binding Protein (TDP-43) - positive cytoplasmic inclusions [3-4]. The distribution of cytopathology and neuronal loss in patients is variable and this variability is directly related to phenotypic variability. Clinically, ALS phenotypes depend on the areas of the body that are affected, the different degrees of involvement of UMN and LMN, the degrees of involvement of other systems, particularly cognition and behavior, and rates of progression. Phenotypic variability of ALS is characteristic and can be declined on the distribution of motor manifestations but also on the presence of extra-motor signs present in a variable manner in ALS patients (Table 1). In this article, the clinical and neuropathological archetypes of ALS will be reviewed.

2. Clinical phenotypes of ALS

2.1 Based on body region of involvement

2.1.1 The archetypic form of ALS: spinal form

The major type of ALS has a spinal onset, known as Charcot's type. This type begins with asymmetric weakness in a limb around the age of 60 years. Most patients demonstrate a gradual worsening of weakness within a year, which progresses to a contralateral limb or to

other spinal and/or bulbar areas. On neurological examination, muscle atrophy with fasciculations and hyperreflexia of limbs are detected. Babinski's sign is occasionally positive. Typically, hyperreflexia is more evident in the lower limbs than in the upper limbs. As muscle atrophy progresses, the pyramidal signs are less evident on clinical examination. Some young patients may develop a predominant upper motor neuron form with spasticity. Patients may face a life-threatening condition as respiratory muscle weakness progresses and mean survival time has been reported to be approximately 3 years [5].

2.1.2 Flail arm phenotype

The term flail arm syndrome (FAS) is most common, but it is also referred to as Vulpian-Bernhardt's type, neurogenic man-in-a-barrel syndrome, or scapulohumeral form of ALS. Patients with FAS present with predominantly proximal, progressive and symmetric wasting and paresis of the upper limb muscles, while lower limbs and bulbar muscles are spared [6]. Upper motor neuron signs in the legs are occasionally present [7]. Wijesekera et al. defined FAS as weakness of both upper limbs without bulbar and lower-limb symptoms for a period of at least 12 months from disease onset [8]. Chio et al. demonstrated on a population-based study that FAS was relative rare and more common in men (incidence rates, 0.28 in men and 0.07 in women), with a men to women rate ratio of 4:1 and mean age at onset was 62.6 years (SD 11.8). In this phenotype, Frontotemporal-Dementia (FTD) is very rare (1.4%). Flail arm phenotype is relatively benign, with a median survival time of 4.0 years and a 10-year survival rate of 17% [9].

2.1.3 Flail leg phenotype

Some ALS patients have weakness confined to the lumbosacral spinal cord region. This subtype is known as flail leg syndrome, Marie-Patrikios' type, or a peroneal form of ALS [8]. Flail leg accounts for between 2.5–6.3% of motor neuron disease, and has a similar mean age of symptom onset to classic ALS. This phenotype has a similar incidence in the two genders. Onset is asymmetric in about half of patients, but typically progresses to include both lower extremities, and muscle stretch reflexes are absent or diminished. The definitions for Flail leg differ by case series but common features include insidious onset of weakness isolated to the legs, decreased or absent reflexes at presentation and symptoms confined to one spinal region for 12–24 months [10]. About half of patients show an initial pattern of weakness described as pelviperoneal, with sparing of the quadriceps and ankle plantarflexors. The remaining patients show either diffuse weakness, or a distal pattern of weakness. The

median survival time (3.0 years) and the 10-year survival rate (13%) of this phenotype are similar to those of classic ALS. FTD is present in 4% of patients with this phenotype.

2.1.4 Bulbar form : progressive bulbar palsy (PBP)

This phenotype is characterized by the onset of dysarthria or dysphagia with bulbar muscle atrophy. The first report of the bulbar type of ALS was likely carried out by Gombault, who was a student of Charcot [11]. Bulbar phenotype accounts for 20% of patients with ALS [12]. Some patients have isolated bulbar palsy (IBP) marked by speech abnormalities or dysphagia but lack bulbar muscle atrophy or fasciculation. This condition should not be diagnosed as PBP; instead, it should be considered pseudobulbar palsy in the strictest sense. IBP patients are predominantly female and are characterized by the presence of UMN bulbar symptoms such as spastic dysarthria and emotional lability. In contrast, more typical bulbar ALS patients exhibit mixed or flaccid dysarthria, more prominent tongue fasciculations and more prominent limb involvement. Although progressive tongue atrophy and fasciculations are relatively specific to ALS, they must be distinguished from Kennedy's disease [13]. There is an increase in frequency of bulbar phenotype with increasing age [9]. The bulbar type of ALS with a mean survival of 2 years has poorer prognosis compared to that of the limb onset. This is because the patients are more likely to develop aspiration pneumonia and malnutrition due to dysphagia [9].

2.1.5 Respiratory phenotype.

This is the rarest phenotype (annual incidence rate: men, 0.06/100,000; women, 0,01/100,000). Its median survival time is 1.4 years and no patient with this phenotype survive up to 10 years [9].

2.2 Based on Level of involvement of LMN and UMN

2.2.1 Progressive muscular atrophy (PMA)

PMA is a rare, sporadic, adult-onset, clinically isolated LMN syndrome due to the degeneration of LMN, including anterior horn cells and brainstem motor nuclei. It is clinically characterized by progressive flaccid weakness, muscle atrophy, fasciculations, and reduced or absent tendon reflexes. The term PMA was first coined by the French neurologists Aran and Duchenne in 1850 to describe patients with progressive muscle atrophy. In 1853, Cruveilhier

provided the first evidence of PMA being a neurogenic disorder based on the atrophy of the ventral spinal roots and the motor nerves found on autopsy of Aran's patients [14-15]. It has been recognized that a substantial number of patients with the initial diagnosis of PMA progress to a diagnosis of ALS through the development of UMN signs or may have UMN pathology at autopsy despite the absence of clinical UMN features during their lifetime [16]. These observations support the notion of PMA belonging to an ALS spectrum rather than being a unique variant of MNDs. However, there remains a significant proportion of patients with PMA who have no clinical or subclinical evidence of UMN dysfunction, supporting the existence of PMA as a separate entity. At present, the term PMA is reserved for sporadic patients with MND with pure LMN findings on examination, who may or may not later develop clinically defined UMN features. Patients who subsequently develop UMN signs are reclassified as having ALS. Patients with PMA have LMN features, namely, progressive flaccid weakness, muscle atrophy, fasciculations, and hyporeflexia or areflexia. Weakness and atrophy typically starts in distal limb muscles in an asymmetric manner following neuropathy pattern and then spreads over months and years. There is a mean delay of approximately 23 months between the onset and the diagnosis. Symmetric proximal limb weakness (myopathy pattern) occurs in only 20% of patients. Bulbar muscles are generally spared at onset but may be involved in up to 40% of patients within a median of 19 months from onset of limb weakness. Patients with bulbar involvement are more likely to progress to ALS or run a relentless course, as seen in ALS. It is uncommon for respiratory muscles to be involved at the onset of PMA [17]. The rate of progression in patients with PMA varies from slow (over years and decades) to very rapid (months to a year). The median survival duration after onset in patients with PMA is about 12 months longer than in patients with ALS (48.3 vs 36 months) [18].

2.2.2 Primary lateral sclerosis

In 1865, Charcot reported on a patient with isolated degeneration of the spinal lateral cord who clinically manifested severe spastic tetraparesis [19]. Erb described the clinical and pathological features, naming this condition PLS [20]. Patients with PLS present with upper motor neuron signs only. Therefore, they do not meet the clinical criteria of Awaji [21]. Many patients with PLS develop lower motor neuron signs within 4 years of onset [22-24] and some patients manifest with frontotemporal dementia [25]. PLS constitutes approximately 1–5% of all cases of ALS. Mean survival time is reported to be approximately 8 years [26]. The differences and similarities between PLS and ALS are still not well understood, but recent

reports suggest that the majority of clinical features of PLS resemble those of ALS [27]. Thus, if PLS is seemingly regarded as a subtype of ALS, at least for the first four years of follow-up, examination by needle electromyography is required to assess LMN involvement. New criteria have been established in 2020 [28].

2.2.3 Hemiplegic form

Some patients manifest with unilateral upper motor neuron involvement. This extremely rare clinical syndrome of UMN–predominant (1% of all patients with ALS), progressive hemiparesis was first described by American neurologist Charles Karsner Mills [29]. This form slowly develops ipsilateral involvement and spreads to eventually involve the contralateral side. After a variable period, lower motor neuron signs will gradually be evident, suggestive of ALS [30]. Some patients with this variant could develop frontotemporal degeneration [31]. Estimated survival periods are variable, but are usually longer than 10 years [30].

2.3 Based on involvement of non-motor regions

2.3.1 ALS and frontotemporal dementia (FTD) spectrum

The overlap of FTD and ALS has been well documented in FTD patients with comorbid motor neuron degeneration and in ALS patients with frontotemporal dysfunction [32-35]. Cognitive impairment has been reported in approximately 50% of patients with ALS [36]. Of these patients, 10–20% manifest with FTD [37-38]. Cognitive decline in ALS is variable and is characterized by personality changes, irritability, social misconduct, executive dysfunction, language problems, and memory impairments [39]. Behavioral or cognitive abnormalities may be subtle leading to identify behaviorally impaired (ALS-bvi) and cognitively impaired (ALS-ci) ALS patients as compared to patients without deficit, according to the revised criteria for the diagnosis of frontotemporal cognitive and behavioural syndromes in ALS [40]. The Edinburgh team proposed a new scale, ECAS avoiding the potential interaction of motor deficit with cognitive-behavioural assessment [41]. In ALS-FTLD patients, frontotemporal atrophy may be detected by magnetic resonance imaging of the brain with decreased cerebral blood flow in single photon emission computed tomography [42]. Neuropathologically, spreading of TDP-43 pathology and neuronal loss are involved in the frontotemporal cortices and subcortical regions, known as FTLD-TDP.

2.3.2 ALS and parkinsonism

In the Western Pacific area (West New Guinea, the Mariana Islands and the Kii peninsula), several endemic foci with a high incidence of ALS and PDC have been reported. Epidemiological investigations begun in 1960 have revealed the incidence of ALS in West New Guinea to be surprisingly high, at approximately 1.4%. This incidence was ten times higher than that in Guam or Kii and was estimated to be a 100 times higher than that in the continental United States [43]. The clinical phenotype of ALS in ALS/PDC resembles that of sporadic ALS. Phenotypic variations exist, such as PBP or PMA types. ALS/PDC has a similar neuropathology to that of sporadic ALS, characterized by the presence of Bunina bodies and TDP-43-positive cytoplasmic inclusions. The key clinical features of PDC are a lack of spontaneity and decrease in verbal frequency. Akinesia and rigidity are typically observed as parkinsonian signs in patients with PDC. The neuropathology of PDC is characterized by frontotemporal atrophy and the presence of neurofibrillary tangles (NFTs) positive for both 3- and 4-repeat tau and the absence of senile plaques [44]. Interestingly, the abundance of NFTs was well observed not only in Chamorro patients with PDC but also in healthy Chamorro. In contrast, the number of NFTs in the brains of Kii ALS/PDC varied, whereas, in the brains of non-ALS/PDC patients from the village, the number of NFTs was similar to that in Japanese controls from other areas. A previous study revealed that the coexistence of TDP-43, tau, and α-synuclein is a key feature of Western Pacific ALS/PDC [45].

Besides these endemic focal cases, an association between sporadic and familial Parkinson's disease (PD) and ALS, i.e., Brait–Fahn–Schwartz disease, has been proposed as a syndrome characterized by the co-presence of these two disorders without dementia or dysautonomia. Parkinsonian symptoms and signs have been described in cross-sectional studies in ALS patients, with frequency from 5 to 17% [46-47] Backward falls, impaired postural reflexes, retropulsion, bradykinesia, and decreased arm swing in ALS have been reported in early-stage ALS and are often linked to basal ganglia alterations [48]. A recent paper confirmed gait initiation in ALS patients with postural instability [49]. On the neuropathologic level, the demonstration of a pallido-nigro-luysian (PNL) degeneration with TDP-43 pathology remains rare. Some patients manifest with parkinsonism [50-51] whereas some do not manifest these symptoms [52] and undetectable parkinsonism in patients with PNL involvement may be masked by motor paralysis. A recent case report described increased glial TDP-43 pathology in the PNL system and brainstem motor neurons in facial-onset sensory motor neuropathy,

suggesting that the molecular pathogenesis in PNL-involved type and sporadic ALS/FTLD spectrum differs [53]. Nigral degeneration in patients with ALS had been recognized as a rare condition [54]. In 1993, Kato et al. performed a clinicopathological retrospective analysis of 15 patients with sporadic ALS, finding a decreased number of nigral melanin-containing neurons in seven patients (46.7%) and they described supranuclear ophthalmoparesis in four patients [55]. Nishihira et al. reported TDP-43 pathology in the substantia nigra of 16 out of 35 patients (45.7%) with ALS, in addition to nigral neuronal loss in 12 out of 35 patients (34.3%) [56]. Nigral degeneration may be related to cognitive dysfunction with concomitant degeneration of frontotemporal cortices, hippocampus, and striatum. Further investigation should be performed to clarify the clinicopathological relationship of nigral degeneration in patients with ALS.

2.3.3 ALS with cerebellar degeneration

Cerebellar ataxia is a very rare symptom in patients with ALS. The ataxia could occur in some patients with *C9orf72* mutation. Polyglutamine (polyQ) expansion in ataxin-2 (*ATXN2*) is known to cause the onset of spinocerebellar ataxia 2 (SCA2). In 2010, intermediate-length expansions (27–33 Qs) of polyQ was identified as a potent risk factor for ALS [57]. Both phenotypes of SCA and ALS may coexist in the same family [58]. A case report demonstrated that the initial manifestation was SCA followed by motor neuron signs 16 years later [59]. Motor neurons in patients with ALS that have *ATXN2* expansions (27–33 Qs) may contain filamentous inclusions, such as skein-like inclusions, while those in ALS without *ATXN2* expansion (22–24 Qs) may contain large rounded inclusions [60].

2.3.4 ALS with vacuolar degeneration of cerebral white matter

In the majority of patients with ALS, ocular movement is preserved [61]. However, Takeda et al. previously reported that approximately 10% of all ALS patients with subcortical white matter vacuolation presented with vertical ophthalmoparesis and suggested that the symptoms could be related to impairments in the upper motor neuron system innervating nuclei of external ocular muscles [62].

2.3.5 ALS with autonomic dysfunction

Autonomic dysfunction in ALS is a rare symptom, at least in the early stage of illness [63]. However, literature increasingly revealed the manifestation of urinary impairments in patients with ALS. Arlandis et al. reported that approximately 26% of patients with ALS

demonstrated symptomatic urinary urgency [64]. With disease progression, Onuf's nucleus may be involved and the number of neurons decreases by almost half in the advanced phase of illness [65]. Thus, patients with ALS may manifest with urinary impairments more frequently than previously thought. A subset of patients treated with tracheostomy-positive pressure ventilation (TPPV) may develop abnormal ocular movements and autonomic impairments [66].

2.3.6 ALS with sensory symptoms

In conjunction with the progressive damage of the corticospinal tract (CST), autopsy cases and animal studies showed involvement of sensory pathways further confirmed by morphometric measures in the somatosensory cortex as well as functional imaging and structural imaging in the white matter. Moreover, electrophysiological measurements in ALS patients showed sensory symptoms and lower amplitude of compound action potential amplitudes of the sural nerve [67].

3. Factors that influence phenotypic variability

3.1 Lessons from neuropathology: the role of TDP-43 inclusions

Upper motor neuron degeneration is based on histological demonstration of neuronophagia of Betz cells and myelin pallor of the pyramidal tract. Historically it was proposed that pyramidal degeneration progresses from its distal site, associated with the dying back phenomenon [68]. In fact, the site of origin is increasingly recognized as being cortico-fugal, which is a dying-forward process primarily starting in the corticomotoneuronal system. The dyingforward hypothesis proposes that glutamate excitotoxicity at the level of the cortical motorneuron ultimately results in anterior horn cell metabolic deficit.

The involvement of lower motor neurons is characterized by neuronal loss and dendritic retraction of spinal and brainstem motor neurons. The cytopathology common to patients with ALS consists of the formation of inclusions in motor neurons, including Bunina bodies and TDP-43-positive cytoplasmic inclusions. Bunina bodies, first reported in 1962 in patients with familial ALS are immunoreactive to anti-cystatin C [69] and anti-transferrin antibodies [70]. The origin of Bunina bodies is not fully known, but it is suggested that they derived from lysosomes or the endoplasmic reticulum [71]. TDP-43-positive intracytoplasmic inclusions in

spinal and brainstem motor neurons appear in various forms. They can be classified into three categories: dot-like inclusions, skein-like inclusions, and round inclusions. These inclusions were identified in 1988 as ubiquitin-positive cytoplasmic inclusions [72]. The first identification of TDP-43 as a major component of ubiquitin-positive inclusions was reported in 2006 by Neumann et al. and Arai et al. [73]. The most prominent feature of TDP-43 cytopathology is the mislocalization of TDP-43 characterized by loss of native TDP-43 in the nucleus and abnormal aggregation of TDP-43 in the cytoplasm. TDP-43 in cerebral neurons is deposited in a morphologically different manner from that in spinal motor neurons. In the cerebrum, many cytoplasmic inclusions positive for TDP-43 are present in small neurons. They are deposited in rounded, perinuclear, or curved shapes. The cerebral pathology of ALS resembles that of FTLD with motor neuron disease (FTLD-MND), with the majority of abnormal TDP-43 aggregation present in the neuronal cytoplasm and minimal aggregation in neurites and nuclei [74]. FTLD with mutations in progranulin (FTLD-GRN) is characterized by short neuritic deposition of TDP-43 and cytoplasmic aggregation of TDP-43. In *C9orf72*-mutated FTLD-MND patients, a type B TDP-43 pathology is mostly found but some reported type A [75]. Although a genetic mutation is not the only factor determining the topography of TDP-43 deposition, knowing the type is sometimes useful for understanding the relationship between genetic factors and clinical conditions in patients with ALS and FTLD. However, some patients cannot be classified into any subtype. It remains unknown how subcortical TDP-43 pathologies differ from one another [76]. Further analyses will be needed to identify cases determining the morphology of TDP-43 aggregation.

3.2 The regional discrepancy in relationship of TDP-43 accumulation and neuronal loss

The relationship between inclusion cytopathology and neuronal loss is inconsistent based on the involved area. In the spinal anterior horn or hypoglossal nucleus, the prevalence of TDP-43 pathology and neuronal loss may almost be equivalent. The second most representative regions in which the prevalence of TDP-43 aggregation and neuronal loss are equivalent are the amygdala, orbitofrontal cortex, entorhinal cortex, and frontotemporal cortices. In contrast, there are areas in which the degree of neuronal loss is very mild despite the frequent detection of TDP-43 aggregation. These include granular cells of the dentate gyrus, inferior olivary nucleus, red nucleus, and brainstem reticular formation. The neurons least sensitive for TDP-43 aggregation relative to neuronal loss are pyramidal neurons (Betz cells). It has been reported that despite the evident loss of native TDP-43 from the nucleus, abnormal aggregation in the cytoplasm is relatively rare in these neurons [77]. The

inconsistent relationship between TDP-43 pathology and neuronal loss obscures how TDP-43 contributes to neuronal degeneration linked to neuronal loss. These discrepancies suggest that neuronal loss is plausible to be linked to decrement of the normal function of TDP-43 rather than gain of toxic function of TDP-43 and there are differences in susceptibility to TDP-43 dysfunction among the neuronal system [78].

3.3 Variability of disease progression in ALS

The selective vulnerability of distinct regions of the brain and spinal cord is a critical factor. The sites where ALS lesions begin and how they spread into the central nervous system have not yet been fully elucidated. Lesions may occur in one or more of susceptible areas and progress locally at various rates in each region [79]. So, a different histological susceptibility, resulting in abnormal TDP-43 function among neuronal groups, or a different cellular susceptibility associated with cellular characteristics, may at least partly explain patterns of onset and progression. A systemic TDP-43 dysfunction but also region-specific susceptibility of the motor neurons and frontotemporal cortices could contribute to lesion formation and its progression [80]. The focal susceptibility related to onset may not be random, as it is determined by the age at onset and gender: bulbar onset ALS has been shown to increase with advancing years and flail arm syndrome has been shown to affect mostly men [9]. Thus, ALS lesions seem to be multicentric, region-oriented, and have different rates of progression and phenotypic variability is based on these underlying pathological features.

3.4 Role of genetic factors

Sporadic ALS (SALS) occurs in 90% of cases, and familial ALS (FALS) in 10%, are essentially indistinguishable from each other by phenotype. In populations of European origin, the 4 major ALS causing genes are *C9orf72*, *SOD1*, *TARDBP* and *FUS* and concern two third of FALS [81-82]. For these genes it is possible to establish genotype-phenotype correlations. *C9orf72* is the major genetic cause of disease over 40 years of age, whereas *FUS* is the the major cause for the juvenile ALS and for disease occurring in younger adults. Trio analyses allows to confirm that de novo occurrence was preponderant in the *FUS*-linked SALS. For all major ALS causing genes, penetrance is incomplete. Clinically, ALS patients with *SOD1* mutations frequently present with lower limbs onset, predominant lower motor neuron signs and very rarely a frontal cognitive dysfunction is associated. Disease progression appears to be bimodal in SOD1-ALS patients, with some patients showing either rather rapid

(<3 years, fast progressors) or rather slow (>7 years, slow progressors) disease course. Some *SOD1* mutations, such as the G41S mutation, are associated with a particularly short survival, of around one year following the diagnosis; at the opposite, the N139D mutation leads to a long disease duration of more than 10 years. Moreover, the disease course can also be different among members of the same family carrying the same mutation, as D83G with a disease course of several months to more than 10 years. In *TARDBP*-mutated patients, disease onset appears to be predominantly in the upper limbs, frequently associated with marked bulbar dysfunction and with FTD. *FUS*-related ALS phenotype is severe, with early onset and fast progression of disease leading to shorter survival. *C9orf72*-linked patients have more frequent bulbar onset, disease starts later in life, compared to *FUS* or *SOD1*, and is more frequently associated with FTD. Prognosis in terms of survival appears to be pejorative, compared to *SOD1* or *TARDBP* mutation carriers.

4. Conclusion

The highly distinctive molecular neuropathological subtypes of ALS do not completely correlate with the various clinical phenotypes. This point is crucial as it raises the following question: is ALS a single disease with common biological mechanisms or is it several diseases with different mechanisms? Advances in genetics have shown that different genetic mutations can induce common phenotypes. This suggests that ALS is more like a syndrome. Key regulators of phenotypic variability in ALS have not been determined. The functional decrement of TDP-43 and region-specific neuronal susceptibility to ALS may be involved. Due to the selective vulnerability among different neuronal systems, lesions are multicentric, region-oriented, and progress at different rates. They may vary from patient to patient, which may be linked to the clinicopathological variability across patients.

References

[1]. Charcot J-M. Amyotrophies spinales deuteropathiques sclérose latérale amyotrophique. In: *Oeuvres Complètes*, vol. **2**. Paris: Bureaux du Progrès Médical, 1874; 234– 248.

[2]. Goetz CG. Amyotrophic lateral sclerosis: Early contributions of Jean-Martin Charcot. *Muscle Nerve* 2000; **23**: 336– 343.

[3]. Okamoto K, Morimatsu M, Hirai S, Ishida Y. Intracytoplasmic inclusions (Bunina bodies) in amyotrophic lateral sclerosis. *Acta Pathol Jpn* 1980; **30**: 591– 597.

[4]. Neumann M, Sampathu DM, Kwong LK *et al*. Ubiquitinated TDP-43 in frontotemporal lobar degeneration and amyotrophic lateral sclerosis. *Science* 2006; **314**: 130– 133.

[5]. Oskarsson B, Gendron TF, Staff NP. Amyotrophic lateral sclerosis: An update for 2018. *Mayo Clin Proc* 2018; **93**: 1617– 1628.

[6]. Couratier P, Truong C, Khalil M, Deviere F, Vallat JM Clinical features of flail arm syndrome. *Muscle Nerve* 2000 ; **23**: 646–648.

[7]. Hu MT, Ellis CM, Al-Chalabi A, Leigh PN, Shaw CE. Flail arm syndrome: A distinctive variant of amyotrophic lateral sclerosis. *J Neurol Neurosurg Psychiatry* 1998; **65**: 950– 951.

[8].Wijesekera LC, Mathers S, Talman P, Galtrey C, Parkinson MH, Ganesalingam J et al. Natural history and clinical features of the flail arm and flail leg ALS variants. *Neurology* 2009; **72**:1087–94.

[9]. Chio A, Calvo A, Moglia C, Mazzini L, Mora G, PARALS Study Group. Phenotypic heterogeneity of amyotrophic lateral sclerosis: a population based study. *J Neurol Neurosurg Psychiatry*. 201; **82**:740–6.

[10]. Dimachkie MM, et al. Leg amyotrophic diplegia: prevalence and pattern of weakness at US neuromuscular centers. *J Clin Neuromuscul Dis*. 2013; **15**: 7–12.

[11]. Gombault A. Sclérose symétrique des cordons latéraux de la moelle et des pyramides antérieurses dans le bulbe. *Arch Physiol Norm Pathol* 1871–1872; **4**: 509– 518.

[12]. Winnen B, Robberecht W. The phenotypic variability of amyotrophic lateral sclerosis. *Nat Rev Neurol* 2014; **10**: 661– 670.

[13]. Garg N, Park SB, Vucic S *et al*. Differentiating lower motor neuron syndromes. *J Neurol Neurosurg Psychiatry* 2017; **88**: 474– 483.

[14]. Aran FA. Recherches sur une maladie non encore décrite du système musculaire: Atrophie musculaire progressive. *Arch Gén Méd* 1850; **24**: 5– 36.

[15]. Cruveilhier J. Sur la paralysie musculaire progressive amyotrophique. *Bull Acad Méd* 1853; **18**: 490– 502.

[16]. Ince PG, Evans J, Knopp M *et al*. Corticospinal tract degeneration in the progressive muscular atrophy variant of ALS. *Neurology* 2003; **60**: 1252– 1258.

[17]. Kim WK, Liu X, Sandner J, et al. Study of 962 patients indicates progressive muscular atrophy is a form of ALS. Neurology 2009; **73**:1686–92.

[18]. Visser J, van den Berg-Vos RM, Franssen H, et al. Disease course and prognostic factors of progressive muscular atrophy. Arch Neurol 2007; **64**:522–8.

[19]. Charcot JM. Sclérose des cordons latéraux de la moelle épiniére chez une femme hystérique atteinte de contracture permanente des quatre membres. *Bull Soc Med*1865: 24–35.

[20]. Erb W. Uber einen wenig bekannten spinalen Symptomencomplex. *Berliner Klinische Wochenschrift* 1875; **12**: 357– 359.

[21]. Boekestein WA, Kleine BU, Hageman G, Schelhaas HJ, Zwarts MJ. Sensitivity and specificity of the 'Awaji' electrodiagnostic criteria for amyotrophic lateral sclerosis: Retrospective comparison of the Awaji and revised El Escorial criteria for ALS. *Amyotroph Lateral Scler* 2010; **11**: 497– 501.

[22]. Finegan E, Chipika RH, Shing SLH, Hardiman O, Bede P. Primary lateral sclerosis: A distinct entity or part of the ALS spectrum? *Amyotroph Lateral Scler Frontotemporal Degener* 2019; **20**: 133– 145.

[23]. Tartaglia MC, Rowe A, Findlater K, Orange JB, Grace G, Strong MJ. Differentiation between primary lateral sclerosis and amyotrophic lateral sclerosis: Examination of symptoms and signs at disease onset and during follow-up. *Arch Neurol* 2007; **64**: 232– 236.

[24]. Gordon P, Cheng B, Katz IB *et al*. The natural history of primary lateral sclerosis. *Neurology* 2006; **66**: 647– 653.

[25]. Kosaka T, Fu YJ, Shiga A *et al*. Primary lateral sclerosis: Upper-motor-predominant amyotrophic lateral sclerosis with frontotemporal lobar degeneration-immunohistochemical and biochemical analyses of TDP-43. *Neuropathology* 2012; **32**: 373– 384.

[26]. Finegan E, Chipika RH, Shing SLH, Hardiman O, Bede P. Primary lateral sclerosis: A distinct entity or part of the ALS spectrum? *Amyotroph Lateral Scler Frontotemporal Degener* 2019; **20**: 133– 145.

[27]. Wais V, Rosenbohm A, Petri S *et al*. The concept and diagnostic criteria of primary lateral sclerosis. *Acta Neurol Scand* 2017; **136**: 204– 211.

[28] Turner MR, Barohn RJ, Corcia P, et al. Primary lateral sclerosis: consensus diagnostic criteria. *J Neurol Neurosurg Psychiatry* 2020; **91**:373-377.

[29]. Mills CK. A case of unilateral progressive ascending paral- ysis, probably representing a new form of degenerative dis- ease. J Nerv Ment Dis 1900; **27**: 195–200.

[30]. Jaiser SR, Mitra D, Williams TL, Baker MR. Mills' syndrome revisited. *J Neurol* 2019; **266**: 667– 679.

[31]. Doran M, Enevoldson TP, Ghadiali EJ, Larner AJ. Mills syndrome with dementia: Broadening the phenotype of FTD/MND. *J Neurol* 2005; **252**: 846– 847.

[32]. Kiernan JA, Hudson AJ. Frontal lobe atrophy in motor neuron diseases. *Brain.* 1994; **117**: 747–57.

[33]. Abe K, Fujimura H, Toyooka K, Sakoda S, Yorifuji S, Yanagihara T. Cognitive function in amyotrophic lateral sclerosis. *J Neurol Sci* 1997; **148**: 95–100.

[34]. Lomen-Hoerth C, Anderson T, Miller B. The overlap of amyotrophic lateral sclerosis and frontotemporal dementia. *Neurology* 2002; **59**: 1077–9.

[35]. Lomen-Hoerth C, Murphy J, Langmore S, Kramer JH, Olney RK, Miller B. Are amyotrophic lateral sclerosis patients cognitively normal? *Neurology* 2003; **60**: 1094–7.

[36]. Ringholz GM, Appel SH, Bradshaw M, Cooke NA, Mosnik DM, Schulz PE. Prevalence and patterns of cognitive impairment in sporadic ALS. *Neurology* 2005; **65**: 586– 590.

[37]. Rippon GA, Scarmeas N, Gordon PH *et al*. An observational study of cognitive impairment in amyotrophic lateral sclerosis. *Arch Neurol* 2006; **63**: 345– 352.

[38]. Phukan J, Pender NP, Hardiman O. Cognitive impairment in amyotrophic lateral sclerosis. *Lancet Neurol* 2007; **6**: 994– 1003.

[39]. Beeldman E, Raaphorst J, Klein Twennaar M, de Visser M, Schmand BA, de Haan RJ. The cognitive profile of ALS: A systematic review and meta-analysis update. *J Neurol Neurosurg Psychiatry* 2016; **87**: 611– 619.

[40]. Strong MJ, Abrahams S, Goldstein LH et al. Amyotrophic lateral sclerosis - frontotemporal spectrum disorder (ALS-FTSD): Revised diagnostic criteria. *Amyotroph Lateral Scler Frontotemporal Degener*. 2017; **18**:153-174.

[41]. Abrahams S, Newton J, Niven E, Foley J, Bak TH. Screening for cognition and behaviour changes in ALS *Amyotrophic Lateral Sclerosis and Frontotemporal Degeneration* 2014; **15**: 9-14.

[42]. Waldemar G, Vorstrup S, Jensen TS, Johnsen A, Boysen G. Focal reductions of cerebral blood flow in amyotrophic lateral sclerosis: A [99mTc]-d,l-HMPAO SPECT study. *J Neurol Sci* 1992; **107**: 19– 28.

[43]. Garruto RM, Yanagihara R. Amyotrophic lateral sclerosis in the Mariana Islands. In: JMBV De Jong, (ed). *Handbook of Clinical Neurology*, vol. **15**. Amsterdam: Elsevier Science Publishers, 1991; 253– 271.

[44]. Itoh N, Ishiguro K, Arai H *et al*. Biochemical and ultrastructural study of neurofibrillary tangles in amyotrophic lateral sclerosis/parkinsonism-dementia complex in the Kii peninsula of Japan. *J Neuropathol Exp Neurol* 2003; **62**: 791– 798.

[45]. Mimuro M, Yoshida M, Kuzuhara S, Kokubo Y. Amyotrophic lateral sclerosis and parkinsonism-dementia complex of the Hohara focus of the Kii Peninsula: A multiple proteinopathy? *Neuropathology* 2018; **38**: 98– 107.

[46]. Pradat PF, Bruneteau G, Munerati E, *et al.* Extrapyramidal stifness in patients with amyotrophic lateral sclerosis. *Mov Disord* 2009 **24**: 2143–2148.

[47]. Pupillo E, Bianchi E, Messina P, *et al.* Extrapyramidal and cognitive signs in amyotrophic lateral sclerosis: a population based cross-sectional study. *Amyotroph Lateral Scler Frontotemporal Degener* 2015 **16**: 324–330.

[48]. Desai J, Swash M. Extrapyramidal involvement in amyotrophic lateral sclerosis: backward falls and retropulsion. *J Neurol Neurosurg Psychiatry* 1999 **67**:214–216.

[49]. Feron M, Couillandre A, Mseddi E et al. Extrapyramidal deficits in ALS: a combined biomechanical and neuroimaging study. *J Neurol.* 2018 **265**: 2125-2136.

[50]. Gray F, Eizenbaum JF, Gherardi R, Degos JD, Poirier J. Luyso□pallido□nigral atrophy and amyotrophic lateral sclerosis. *Acta Neuropathol* 1985; **66**: 78– 82.

[51]. Bergmann M, Kuchelmeister K, Migheli A, Schiffer D, Gullotta F. Motor neuron disease with pallido-luysio-nigral atrophy. *Acta Neuropathol* 1993; **86**: 105– 108.

[52]. Miki Y, Mori F, Nunomura J *et al*. Sporadic amyotrophic lateral sclerosis with pallido-nigro-luysian degeneration: A TDP-43 immunohistochemical study. *Neuropathology* 2010; **30**: 149– 153.

[53]. Rossor AM, Jaunmuktane Z, Rossor MN, Hoti G, Reilly MM. TDP43 pathology in the brain, spinal cord, and dorsal root ganglia of a patient with FOSMN. *Neurology* 2019; **92**: 951– 956.

[54]. Bonduelle M. Amyotrophic lateral sclerosis. In: PJ Vinken, GW Bruyn, (eds). *Handbook of Clinical Neurology*, vol. **22**. New York: American Elsevier Publishing Co, Inc, 1975; 281–338.

[55]. Kato S, Oda M, Tanabe H. Diminution of dopaminergic neurons in the substantia nigra of sporadic amyotrophic lateral sclerosis. *Neuropathol Appl Neurobiol* 1993; **19**: 300– 304.

[56]. Nishihira Y, Tan CF, Onodera O *et al*. Sporadic amyotrophic lateral sclerosis: Two pathological patterns shown by analysis of distribution of TDP-43-immunoreactive neuronal and glial cytolasmic inclusions. *Acta Neuropathol* 2008; **116**: 169– 182.

[57]. Elden AC, Kim HJ, Hart MP *et al*. Ataxin-2 intermediate-length polyglutamine expansions are associated with increased risk for ALS. *Nature* 2010; **466**: 1069– 1075.

[58]. Bäumer D, East SZ, Tseu B *et al*. FTLD-ALS of TDP-43 type and SCA2 in a family with a full ataxin-2 polyglutamine expansion. *Acta Neuropathol* 2014; **128**: 597– 604.

[59]. Nanetti L, Fancellu R, Tomasello C, Gellera C, Pareyson D, Mariotti C. Rare association of motor neuron disease and spinocerebellar ataxia type 2 (SCA2): A new case and review of the literature. *J Neurol* 2009; **256**: 1926– 1928.

[60]. Hart MP, Brettschneider J, Lee VM, Trojanowski JQ, Gitler AD. Distinct TDP-43 pathology in ALS patients with ataxin 2 intermediate-length polyQ expansions. *Acta Neuropathol* 2012; **124**: 221– 230.

[61]. Leveille A, Kiernan J, Goodwin JA, Antel J. Eye movements in amyotrophic lateral sclerosis. *Arch Neurol* 1982; **39**: 684– 686.

[62]. Takeda T, Uchihara T, Mochizuki Y *et al*. Supranuclear ophthalmoparesis and vacuolar degeneration of the cerebral white matter in amyotrophic lateral sclerosis: A clinicopathological study. *Amyotroph Lateral Scler* 2012; **13**: 74– 83.

[63]. Mannen T, Iwata M, Toyokura Y, Nagashima K. Preservation of a certain motoneurone group of the sacral cord in amyotrophic lateral sclerosis: Its clinical significance. *J Neurol Neurosurg Psychiatry* 1977; **40**: 464– 469.

[64]. Arlandis S, Vázquez-Costa JF, Martínez-Cuenca E, Sevilla T, Boronat F, Broseta E. Urodynamic findings in amyotrophic lateral sclerosis patients with lower urinary tract symptoms: Results from a pilot study. *NeurourolUrodyn* 2017; **36**: 626– 631.

[65]. Takeda T, Uchihara T, Nakayama Y *et al*. Dendritic retraction, but not atrophy, is consistent in amyotrophic lateral sclerosis-comparison between Onuf's neurons and other sacral motor neurons. *Acta Neuropathol Commun* 2014; **2**: 11.

[66]. Atsuta N, Watanabe H, Ito M *et al*. Age at onset influences on wide-ranged clinical features of sporadic amyotrophic lateral sclerosis. *J Neurol Sci* 2009; **276**: 163– 169.

[67] Hammad M, Silva A, Glass J, *et al*. Clinical electrophysiologic and pathologic evidence for sensory abnormalities in ALS. *Neurology.*2007; **69** : 2236-42.

[68]. Ince PG, Highley JR, Wharton SB. Motor neuron disorders. In: S Love, H Budka, J Ironside, A Perry, (eds). *Greenfield's Neuropathology*, 9th edn, vol. **1**. Boca Raton: CRC Press, 2015; 817– 848.

[69]. Okamoto K, Hirai S, Amari M, Watanabe M, Sakurai A. Bunina bodies in amyotrophic lateral sclerosis immunostained with rabbit anti-cystatin C serum. *Neurosci Lett* 1993; **162**: 125– 128.

[70]. Mizuno Y, Amari M, Takatama M, Aizawa H, Mihara B, Okamoto K. Transferrin localizes in Bunina bodies in amyotrophic lateral sclerosis. *Acta Neuropathol* 2006; **112**: 597–603.

[71]. Sasaki S, Maruyama S. Ultrastructural study of Bunina bodies in the anterior horn neurons of patients with amyotrophic lateral sclerosis. *Neurosci Lett* 1993; **154**: 117– 120.

[72]. Chou S. Motoneuron inclusions in ALS are heavily ubiquitinated. *J Neuropathol Exp Neurol* 1988; **47**: 334.

[73]. Arai T, Hasegawa M, Akiyama H *et al*. TDP-43 is a component of ubiquitin-positive tau-negative inclusions in frontotemporal lobar degeneration and amyotrophic lateral sclerosis. *Biochem Biophys Res Commun* 2006; **351**: 602– 611.

[74]. Mackenzie IR, Neumann M, Baborie A *et al*. A harmonized classification system for FTLD-TDP pathology. *Acta Neuropathol* 2011; **122**: 111– 113.

[75]. Mackenzie IR, Neumann M. Reappraisal of TDP-43 pathology in FTLD-U subtypes. *Acta Neuropathol* 2017; **134**: 79– 96.

[76]. Nishihira Y, Gefen T, Mao Q *et al*. Revisiting the utility of TDP-43 immunoreactive (TDP-43-ir) pathology to classify FTLD-TDP subtypes. *Acta Neuropathol* 2019; **138**: 167–169.

[77]. Braak H, Ludolph AC, Neumann M, Ravits J, Del Tredici K. Pathological TDP-43 changes in Betz cells differ from those in bulbar and spinal α-motoneurons in sporadic amyotrophic lateral sclerosis. *Acta Neuropathol* 2017; **133**: 79– 90.

[78]. Nana AL, Sidhu M, Gaus SE *et al*. Neurons selectively targeted in frontotemporal dementia reveal early stage TDP-43 pathobiology. *Acta Neuropathol* 2019; **137**: 27– 46.

[79]. Sekiguchi T, Kanouchi T, Shibuya K *et al*. Spreading of amyotrophic lateral sclerosis lesions–multifocal hits and local propagation? *J Neurol Neurosurg Psychiatry*2014; **85**: 85–91.

[80]. Ragagnin AMG, Shadfar S, Vidal M, Jamali MS, Atkin JD. Motor neuron susceptibility in ALS/FTD. *Front Neurosci* 2019; **13**: 532.

[81]. Millecamps S, Salachas F, Cazeneuve C, Gordon P, Bricka B, Camuzat A, et al. SOD1, ANG, VAPB, TARDBP, and FUS mutations in familial amyotrophic lateral sclerosis: genotype-phenotype correlations.J Med Genet 2010; **47**: 554- 60.

[82]. Millecamps S, Boillee S, Le Ber I, Seilhean D, Teyssou E, Giraudeau M, et al. Phenotype difference between ALS patients with expanded repeats in C9ORF72 and patients with mutations in other ALS-related genes.J Med Genet 2012; **49**: 258-63.

Table 1: Motor and extra motor variability in ALS

Phenotype			Prevalence
Motor variability			
	Bulbar onset	Bulbar form	20%
	Spinal onset	Spinal form	60%
	Lower motor neuron dominant	Progressive muscular atrophy	≈5-10%
		Flail arm syndrome	≈10%
		Flail leg syndrome	≈5%
	Upper motor neuron dominant	Hemiplegic form	1%
		Upper-motorneuron dominant ALS	
		Primary Lateral sclerosis	1-5% of ALS
Extra motorvariability			
	Cognition and Behavior	ALS/FTLD	50% of ALS patients
	Extrapyramidal signs	ALS-Parkinsonism	≈5-10%
		ALS with pallido-nigro-luysian degeneration	rare
	Cerebellar degeneration	ALS-spino cerebellar ataxia	rare
		ALS patients with *C9ORF72* mutation	
	Neurogenic bladder	Primary Lateral Sclerosis	50% of PLS patients
		ALS	rare
	Sensory signs		Variable
	Abnormal ocular movement	Advanced phase of ALS patients	rare
		ALS with vacuolar degeneration of the cerebral white matter	
		ALS with multisystem degeneration	