



HAL
open science

Primary Lateral Sclerosis: Clinical, radiological and molecular features

P. Bede, P.-F. Pradat, J. Lope, P. Vourc'h, H. Blasco, P. Corcia

► **To cite this version:**

P. Bede, P.-F. Pradat, J. Lope, P. Vourc'h, H. Blasco, et al.. Primary Lateral Sclerosis: Clinical, radiological and molecular features. *Revue Neurologique*, 2021, 10.1016/j.neurol.2021.04.008 . hal-03284185

HAL Id: hal-03284185

<https://hal.sorbonne-universite.fr/hal-03284185v1>

Submitted on 12 Jul 2021

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.



Available online at
ScienceDirect
www.sciencedirect.com

Elsevier Masson France
EM|consulte
www.em-consulte.com



General review

Primary Lateral Sclerosis: Clinical, radiological and molecular features

P. Bede^{a,b,*}, P.-F. Pradat^a, J. Lope^b, P. Vourc'h^{c,d}, H. Blasco^{c,d}, P. Corcia^{d,e}

^a Pitié-Salpêtrière University Hospital, Sorbonne University, Paris, France

^b Computational Neuroimaging Group, Trinity College Dublin, Ireland

^c Department of Biochemistry and Molecular Biology, CHRU Bretonneau, Tours, France

^d UMR 1253 iBrain, Université de Tours, Inserm, France

^e ALS and MND centre (FILSLAN), University of Tours, "iBrain", inserm, France

INFO ARTICLE

Article history:

Received 19 February 2021

Received in revised form

23 April 2021

Accepted 29 April 2021

Available online xxx

Keywords:

Primary Lateral Sclerosis

Motor Neuron Disease

Biomarkers

Neuroimaging

ABSTRACT

Primary Lateral Sclerosis (PLS) is an uncommon motor neuron disorder. Despite the well-recognisable constellation of clinical manifestations, the initial diagnosis can be challenging and therapeutic options are currently limited. There have been no recent clinical trials of disease-modifying therapies dedicated to this patient cohort and awareness of recent research developments is limited. The recent consensus diagnostic criteria introduced the category 'probable' PLS which is likely to curtail the diagnostic journey of patients. Extra-motor clinical manifestations are increasingly recognised, challenging the view of PLS as a 'pure' upper motor neuron condition. The post mortem literature of PLS has been expanded by seminal TDP-43 reports and recent PLS studies increasingly avail of meticulous genetic profiling. Research in PLS has gained unprecedented momentum in recent years generating novel academic insights, which may have important clinical ramifications.

© 2021 The Authors. Published by Elsevier Masson SAS. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

* Corresponding author: Professor Peter Bede, Trinity College Dublin, Pearse Street, D2, Ireland.

E-mail address: pbede@tcd.ie (P. Bede).

Abbreviations: ALS, Amyotrophic lateral sclerosis; AD, Axial diffusivity; C9, orf72hexanucleotide repeat expansion on C9orf72; bvFTD, behavioural variant frontotemporal dementia; CBF, cerebral blood flow; CBT, corticobulbar tract; CC, corpus callosum; Chit1, chitotrioidase; CSF, Cerebrospinal fluid; CST, Corticospinal tract; DCTN1, Dynactin; DTI, Diffusion tensor imaging; DWI, diffusion-weighted imaging; EMG, Electromyography; ERLIN2, ER Lipid Raft Associated 2; fMRI, functional MRI; FTD, Frontotemporal dementia; FUS, fused in sarcoma gene; GM, grey matter; HC, Healthy controls; HSP, Hereditary spastic paraplegia; IR, immunoreactive; JPLS, Juvenile primary lateral sclerosis; LMN, Lower motor neuron; MD, Mean diffusivity; MEG, Magnetoencephalography; MND, Motor Neuron Disease; MRI, Magnetic resonance imaging; MRS, magnetic resonance spectroscopy; MI/Cr, Myo-inositol/Creatine; NAA/Cr, N-acetylaspartate/creatine; NAA/Cho, N-acetylaspartate/choline; OPTN, Optineurin; PBA, Pseudobulbar affect; NCI, neuronal cytoplasmic inclusions; PCL, pathological crying and laughing (PCL); PET, Positron emission tomography; PLS, Primary lateral sclerosis; pNFH, phosphorylated neuro-filament heavy chain; PPA, primary progressive aphasia; RD, Radial diffusivity; SOD1, superoxide dismutase; SPECT, Single-photon emission computed tomography; SSRI, Selective serotonin reuptake inhibitors; TARDBP, transactive response DNA-binding protein gene; TBK1, TANK-binding kinase 1; TCA, Tricyclic antidepressants; TDP-43, TAR DNA-binding protein 43; UBQLN, ubiquitin-like protein gene; UMN, Upper motor neuron; VBM, Voxel-based morphometry.

<https://doi.org/10.1016/j.neurol.2021.04.008>

0035-3787/© 2021 The Authors. Published by Elsevier Masson SAS. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

1. Introduction

Recent clinical trials in motor neuron disease (MND) invariably restrict recruitment to patients with amyotrophic lateral sclerosis (ALS), and PLS patients are often left out of therapeutic initiatives. The mainstay of therapy in PLS remains supportive and is limited to multidisciplinary interventions to improve mobility, reduce muscle tone and facilitate activities of daily living. There is limited awareness among patients and caregivers of recent advances in PLS research which has generated important novel academic insights in recent years. Research efforts in PLS are very easy to justify on clinical grounds; patients face an unacceptably long diagnostic journey with the fear of converting to ALS, there have been no recent pharmaceutical trials, and the limited awareness of the condition often translates into limited resources and limited research funding. The rationale to review recent advances in PLS is twofold; a number of unresolved academic debates persist and recent research findings may have pragmatic implications for clinical care. Accordingly, our objective is the systematic review of recent advances in PLS research with particular attention to reports that challenge traditional views and may have direct clinical ramifications.

2. Methods

A formal literature review was conducted on PubMed between November 2020 and December 2020 in accordance with the Strobe guidelines. The search terms “Primary Lateral Sclerosis” was paired individually with the following keywords

“post mortem”, “pathology”, “ubiquitin”, “TDP-43”, “neuroimaging”, “magnetic resonance imaging”, “diffusion tensor imaging”, “genetics”, “frontotemporal lobar degeneration”, “neuropsychology”, “functional MRI”, “single photon emission computed tomography”, “positron emission tomography”, “diagnosis”, “monitoring”, “outcomes”, “clinical trials”, “staging”, “neurophysiology”, “electrophysiology”, “transcranial magnetic stimulation”. Selection criteria included original research articles only; opinion pieces, review articles, case reports, and editorials were not reviewed. Only articles written in English were selected for review. References of original research papers were also reviewed if not captured by the initial search.

3. Results

3.1. Expanding the clinical profile of PLS

The core clinical feature of PLS is a slowly progressive upper motor neuron (UMN) dysfunction which is typically adult-onset, often manifests initially in the lower limbs but may also involve the bulbar and respiratory muscles [1,2]. While PLS only represents about 3-5% of MNDs, it carries a markedly better prognosis with longer survival [3]. A distinguishing feature of PLS is the lack of overt lower motor neuron (LMN) dysfunction [4,5] which distinguishes it from other motor

neuron disorders. While rare unilateral variants have been described, the majority of patients eventually exhibit bilateral spasticity [6,7]. Mills’ syndrome [6] is a low-incidence unilateral form of PLS [8] that has been linked to asymmetric frontal signal alterations on both magnetic resonance imaging (MRI) [9] and positron emission tomography (PET) [7] studies. Unlike in ALS [10], feeding tube insertions are rarely needed in PLS, and full anarthria seldom develops [11]. A common symptom of PLS is pseudobulbar affect (PBA) or pathological crying and laughing (PCL), which refers to context-inappropriate or exaggerated involuntary laughter or crying in response even to minimal stimulus. This symptom has been traditionally linked to corticobulbar tract degeneration, but more recent studies highlight the role of impaired cerebellar gating mechanisms [12–14]. The impact of PBA/PCL is often underestimated; it may lead to gradual withdrawal from social interactions and result in self-imposed isolation. Tricyclic antidepressants (TCAs) and selective serotonin reuptake inhibitors (SSRIs) were the mainstay of therapy until the recent approval of dextromethorphan/quinidine for PBA in some countries [15]. Clinical disability in PLS is often evaluated by clinical examination, but composite reflex scores, spasticity scales, PBA questionnaires, combined UMN scores and scales developed for other MNDs are also commonly utilised [16]. These scales include the revised ALS Functional Rating Scale (ALSFRS-r) [17], the Penn Upper Motor Neuron Score (PUMNS) [18], the Modified Ashworth Scale [19], and the emotional lability questionnaire [20]. 2020 has seen the introduction of the first PLS-specific functional rating scale (PLSFRS) [21] which promises to be more accurate in tracking disease-associated functional disability than generic instruments. Contrary to ALS, where non-motor manifestations are universally recognised [22–26], PLS has been traditionally viewed as a ‘pure’ motor neuron disorder without significant cognitive deficits and the term ‘PLS-plus’ is sometimes used to label PLS patients with additional extra-motor deficits [27]. While cognitive deficits have been sporadically reported in PLS [1,28,29], these have only been recently corroborated by larger case series and linked to neuroimaging changes [30–33]. The most commonly identified neuropsychological deficits in PLS include deficits in social cognition, apathy, executive dysfunction, and language and verbal fluency deficits [32,33]. Alterations in personality, such as obsessive compulsive behaviour, have also been described in PLS [34]. Some patients may exhibit frank frontotemporal dementia [32], but this is thought to be relatively rare (3.3%) and not associated with GGGGCC hexanucleotide repeat expansions in C9orf72 [32]. The identification of neuropsychological deficits in PLS are in line with post mortem [35,36] and imaging reports [11,37–44] that have consistently captured cortical and subcortical changes beyond the motor cortex and corticospinal tracts. The characterisation of frontotemporal changes in PLS is clinically relevant, as these may impact on compliance with assistive devices, rehabilitation efforts, fall prevention and participation in clinical trials. Another relatively understudied clinical aspect of PLS is the extra-pyramidal manifestation of the disease, which, coupled with the considerable lower limb spasticity, may increase the risk of falls in this cohort. The clinical evaluation of extra-pyramidal deficits is notoriously challenging in the presence of widespread UMN dysfunction,

but novel strategies such as computational gait analyses may help to ascertain these deficits [45]. Just like in ALS [45,46], parkinsonism, freezing and postural instability have been previously reported in PLS.

3.2. Successive diagnostic criteria

The diagnosis of PLS is challenging as ALS may initially present as a UMN-predominant syndrome. PLS however carries a considerably better prognosis with a markedly longer survival; therefore the careful distinction between the two syndromes is paramount. Patients with PLS invariably experience a long diagnostic journey and are often apprehensive of conversion to ALS. The attendance of multiple neurologists for diagnostic clarification is not uncommon. The 1945 criteria proposed a minimum symptom duration of five years to establish the diagnosis [47]. In 1992, the Pringle criteria suggested a symptom duration of three years to establish the diagnosis of PLS [4]. The 2006 Gordon criteria put forward a symptom duration threshold of four years to label patients with PLS [27]. Imaging studies have captured MRI alterations in patients with a symptom duration of less than five years [48] and 'suspected' PLS patients have been often included in imaging studies admixed with patients who fulfilled the Gordon criteria [49,50]. In 2020, the new consensus diagnostic criteria [51] recognised the impact of the protracted diagnostic delay, and introduced the category of 'probable PLS' for patients with a symptom duration of two to four years. Few studies have applied the new consensus diagnostic criteria yet, but these have shown that, despite their shorter symptom duration, 'probable PLS' patients already exhibit motor cortex atrophy on imaging, considerable functional disability and widespread UMN dysfunction. [52,53] Therefore emerging data seem to support the introduction of the new 'probable PLS' category, which may curtail the diagnostic journey of patients and facilitate an earlier inclusion into research studies and pharmaceutical trials.

3.3. Post mortem insights

The consensus observation of post mortem PLS studies is primary motor cortex and corticospinal tract degeneration [4,54–56], but the post mortem literature of PLS also includes cases with ante-mortem extra-pyramidal features [57], dementia [58,59], and progressive non-fluent aphasia [60]. Studies predating the availability of immunohistochemistry describe the degeneration of the primary motor cortex and pyramidal tracts with the relative preservation of the LMNs [4,54,61]. Studies availing of immunohistochemistry for ubiquitin describe ubiquitin-immunoreactive neuronal cytoplasmic inclusion bodies in the motor cortex [56,62], but LMN involvement is either mild or absent [56,63]. From a clinical perspective, it is noteworthy that extra-motor ubiquitin-immunoreactive neuronal cytoplasmic inclusion bodies were also detected in hippocampal and prefrontal areas [56,62,64]. Since the identification of TAR DNA-binding protein 43 (TDP-43), extensive frontotemporal and hippocampal burden has been confirmed with limited LMN involvement [56,65]. Widespread cortical TDP-43 burden has been recently reported in association with the TBK1 mutation, where a clinical

constellation of PLS and primary progressive aphasia was ascertained ante mortem [66]. The description of brainstem changes vary in the literature, some studies only highlight descending corticospinal tract (CST) degeneration in the superior brainstem [67] while others also report hypoglossal nucleus degeneration [64]. A recent series of seven PLS cases highlighted the preservation of LMNs; while considerable TDP-43 immunoreactivity was invariably detected in the motor cortex, TDP-43 burden in the LMNs was slight despite the long ante mortem disease duration of the cases [68]. This was one of the very few modern case series in PLS using TDP-43 immunohistochemistry, reporting combined UMN/LMN assessments and providing information on ante mortem extra-motor symptoms. Two out of the seven patients carried the TBK1 mutation and had comorbid primary progressive aphasia (PPA) [66], and one patient had comorbid behavioural-variant frontotemporal dementia (bvFTD). The primary motor cortex showed neuronal loss, reactive gliosis, and microglial activation, and the CST exhibited reduced myelin staining and microglial activation. There is considerable concordance between neuroimaging studies and post mortem reports [69]. Not only is primary motor cortex [11,70] and CST degeneration [71–73] readily captured by imaging, extra-motor neocortex [11] involvement and brainstem [41,74] and hippocampal degeneration has also been detected in vivo [44,75].

3.4. The genetic profile of PLS

Research studies typically screen their PLS cohorts for ALS-associated, and established hereditary spastic paraplegia (HSP) genes. [11] While previous diagnostic criteria, such as the Pringle criteria required the lack of family history [4], families with multiple members affected with PLS have been described [2,76–78]. Even though ALS-associated genes are often evaluated in PLS, with the exception of GGGGCC hexanucleotide repeat expansions [79], these are rarely identified. In larger series, C9orf72 mutations were detected in 1/41 and 1/110 of cases [80,81]. In a large PLS series, mutations have also been identified in PARK2, DCTN1 [81], and SPG7 which is typically linked to HSP [82]. While most PLS case series detect no HSP mutations [44,83], SPG7 mutation has been linked to PLS-like presentation by several groups [82,84]. Heterozygous SPG7 mutations have been also described in five siblings with PLS [84] and a kindred of TBK1 mutation-associated PLS has also been reported [85]. Among ALS-associated mutations, FIG4 [86], UBQLN2 [87,88] and OPTN mutations [89] have been associated with UMN-predominant MND phenotypes reminiscent of PLS. Juvenile primary lateral sclerosis (JPLS) is linked to ALS2 [90,91] and ERLIN2 mutations [92].

3.5. Imaging findings in PLS

The core imaging signature of PLS is associated with motor cortex [11,70], corpus callosum [49] and CST degeneration. [71–73] More recently, brainstem [41,74], subcortical grey matter alterations [44,75], extra-motor cortical changes [11,40,93], and cerebellar degeneration [11] have also been reported. The majority of imaging studies in PLS are either MRI or PET studies

[94], but a multimodal PET-MRI study can also be identified [95]. Quantitative imaging studies readily capture motor cortex atrophy [70,96–98] and white matter changes in the CST [99], corona radiata [100–102], brainstem [97], and corpus callosum [100]. Functional studies highlight connectivity alterations in motor networks [39,103] and spectroscopy typically detects reduced N-acetylaspartate/creatine (NAA/Cr) [104–106], myo-inositol/creatine (MI/Cr) [107], or N-acetylaspartate/choline (NAA/Cho) [104] ratios in the motor cortex. While considerable progress has been made in spinal cord imaging in MNDs [108–112], no quantitative spinal studies have been published in PLS to date; only intensity changes have been reported [113]. A number of imaging papers explored correlations between clinical metrics and disability. Tapping rates, ALSFRS-r, and clinical UMN signs have been linked to white matter degeneration [11,98,102], cortical thinning [70,101,114], volume reductions [96,98], metabolic changes [81,104,107], and proton-density alterations [106]. Compared to ALS [115–118], there is a relative scarcity of longitudinal studies in PLS [105,115,119–124]. There are few studies specifically evaluating the imaging differences between PLS and ALS and their conclusions are inconsistent [125]. Some studies identified marked primary motor cortex degeneration in PLS compared to ALS [98,107] but other studies did not confirm this [50]. A recent study highlighted the relative sparing of the post-central gyrus in PLS despite the longer symptom duration of the cohort [11], and PLS-specific subcortical signatures have also been proposed [44]. PET studies typically report comparable patterns of hypometabolism in ALS and PLS [126]. Lower fractional anisotropy values have been detected in PLS than in ALS by some [49,101], but these observations have not been replicated by others [127]. Studies of early or suspected PLS are scarce [52,53,99,106], but some studies include ‘suspected’ PLS patients with short disease duration who subsequently meet diagnostic criteria on follow-up [50,97]. There are a number of recent studies specifically evaluating ‘pre-PLS’ [48] or ‘probable PLS’ [52] demonstrating motor cortex degeneration before meeting diagnostic criteria. Despite advances in machine learning [128–130] and individual scan interpretation [108,131–133], no study to date has evaluated the value of MRI in predicting conversion to ALS versus fulfilling diagnostic criteria for PLS.

3.6. Wet biomarkers in PLS

Contrary to ALS, where a number of putative wet biomarkers have been proposed [134–136], progress in the validation of cerebrospinal fluid (CSF) and serum markers in PLS has been relatively slow. The main focus of wet biomarker studies is the identification of serum and CSF indicators that may distinguish PLS from ALS [137,138]. A distinctive CSF ‘chitinase’ profile has been proposed by some [139], but not fully corroborated by others [137]. The most commonly investigated CSF markers in MNDs are neurofilaments [138]. Some groups detected no neurofilament level differences between PLS and ALS [140], while others suggest that both phosphorylated neuro-filament heavy chain (pNFH) and chitotriosidase (Chit1) may effectively discriminate between PLS and ALS [141].

4. Discussion

Despite its slower clinical progression and markedly longer survival [124], PLS has a number of overlapping clinical features, shared genetic variants, and comparable cerebral imaging signatures with ALS [125]. Aggregation of ALS and PLS cases in the same family is not uncommon and the reliable distinction of PLS from UMN-predominant ALS on clinical grounds can be challenging in patients with short symptom duration. The field of PLS has seen the publication of seminal research papers in the past couple of years, many of which are directly relevant to the clinical care of patients. The recognition of extra-motor pathology, frontotemporal radiological changes and neuropsychological manifestations is a relatively new facet of PLS research. Recent case series confirm sporadic observations of language deficits, executive dysfunction, and, in some cases, overt dementia in patients with PLS. The chronology of motor and extra-motor changes remains to be elucidated by purpose-designed longitudinal studies. Cognitive screening tests developed for ALS may be particularly well suited to screen for frontotemporal dysfunction in PLS as these instruments have been adapted for motor disability. Extra-pyramidal motor and cerebellar dysfunction may exacerbate the motor disability associated with pyramidal degeneration, increase fall risk, and contribute to impaired mobility. Accordingly, extra-pyramidal and cerebellar factors should be carefully considered when planning multidisciplinary interventions, home modifications and rehabilitation strategies. The management of spasticity should rely on the concomitant use of pharmacological and non-pharmacological therapies. Pseudobulbar affect should be specifically screened for and monitored as it may lead to social withdrawal and impact on quality of life. Given the multitude of pharmacological options available for the treatment of PBA, treatment should be escalated and changed depending on response to therapy. Given the multi-system manifestations of PLS, PLS is best managed in a multidisciplinary setting, relying on expert input of physiotherapists, speech and language therapists, social workers, occupational therapists, clinical geneticists, neuropsychologists, and specialist nurses. Clinical electrophysiology has an important role in making sure that there is no evidence of denervation suggestive of alternative diagnoses. Spinal and cerebral imaging is important to rule out potential mimics. In addition to healthcare providers, patients with PLS are often supported by local charities, advocacy groups and national MND associations. Research in PLS is spearheaded by international consortia and disease-specific research meetings are also regularly organised [142]. The publication of the new consensus criteria is an important step to streamline the diagnostic pathway in PLS and is likely to allow the earlier recruitment of patients into research studies. The development of disease-specific clinical instruments such as the PLSFRS will aid the nuanced characterisation of disability trajectories. Advances in neuroimaging and wet biomarkers are likely to provide objective measures to track PLS cohorts longitudinally, and may also serve as prognostic indicators. While recent studies contributed important insights, studies in PLS are often marred by sample size limitations. Given the low incidence of the

condition, large multicentre studies are urgently needed with carefully harmonised research protocols to meticulously characterise the clinical, genetic and pathological spectrum of PLS.

5. Conclusions

Recent advances in biomarker development, revised diagnostic criteria, disease-specific instruments and increased international interest in the condition may pave the way for the first disease-modifying trials in PLS.

Disclosure of interest

The authors declare that they have no competing interest.

Author contribution

All authors have contributed equally to the drafting of this manuscript

Acknowledgements

This work was supported by the Spastic Paraplegia Foundation, Inc. (SPF). Peter Bede is also sponsored by the Health Research Board (HRB EIA-2017-019), the EU Joint Programme-Neurodegenerative Disease Research (JPND), the Andrew Lydon scholarship, the Irish Institute of Clinical Neuroscience (IICN), and the Iris O'Brien Foundation. Pierre- François Pradat is supported by the Association Française contre les Myopathies (AFM), the Institut pour la Recherche sur la Moelle épinière et l'Encéphale (IRME) and the program "Investissements d'avenir" ANR-10-IAIHU-06. Jasmin Lope is supported by the Health Research Board (HRB-Ireland). Philippe Corcia, Patrick Vourc'h, and Helene Blasco have no financial disclosures to make in relation to this study. The sponsors of the authors had no bearing on the opinions expressed herein.

REFERENCES

- [1] Le Forestier N, Maisonobe T, Piquard A, Rivaud S, Crevier-Buchman L, Salachas F, et al. Does primary lateral sclerosis exist? A study of 20 patients and a review of the literature. *Brain* 2001;124(Pt 10):1989-99.
- [2] Brugman F, Wokke JH, Vianney de Jong JM, Franssen H, Faber CG, Van den Berg LH. Primary lateral sclerosis as a phenotypic manifestation of familial ALS. *Neurology* 2005;64(10):1778-9. <http://dx.doi.org/10.1212/01.wnl.0000162033.47893.f7>.
- [3] Almeida V, de Carvalho M, Scotto M, Pinto S, Pinto A, Ohana B, et al. Primary lateral sclerosis: predicting functional outcome. *Amyotroph Lateral Scler frontotemporal degeneration* 2013;14(2):141-5. <http://dx.doi.org/10.3109/17482968.2012.719237>.
- [4] Pringle CE, Hudson AJ, Munoz DG, Kiernan JA, Brown WF, Ebers GC. Primary lateral sclerosis. Clinical features, neuropathology and diagnostic criteria. *Brain* 1992;115(Pt 2):495-520.
- [5] Fournier CN, Murphy A, Loci L, Mitsumoto H, Lomen-Hoerth C, Kisanuki Y, et al. Primary lateral sclerosis and early upper motor neuron disease: characteristics of a cross-sectional population. *Clin Neuromuscul Dis* 2016;17(3):99-105.
- [6] Mills CK. A case of unilateral progressive ascending paralysis, probably representing a new form of degenerative disease. *J Nerv Ment Dis* 1900;27(4):195-200.
- [7] Turner MR, Gerhard A, Al-Chalabi A, Shaw CE, Hughes RA, Banati RB, et al. Mills' and other isolated upper motor neurone syndromes: in vivo study with 11C-(R)-PK11195 PET. *J Neurol. Neurosurg Psychiatry* 2005;76(6):871-4.
- [8] Gastaut JL, Bartolomei F. Mills' syndrome: Ascending (or descending) progressive hemiplegia: A hemiplegic form of primary lateral sclerosis? [10] *J Neurol Neurosurg Ps* 1994;57(10):1280-1.
- [9] Ekmekci H, Ozturk S, Demir A. Mills' syndrome: a case report. *Eur J Neurol* 2011;18:619. <http://dx.doi.org/10.1111/j.1468-1331.2011.03552.x>.
- [10] Yunusova Y, Plowman EK, Green JR, Barnett C, Bede P. Clinical Measures of Bulbar Dysfunction in ALS. *Frontiers in neurology* 2019;10:106. <http://dx.doi.org/10.3389/fneur.2019.00106>.
- [11] Finegan E, Chipika RH, Li Hi Shing S, Doherty MA, Hengeveld JC, Vajda A, et al. The clinical and radiological profile of primary lateral sclerosis: a population-based study. *J Neurol* 2019;266(11):2718-33. <http://dx.doi.org/10.1007/s00415-019-09473-z>.
- [12] Floeter MK, Katipally R, Kim MP, Schanz O, Stephen M, Danielian L, et al. Impaired corticopontocerebellar tracts underlie pseudobulbar affect in motor neuron disorders. *Neurology* 2014;83(7):620-7. <http://dx.doi.org/10.1212/wnl.0000000000000693>.
- [13] Bede P, Finegan E. Revisiting the pathoanatomy of pseudobulbar affect: mechanisms beyond corticobulbar dysfunction. *Amyotroph Lateral Scler frontotemporal degeneration* 2018;19(1-2):4-6. <http://dx.doi.org/10.1080/21678421.2017.1392578>.
- [14] Christidi F, Karavasilis E, Ferentinos P, Xirou S, Velonakis G, Rentzos M, et al. Investigating the neuroanatomical substrate of pathological laughing and crying in Amyotroph Lateral Scler with multimodal neuroimaging techniques. *Amyotroph Lateral Scler frontotemporal degeneration* 2018;19(1-2):12-20. <http://dx.doi.org/10.1080/21678421.2017.1386689>.
- [15] Piore EP, Brooks BR, Cummings J, Schiffer R, Thisted RA, Wynn D, et al. Dextromethorphan plus ultra low-dose quinidine reduces pseudobulbar affect. *Ann Neurol* 2010;68(5):693-702. <http://dx.doi.org/10.1002/ana.22093>.
- [16] Floeter MK, Wu T. Longitudinal evaluation of upper motor neuron burden scales in primary lateral sclerosis. *Amyotroph Lateral Scler frontotemporal degeneration* 2020;1-7. <http://dx.doi.org/10.1080/21678421.2020.1790609>.
- [17] Cedarbaum JM, Stambler N, Malta E, Fuller C, Hilt D, Thurmond B, et al. The ALSFRS-R: a revised ALS functional rating scale that incorporates assessments of respiratory function. BDNF ALS Study Group (Phase III). *J Neurol Sci* 1999;169(1-2):13-21.
- [18] Quinn C, Edmundson C, Dahodwala N, Elman L. Reliable and efficient scale to assess upper motor neuron disease burden in Amyotroph Lateral Scler. *Muscle Nerve* 2020;61(4):508-11. <http://dx.doi.org/10.1002/mus.26764>.
- [19] Meseguer-Henarejos AB, Sánchez-Meca J, López-Pina JA, Carles-Hernández R. Inter- and intra-rater reliability of the Modified Ashworth Scale: a systematic review and meta-analysis. *Eur J Phys Rehabil Med* 2018;54(4):576-90. <http://dx.doi.org/10.23736/s1973-9087.17.04796-7>.

- [20] Newsom-Davis IC, Abrahams S, Goldstein LH, Leigh PN. The emotional lability questionnaire: a new measure of emotional lability in Amyotroph Lateral Scler. *J Neurol Sci* 1999;169(1-2):22-5.
- [21] Mitsumoto H, Chiuhan C, Gilmore M, Zhang Y, Simmons Z, Paganoni S, et al. Primary lateral sclerosis (PLS) functional rating scale: PLS-specific clinimetric scale. *Muscle Nerve* 2020;61(2):163-72. <http://dx.doi.org/10.1002/mus.26765>.
- [22] Burke T, Pinto-Grau M, Lonergan K, Bede P, O'Sullivan M, Heverin M, et al. A Cross-sectional population-based investigation into behavioral change in Amyotroph Lateral Scler: subphenotypes, staging, cognitive predictors, and survival. *Ann Clin Translat Neurol* 2017;4(5):305-17. <http://dx.doi.org/10.1002/acn3.407>.
- [23] Christidi F, Karavasilis E, Rentzos M, Kelekis N, Evdokimidis I, Bede P. Clinical and radiological markers of extra-motor deficits in Amyotroph Lateral Scler. *Frontiers in neurology* 2018;9:1005. <http://dx.doi.org/10.3389/fneur.2018.01005>.
- [24] Elamin M, Pinto-Grau M, Burke T, Bede P, Rooney J, O'Sullivan M, et al. Identifying behavioural changes in ALS: validation of the Beaumont behavioural inventory (BBI). *Amyotroph Lateral Scler frontotemporal degeneration* 2017;18(1-2):68-73. <http://dx.doi.org/10.1080/21678421.2016.1248976>.
- [25] Burke T, Pinto-Grau M, Lonergan K, Elamin M, Bede P, Costello E, et al. Measurement of social cognition in Amyotroph Lateral Scler: a population based study. *PLoS One* 2016;11(8):e0160850. <http://dx.doi.org/10.1371/journal.pone.0160850>.
- [26] Burke T, Elamin M, Bede P, Pinto-Grau M, Lonergan K, Hardiman O, et al. Discordant performance on the Reading the Mind in the Eyes Test, based on disease onset in Amyotroph Lateral Scler. *Amyotroph Lateral Scler frontotemporal degeneration* 2016;1-6. <http://dx.doi.org/10.1080/21678421.2016.1177088>.
- [27] Gordon PH, Cheng B, Katz IB, Pinto M, Hays AP, Mitsumoto H, et al. The natural history of primary lateral sclerosis. *Neurology* 2006;66(5):647-53.
- [28] Piquard A, Le Forestier N, Baudoin-Madec V, Delgadillo D, Salachas F, Pradat PF, et al. Neuropsychological changes in patients with primary lateral sclerosis. *Amyotroph Lateral Scler* 2006;7(3):150-60.
- [29] Grace GM, Orange JB, Rowe A, Findlater K, Freedman M, Strong MJ. Neuropsychological functioning in PLS: a comparison with ALS. *Can J Neurol Sci* 2011;38(1):88-97.
- [30] de Vries BS, Rustemeijer LMM, Bakker LA, Schröder CD, Veldink JH, van den Berg LH, et al. Cognitive and behavioural changes in PLS and PMA: challenging the concept of restricted phenotypes. *J Neurol Neurosurg Psychiatry* 2019;90(2):141-7. <http://dx.doi.org/10.1136/jnnp-2018-318788>.
- [31] Agarwal S, Highton-Williamson E, Caga J, Matamala JM, Dharmadasa T, Howells J, et al. Primary lateral sclerosis and the Amyotroph Lateral Scler-frontotemporal dementia spectrum. *J Neurol* 2018;265(8):1819-28. <http://dx.doi.org/10.1007/s00415-018-8917-5>.
- [32] de Vries BS, Rustemeijer LMM, van der Kooij AJ, Raaphorst J, Schröder CD, Nijboer TCM, et al. A case series of PLS patients with frontotemporal dementia and overview of the literature. *Amyotroph Lateral Scler frontotemporal degeneration* 2017;18(7-8):534-48. <http://dx.doi.org/10.1080/21678421.2017.1354996>.
- [33] Finegan E, Shing SLH, Chipika RH, Chang KM, McKenna MC, Doherty MA, et al. Extra-motor cerebral changes and manifestations in primary lateral sclerosis. *Brain Imaging Behav* 2021. <http://dx.doi.org/10.1007/s11682-020-00421-4>.
- [34] Bersano E, Sarnelli MF, Solara V, De Marchi F, Sacchetti GM, Stecco A, et al. A case of late-onset OCD developing PLS and FTD. *Amyotroph Lateral Scler and Frontotemporal Degeneration* 2018;1-3. <http://dx.doi.org/10.1080/21678421.2018.1440405>.
- [35] Gazulla J, Ferrer I, Izquierdo-Alvarez S, Alvarez S, Sánchez-Alcudia R, Bestué-Cardiel M, et al. Hereditary primary lateral sclerosis and progressive nonfluent aphasia. *J Neurol* 2019;266(5):1079-90. <http://dx.doi.org/10.1007/s00415-019-09235-x>.
- [36] Kobayashi Z, Tsuchiya K, Arai T, Yokota O, Yoshida M, Shimomura Y, et al. Clinicopathological characteristics of FTLD-TDP showing corticospinal tract degeneration but lacking lower motor neuron loss. *J Neurol Sci* 2010;298(1-2):70-7. <http://dx.doi.org/10.1016/j.jns.2010.08.013>.
- [37] Chipika RH, Christidi F, Finegan E, Li Hi Shing S, McKenna MC, Chang KM, et al. Amygdala pathology in Amyotroph Lateral Scler and primary lateral sclerosis. *J Neurol Sci* 2020;117039. <http://dx.doi.org/10.1016/j.jns.2020.117039>.
- [38] Murphy MJ, Grace GM, Tartaglia MC, Orange JB, Chen X, Rowe A, et al. Cerebral haemodynamic changes accompanying cognitive impairment in primary lateral sclerosis. *Amyotroph Lateral Scler* 2008;9(6):359-68.
- [39] Agosta F, Canu E, Inuggi A, Chio A, Riva N, Silani V, et al. Resting state functional connectivity alterations in primary lateral sclerosis. *Neurobiol Aging* 2014;35(4):916-25.
- [40] Canu E, Agosta F, Galantucci S, Chio A, Riva N, Silani V, et al. Extramotor damage is associated with cognition in primary lateral sclerosis patients. *PLoS ONE [Electronic Resource]* 2013;8(12):e82017.
- [41] Bede P, Chipika RH, Finegan E, Li Hi Shing S, Doherty MA, Hengeveld JC, et al. Brainstem pathology in amyotroph lateral scler and primary lateral sclerosis: a longitudinal neuroimaging study. *Neuro Image Clinical* 2019;24:102054. <http://dx.doi.org/10.1016/j.nicl.2019.102054>.
- [42] Tu S, Menke RAL, Talbot K, Kiernan MC, Turner MR. Cerebellar tract alterations in PLS and ALS. *Amyotroph Lateral Scler frontotemporal degeneration* 2019;20(3-4):281-4. <http://dx.doi.org/10.1080/21678421.2018.1562554>.
- [43] Chipika RH, Finegan E, Li Hi Shing S, McKenna MC, Christidi F, Chang KM, et al. Switchboard malfunction in motor neuron diseases: selective pathology of thalamic nuclei in Amyotroph Lateral Scler and primary lateral sclerosis. *NeuroImage Clinical* 2020;27:102300. <http://dx.doi.org/10.1016/j.nicl.2020.102300>.
- [44] Finegan E, Li Hi Shing S, Chipika RH, Doherty MA, Hengeveld JC, Vajda A, et al. Widespread subcortical grey matter degeneration in primary lateral sclerosis: a multimodal imaging study with genetic profiling. *NeuroImage Clinical* 2019;24:102089. <http://dx.doi.org/10.1016/j.nicl.2019.102089>.
- [45] Feron M, Couillandre A, Mseddi E, Termoz N, Abidi M, Bardinet E, et al. Extrapyramidal deficits in ALS: a combined biomechanical and neuroimaging study. *J Neurol* 2018. <http://dx.doi.org/10.1007/s00415-018-8964-y>.
- [46] Abidi M, de Marco G, Grami F, Termoz N, Couillandre A, Querin G, et al. Neural Correlates of Motor Imagery of Gait in Amyotroph Lateral Scler. *J Magn Reson Imaging* 2020. <http://dx.doi.org/10.1002/jmri.27335>.
- [47] Stark FM, Moersch FP. Primary lateral sclerosis: a distinct clinical entity. *J Nervous Mental Disease* 1945;102:332-7.
- [48] Clark MG, Smallwood Shoukry R, Huang CJ, Danielian LE, Bageac D, Floeter MK. Loss of functional connectivity is an early imaging marker in primary lateral sclerosis. *Amyotroph Lateral Scler frontotemporal degeneration* 2018;19(7-8):562-9. <http://dx.doi.org/10.1080/21678421.2018.1517180>.
- [49] van der Graaff MM, Sage CA, Caan MW, Akkerman EM, Lavini C, Majoie CB, et al. Upper and extra-motoneuron involvement in early motoneuron disease: a diffusion

- tensor imaging study. *Brain: a J Neurol* 2011;134(Pt 4):1211–28. <http://dx.doi.org/10.1093/brain/awr016>.
- [50] Ferraro PM, Agosta F, Riva N, Copetti M, Spinelli EG, Falzone Y, et al. Multimodal structural MRI in the diagnosis of motor neuron diseases. *NeuroImage Clinical* 2017;16:240–7. <http://dx.doi.org/10.1016/j.nicl.2017.08.002>.
- [51] Turner MR, Barohn RJ, Corcia P, Fink JK, Harms MB, Kiernan MC, et al. Primary lateral sclerosis: consensus diagnostic criteria. *J Neurol Neurosurg Psychiatry* 2020;91(4):373–7. <http://dx.doi.org/10.1136/jnnp-2019-322541>.
- [52] Finegan E, Li Hi Shing S, Siah WF, Chipika RH, Chang KM, McKenna MC, et al. Evolving diagnostic criteria in primary lateral sclerosis: the clinical and radiological basis of “probable PLS”. *J Neurol Sci* 2020;417:117052. <http://dx.doi.org/10.1016/j.jns.2020.117052>.
- [53] Finegan E, Siah WF, Shing SLH, Chipika RH, Chang KM, McKenna MC, et al. Imaging and clinical data indicate considerable disease burden in ‘probable’ PLS: patients with UMN symptoms for 2–4 years. Data in brief 2020;106247. <http://dx.doi.org/10.1016/j.dib.2020.106247>.
- [54] Fisher CM. Pure spastic paralysis of corticospinal origin. *Can J Neurol Sci* 1977;4(4):251–8.
- [55] Sugihara H, Horiuchi M, Kamo T, Fujisawa K, Abe M, Sakiyama T, et al. A case of primary lateral sclerosis taking a prolonged clinical course with dementia and having an unusual dendritic ballooning. *Neuropathology* 1999;19(1):77–84. <http://dx.doi.org/10.1046/j.1440-1789.1999.00203.x>.
- [56] Tan CF, Kakita A, Piao YS, Kikugawa K, Endo K, Tanaka M, et al. Primary lateral sclerosis: a rare upper-motor-predominant form of Amyotroph Lateral Scler often accompanied by frontotemporal lobar degeneration with ubiquitinated neuronal inclusions? Report of an autopsy case and a review of the literature. *Acta neuropathologica* 2003;105(6):615–20.
- [57] Mochizuki A, Komatsuzaki Y, Iwamoto H, Shoji S. Frontotemporal dementia with ubiquitinated neuronal inclusions presenting with primary lateral sclerosis and parkinsonism: clinicopathological report of an autopsy case. *Acta neuropathologica* 2004;107(4):377–80. <http://dx.doi.org/10.1007/s00401-003-0818-7>.
- [58] Mackenzie IR, Feldman H. Neurofilament inclusion body disease with early onset frontotemporal dementia and primary lateral sclerosis. *Clin Neuropathol* 2004;23(4):183–93.
- [59] Josephs K, Whitwell J, Murray M, Parisi J, Graff-Radford N, Knopman D, et al. Semantic dementia with primary lateral sclerosis (SD-PLS): a variant of FTLN-TDP type C pathology. *Dement Geriatr Cogn Disord* 2012;34:37–8.
- [60] Kawakatsu S, Kobayashi R, Shibuya Y, Miura Y, Shibuya N, Nishida A, et al. A case of FTLN-TDP type A with primary lateral sclerosis presenting progressive nonfluent aphasia, anterior operculum syndrome and left pyramidal tract lesion on MRI. *Neuropathology* 2013;33(3):364. <http://dx.doi.org/10.1111/neup.12034>.
- [61] Beal MF, Richardson Jr EP. Primary lateral sclerosis. A case report. *Arch Neurol* 1981;38(10):630–3.
- [62] Mochizuki A, Komatsuzaki Y, Iwamoto H, Shoji S. Frontotemporal dementia with ubiquitinated neuronal inclusions presenting with primary lateral sclerosis and parkinsonism: clinicopathological report of an autopsy case. *Acta neuropathologica* 2004;107(4):377–80. <http://dx.doi.org/10.1007/s00401-003-0818-7>.
- [63] Watanabe R, Iino M, Honda M, Sano J, Hara M. Primary lateral sclerosis. *Neuropathology* 1997;17(3):220–4.
- [64] Koga H, Ozeki T, Makiura Y, Nokura K, Yamamoto H, Matsumoto Y. Sporadic motor neuron disease with marked frontotemporal atrophy: an autopsied case mimicking primary lateral sclerosis. *Neuropathology* 2003;23:A40.
- [65] Kosaka T, Fu YJ, Shiga A, Ishidaira H, Tan CF, Tani T, et al. Primary lateral sclerosis: upper-motor-predominant Amyotroph Lateral Scler with frontotemporal lobar degeneration—immunohistochemical and biochemical analyses of TDP-43. *Neuropathology* 2012;32(4):373–84. <http://dx.doi.org/10.1111/j.1440-1789.2011.01271.x>.
- [66] Hirsch-Reinshagen V, Alfiay OA, Hsiung GR, Pottier C, Baker M, Perkerson 3rd RB, et al. Clinicopathologic correlations in a family with a TBK1 mutation presenting as primary progressive aphasia and primary lateral sclerosis. *Amyotroph Lateral Scler frontotemporal degeneration* 2019;20(7–8):568–75. <http://dx.doi.org/10.1080/21678421.2019.1632347>.
- [67] Younger DS, Chou S, Hays AP, Lange DJ, Emerson R, Brin M, et al. Primary lateral sclerosis. A clinical diagnosis reemerges. *Arch Neurol* 1988;45(12):1304–7.
- [68] Mackenzie IRA, Briemberg H. TDP-43 pathology in primary lateral sclerosis. *Amyotroph Lateral Scler frontotemporal degeneration* 2020;1–7. <http://dx.doi.org/10.1080/21678421.2020.1790607>.
- [69] Pioro EP, Turner MR, Bede P. Neuroimaging in primary lateral sclerosis. *Amyotroph Lateral Scler frontotemporal degeneration* 2020;21(sup1):18–27. <http://dx.doi.org/10.1080/21678421.2020.1837176>.
- [70] Butman JA, Floeter MK. Decreased thickness of primary motor cortex in primary lateral sclerosis. *Am J Neuroradiol* 2007;28(1):87–91.
- [71] Tzarouchi LC, Kyritsis AP, Giannopoulos S, Astrakas LG, Diakou M, Argyropoulou MI. Voxel-based diffusion tensor imaging detects pyramidal tract degeneration in primary lateral sclerosis. *Brit J Radiol* 2011;84(997):78–80.
- [72] Suh SI, Song IC, Koh SB. Primary lateral sclerosis with MR diffusion tensor image and tract tracking. *Am J Phys Med Rehabil* 2006;85(11):863–4. <http://dx.doi.org/10.1097/01.phm.0000242651.30244.a4>.
- [73] Salameh JS, Patel N, Zheng S, Cauley KA. Focal absence of diffusion tensor tracts from primary motor cortex in primary lateral sclerosis. *Eur J Neurol* 2013;20(4):e63–4. <http://dx.doi.org/10.1111/ene.12093>.
- [74] Bede P, Chipika RH, Finegan E, Li Hi Shing S, Chang KM, Doherty MA, et al. Progressive brainstem pathology in motor neuron diseases: imaging data from Amyotroph Lateral Scler and primary lateral sclerosis. Data in brief 2020;29:105229. <http://dx.doi.org/10.1016/j.dib.2020.105229>.
- [75] Finegan E, Hi Shing SL, Chipika RH, McKenna MC, Doherty MA, Hengeveld JC, et al. Thalamic, hippocampal and basal ganglia pathology in primary lateral sclerosis and Amyotroph Lateral Scler: Evidence from quantitative imaging data. Data in brief 2020;29:105115. <http://dx.doi.org/10.1016/j.dib.2020.105115>.
- [76] Dupre N, Valdmanis PN, Bouchard JP, Rouleau GA. Autosomal dominant primary lateral sclerosis. *Neurology* 2007;68(14):1156–7.
- [77] Praline J, Guennoc AM, Vourc’h P, De Toffol B, Corcia P. Primary lateral sclerosis may occur within familial Amyotroph Lateral Scler pedigrees. *Amyotroph Lateral Scler* 2010;11(1–2):154–6. <http://dx.doi.org/10.3109/17482960802483038>.
- [78] Appelbaum JS, Roos RP, Salazar-Grueso EF, Buchman A, Iannaccone S, Glantz R, et al. Intrafamilial heterogeneity in hereditary motor neuron disease. *Neurology* 1992;42(8):1488–92. <http://dx.doi.org/10.1212/wnl.42.8.1488>.
- [79] Ticozzi N, Tiloca C, Calini D, Gagliardi S, Altieri A, Colombrita C, et al. C9orf72 repeat expansions are

- restricted to the ALS-FTD spectrum. *NeurobiolAging* 2014;35(4). <http://dx.doi.org/10.1016/j.neurobiolaging.2013.09.037>. 936.e13- 7.
- [80] van Rheenen W, van Blitterswijk M, Huisman MH, Vlam L, van Doormaal PT, Seelen M, et al. Hexanucleotide repeat expansions in C9ORF72 in the spectrum of motor neuron diseases. *Neurology* 2012;79(9):878–82. <http://dx.doi.org/10.1212/WNL.0b013e3182661d14>.
- [81] Mitsumoto H, Nagy PL, Gennings C, Murphy J, Andrews H, Goetz R, et al. Phenotypic and molecular analyses of primary lateral sclerosis. *Neurology Genetics* 2015;1(1). <http://dx.doi.org/10.1212/01.NXG.0000464294.88607.dd>.
- [82] Sánchez-Ferrero E, Coto E, Beetz C, Gámez J, Corao AI, Díaz M, et al. SPG7 mutational screening in spastic paraplegia patients supports a dominant effect for some mutations and a pathogenic role for p.A510V. *Clinical genetics* 2013;83(3):257–62. <http://dx.doi.org/10.1111/j.1399-0004.2012.01896.x>.
- [83] McDermott CJ, Roberts D, Tomkins J, Bushby KM, Shaw PJ. Spastin and paraplegin gene analysis in selected cases of motor neurone disease (MND). *Amyotroph Lateral Scler and other motor neuron disorders: official publication of the World Federation of Neurology. Research Group on Motor Neuron Diseases* 2003;4(2):96–9. <http://dx.doi.org/10.1080/14660820310012718>.
- [84] Yang Y, Zhang L, Lynch DR, Lukas T, Ahmeti K, Sleiman PM, et al. Compound heterozygote mutations in SPG7 in a family with adult-onset primary lateral sclerosis. *Neurology Genetics* 2016;2(2):e60. <http://dx.doi.org/10.1212/nxg.0000000000000060>.
- [85] Gómez-Tortosa E, Van der Zee J, Ruggiero M, Gijssels I, Esteban-Pérez J, García-Redondo A, et al. Familial primary lateral sclerosis or dementia associated with Arg573Gly TBK1 mutation. *J Neurol Neurosurg Psychiatry* 2017;88(11):996–7. <http://dx.doi.org/10.1136/jnnp-2016-315250>.
- [86] Chow CY, Landers JE, Bergren SK, Sapp PC, Grant AE, Jones JM, et al. Deleterious variants of FIG4, a phosphoinositide phosphatase, in patients with ALS. *Am Journal Hum Genetics* 2009;84(1):85–8. <http://dx.doi.org/10.1016/j.ajhg.2008.12.010>.
- [87] Gellera C, Tiloca C, Del Bo R, Corrado L, Pensato V, Agostini J, et al. Ubiquilin 2 mutations in Italian patients with Amyotroph Lateral Scler and frontotemporal dementia. *J Neurol Neurosurg Psychiatry* 2013;84(2):183–7. <http://dx.doi.org/10.1136/jnnp-2012-303433>.
- [88] Deng HX, Chen W, Hong ST, Boycott KM, Gorrie GH, Siddique N, et al. Mutations in UBQLN2 cause dominant X-linked juvenile and adult-onset ALS and ALS/dementia. *Nature* 2011;477(7363):211–5. <http://dx.doi.org/10.1038/nature10353>.
- [89] Maruyama H, Morino H, Ito H, Izumi Y, Kato H, Watanabe Y, et al. Mutations of optineurin in Amyotroph Lateral Scler. *Nature* 2010;465(7295):223–6. <http://dx.doi.org/10.1038/nature08971>.
- [90] Mintchev N, Zamba-Papanicolaou E, Kleopa KA, Christodoulou K. A novel ALS2 splice-site mutation in a Cypriot juvenile-onset primary lateral sclerosis family. *Neurology* 2009;72(1):28–32. <http://dx.doi.org/10.1212/01.wnl.0000338530.77394.60>.
- [91] Panzeri C, De Palma C, Martinuzzi A, Daga A, De Polo G, Bresolin N, et al. The first ALS2 missense mutation associated with JPLS reveals new aspects of alsin biological function. *Brain* 2006;129(Pt 7):1710–9. <http://dx.doi.org/10.1093/brain/awl104>.
- [92] Al-Saif A, Bohlega S, Al-Mohanna F. Loss of ERLIN2 function leads to juvenile primary lateral sclerosis. *Ann Neurol* 2012;72(4):510–6. <http://dx.doi.org/10.1002/ana.23641>.
- [93] Meoded A, Kwan JY, Peters TL, Huey ED, Danielian LE, Wiggs E, et al. Imaging findings associated with cognitive performance in primary lateral sclerosis and Amyotrophic Lateral Sclerosis. *Dementia and geriatric cognitive disorders extra* 2013;3(1):233–50.
- [94] Bede P, Querin G, Pradat PF. The changing landscape of motor neuron disease imaging: the transition from descriptive studies to precision clinical tools. *Curr Opin Neurol* 2018;31(4):431–8. <http://dx.doi.org/10.1097/wco.0000000000000569>.
- [95] Paganoni S, Alshikho MJ, Zürcher NR, Cernasov P, Babu S, Loggia ML, et al. Imaging of glia activation in people with primary lateral sclerosis. *NeuroImage Clinical* 2018;17:347–53. <http://dx.doi.org/10.1016/j.nicl.2017.10.024>.
- [96] Tartaglia MC, Laluz V, Rowe A, Findlater K, Lee DH, Kennedy K, et al. Brain atrophy in primary lateral sclerosis. *Neurology* 2009;72(14):1236–41. <http://dx.doi.org/10.1212/01.wnl.0000345665.75512.f9>.
- [97] Van Der Graaff MM, Sage CA, Caan MWA, Akkerman EM, Lavini C, Majoie CB, et al. Upper and extra-motoneuron involvement in early motoneuron disease: a diffusion tensor imaging study. *Brain* 2011;134(4):1211–28. <http://dx.doi.org/10.1093/brain/awr016>.
- [98] Kiernan JA, Hudson AJ. Frontal lobe atrophy in motor neuron diseases. *Brain* 1994;117(Pt 4):747–57.
- [99] Ulug AM, Grunewald T, Lin MT, Kamal AK, Filippi CG, Zimmerman RD, et al. Diffusion tensor imaging in the diagnosis of primary lateral sclerosis. *J Magn Reson Imaging* 2004;19(1):34–9.
- [100] Ciccirelli O, Behrens TE, Johansen-Berg H, Talbot K, Orrell RW, Howard RS, et al. Investigation of white matter pathology in ALS and PLS using tract-based spatial statistics. *Hum Brain Mapp* 2009;30(2):615–24.
- [101] Iwata NK, Kwan JY, Danielian LE, Butman JA, Tovar-Moll F, Bayat E, et al. White matter alterations differ in primary lateral sclerosis and Amyotroph Lateral Scler. *Brain* 2011;134(Pt 9):2642–55. <http://dx.doi.org/10.1093/brain/awr178>.
- [102] Agosta F, Galantucci S, Riva N, Chiò A, Messina S, Iannaccone S, et al. Intra-hemispheric and inter-hemispheric structural network abnormalities in PLS and ALS. *Hum Brain Mapp* 2014;35(4):1710–22. <http://dx.doi.org/10.1002/hbm.22286>.
- [103] Meoded A, Morrisette AE, Katipally R, Schanz O, Gotts SJ, Floeter MK. Cerebro-cerebellar connectivity is increased in primary lateral sclerosis. *NeuroImage Clinical* 2015;7:288–96.
- [104] Zhai P, Pagan F, Statland J, Butman JA, Floeter MK. Primary lateral sclerosis: a heterogeneous disorder composed of different subtypes? *Neurology* 2003;60(8):1258–65.
- [105] Mitsumoto H, Ulug AM, Pullman SL, Gooch CL, Chan S, Tang MX, et al. Quantitative objective markers for upper and lower motor neuron dysfunction in ALS. *Neurology* 2007;68(17):1402–10. <http://dx.doi.org/10.1212/01.wnl.0000260065.57832.87>.
- [106] Charil A, Corbo M, Filippi M, Kesavadas C, Agosta F, Munerati E, et al. Structural and metabolic changes in the brain of patients with upper motor neuron disorders: A multiparametric MRI study. *Amyotroph Lateral Scler* 2009;10(5–6):269–79. <http://dx.doi.org/10.3109/17482960902777339t>.
- [107] van der Graaff MM, Lavini C, Akkerman EM, Majoie Ch B, Nederveen AJ, Zwiderman AH, et al. MR spectroscopy findings in early stages of motor neuron disease. *AJNR Am J Neuroradiol* 2010;31(10):1799–806.
- [108] Querin G, El Mendili MM, Bede P, Delphine S, Lenglet T, Marchand-Pauvert V, et al. Multimodal spinal cord MRI offers accurate diagnostic classification in ALS. *J Neurol*

- Neurosurg Psychiatry 2018;89(11):1220–1. <http://dx.doi.org/10.1136/jnnp-2017-317214>.
- [109] Bede P, Bokde AL, Byrne S, Elamin M, Fagan AJ, Hardiman O. Spinal cord markers in ALS: diagnostic and biomarker considerations. *Amyotroph Lateral Scler* 2012;13(5):407–15. <http://dx.doi.org/10.3109/17482968.2011.649760>.
- [110] Querin G, El Mendili MM, Lenglet T, Behin A, Stojkovic T, Salachas F, et al. The spinal and cerebral profile of adult spinal-muscular atrophy: a multimodal imaging study. *NeuroImage Clinical* 2019;21:101618. <http://dx.doi.org/10.1016/j.nicl.2018.101618>.
- [111] El Mendili MM, Querin G, Bede P, Pradat PF. Spinal cord imaging in amyotroph lateral scler: historical concepts–novel techniques. *Frontiers in neurology* 2019;10:350. <http://dx.doi.org/10.3389/fneur.2019.00350>.
- [112] Leboutoux MV, Franques J, Guillevin R, Delmont E, Lenglet T, Bede P, et al. Revisiting the spectrum of lower motor neuron diseases with snake eyes appearance on magnetic resonance imaging. *Eur J Neurol* 2014;21(9):1233–41.
- [113] Lindenberg J, Preston DC. MRI imaging in primary lateral sclerosis. *Clin Neuromuscul Dis* 2003;4(3):115–6.
- [114] Kwan JY, Meoded A, Danielian LE, Wu T, Floeter MK. Structural imaging differences and longitudinal changes in primary lateral sclerosis and Amyotroph Lateral Scler. *NeuroImage Clinical* 2013;2(1):151–60. <http://dx.doi.org/10.1016/j.nicl.2012.12.003>.
- [115] Schuster C, Elamin M, Hardiman O, Bede P. Presymptomatic and longitudinal neuroimaging in neurodegeneration—from snapshots to motion picture: a systematic review. *J Neurol Neurosurg Psychiatry* 2015;86(10):1089–96. <http://dx.doi.org/10.1136/jnnp-2014-309888>.
- [116] Bede P, Hardiman O. Longitudinal structural changes in ALS: a three time-point imaging study of white and gray matter degeneration. *Amyotroph Lateral Scler frontotemporal degeneration* 2018;19(3–4):232–41. <http://dx.doi.org/10.1080/21678421.2017.1407795>.
- [117] Chipika RH, Finegan E, Li Hi Shing S, Hardiman O, Bede P. Tracking a fast-moving disease: longitudinal markers, monitoring, and clinical trial endpoints in ALS. *Frontiers in neurology* 2019;10:229. <http://dx.doi.org/10.3389/fneur.2019.00229>.
- [118] Proudfoot M, Bede P, Turner MR. Imaging cerebral activity in Amyotroph Lateral Scler. *Frontiers in neurology* 2018;9:1148. <http://dx.doi.org/10.3389/fneur.2018.01148>.
- [119] Fabes J, Matthews L, Filippini N, Talbot K, Jenkinson M, Turner MR, et al. MRI in Amyotroph Lateral Scler. *Academic radiology* 2017;24(10):1187–94. <http://dx.doi.org/10.1016/j.acra.2017.04.008>.
- [120] Kolind S, Sharma R, Knight S, Johansen-Berg H, Talbot K, Turner MR. Myelin imaging in amyotrophic and primary lateral sclerosis. *Amyotroph Lateral Scler and Frontotemporal Degeneration* 2013;14(7–8):562–73. <http://dx.doi.org/10.3109/21678421.2013.794843>.
- [121] Hardiman O, Doherty CP, Elamin M, Bede P. *Neurodegenerative Disorders: A Clinical Guide*. 2016 ed. Springer Cham Heidelberg New York Dordrecht London © Springer International Publishing Switzerland 2016: Springer International Publishing; 2016.
- [122] Tahedl M, Li Hi Shing S, Finegan E, Chipika RH, Lope J, Hardiman O, et al. Propagation patterns in motor neuron diseases: individual and phenotype-associated disease-burden trajectories across the UMN-LMN spectrum of MNDs. *Neurobiol Aging* 2021. In Press.
- [123] Clark MG, Smallwood Shoukry R, Huang CJ, Danielian LE, Bageac D, Floeter MK. Loss of functional connectivity is an early imaging marker in primary lateral sclerosis. *Amyotroph Lateral Scler and Frontotemporal Degeneration* 2018;1–8. <http://dx.doi.org/10.1080/21678421.2018.1517180>.
- [124] Floeter MK, Mills R. Progression in primary lateral sclerosis: a prospective analysis. *Amyotroph Lateral Scler* 2009;10(5–6):339–46.
- [125] 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 degeneration* 2019;20(3–4):133–45. <http://dx.doi.org/10.1080/21678421.2018.1550518>.
- [126] Turner MR, Hammers A, Al-Chalabi A, Shaw CE, Andersen PM, Brooks DJ, et al. Cortical involvement in four cases of primary lateral sclerosis using [(11)C]-flumazenil PET. *J Neurol* 2007;254(8):1033–6.
- [127] Müller HP, Gorges M, Kassubek R, Dorst J, Ludolph AC, Kassubek J. Identical patterns of cortico-efferent tract involvement in primary lateral sclerosis and Amyotroph Lateral Scler: a tract of interest-based MRI study. *NeuroImage Clinical* 2018;18:762–9. <http://dx.doi.org/10.1016/j.nicl.2018.03.018>.
- [128] Bede P, Iyer PM, Finegan E, Omer T, Hardiman O. Virtual brain biopsies in Amyotroph Lateral Scler: Diagnostic classification based on in vivo pathological patterns. *NeuroImage Clinical* 2017;15:653–8. <http://dx.doi.org/10.1016/j.nicl.2017.06.010>.
- [129] Grollemund V, Le Chat G, Secchi-Buhour MS, Delbot F, Pradat-Peyre JF, Bede P, et al. Manifold learning for Amyotroph Lateral Scler functional loss assessment: development and validation of a prognosis model. *J Neurol* 2020. <http://dx.doi.org/10.1007/s00415-020-10181-2>.
- [130] Grollemund V, Pradat PF, Querin G, Delbot F, Le Chat G, Pradat-Peyre JF, et al. Machine learning in Amyotroph Lateral Scler: achievements, pitfalls, and future directions. *Frontiers in neuroscience* 2019;13:135. <http://dx.doi.org/10.3389/fnins.2019.00135>.
- [131] Schuster C, Hardiman O, Bede P. Development of an automated MRI-Based diagnostic protocol for Amyotroph Lateral Scler using disease-specific pathognomonic features: a quantitative disease-state classification study. *PLoS One* 2016;11(12):e0167331. <http://dx.doi.org/10.1371/journal.pone.0167331>.
- [132] Schuster C, Hardiman O, Bede P. Survival prediction in Amyotroph Lateral Scler based on MRI measures and clinical characteristics. *BMC Neurol* 2017;17(1):73. <http://dx.doi.org/10.1186/s12883-017-0854-x>.
- [133] Tahedl M, Chipika RH, Lope J, Li Hi Shing S, Hardiman O, Bede P. Cortical progression patterns in individual ALS patients across multiple timepoints: a mosaic-based approach for clinical use. *J Neurol* 2021. <http://dx.doi.org/10.1007/s00415-020-10368-7>.
- [134] Devos D, Moreau C, Kyheng M, Garcon G, Rolland AS, Blasco H, et al. A ferroptosis-based panel of prognostic biomarkers for Amyotroph Lateral Scler. *Scientific reports* 2019;9(1):2918. <http://dx.doi.org/10.1038/s41598-019-39739-5>.
- [135] Blasco H, Patin F, Descat A, Garcon G, Corcia P, Gele P, et al. A pharmaco-metabolomics approach in a clinical trial of ALS: identification of predictive markers of progression. *PLoS One* 2018;13(6):e0198116. <http://dx.doi.org/10.1371/journal.pone.0198116>.
- [136] Floeter MK, Gendron TF. Biomarkers for Amyotroph Lateral Scler and frontotemporal dementia associated with hexanucleotide expansion mutations in C9orf72. *Frontiers in neurology* 2018;9:1063. <http://dx.doi.org/10.3389/fneur.2018.01063>.
- [137] Thompson AG, Gray E, Bampton A, Raciborska D, Talbot K, Turner MR. CSF chitinase proteins in Amyotroph Lateral Scler. *J Neurol Neurosurg Psychiatry* 2019;90(11):1215–20. <http://dx.doi.org/10.1136/jnnp-2019-320442>.

- [138] Zucchi E, Bedin R, Fasano A, Fini N, Gessani A, Vinceti M, et al. Cerebrospinal fluid neurofilaments may discriminate upper motor neuron syndromes: a pilot study. *Neurodegenerative diseases* 2018;18(5-6):255-61. <http://dx.doi.org/10.1159/000493986>.
- [139] Thompson AG, Gray E, Thézénas ML, Charles PD, Evetts S, Hu MT, et al. Cerebrospinal fluid macrophage biomarkers in Amyotroph Lateral Scler. *Ann Neurol* 2018;83(2):258-68. <http://dx.doi.org/10.1002/ana.25143>.
- [140] Steinacker P, Feneberg E, Weishaupt J, Brettschneider J, Tumani H, Andersen PM, et al. Neurofilaments in the diagnosis of motoneuron diseases: a prospective study on 455 patients, *J Neurol. Neurosurg Psychiatry* 2016;87(1):12-20. <http://dx.doi.org/10.1136/jnnp-2015-311387>.
- [141] Verde F, Zaina G, Bodio C, Borghi MO, Soranna D, Peverelli S, et al. Cerebrospinal fluid phosphorylated neurofilament heavy chain and chitotriosidase in primary lateral sclerosis. *J Neurol Neurosurg Psychiatry* 2020. <http://dx.doi.org/10.1136/jnnp-2020-324059> [Online ahead of print].
- [142] Mitsumoto H, Turner MR, Ajroud-Driss S, Andres P, Andrews J, Gomez EA, et al. Preface: promoting research in PLS: current knowledge and future challenges. *Amyotroph Lateral Scler frontotemporal degeneration* 2020;21(sup1):1-2. <http://dx.doi.org/10.1080/21678421.2020.1840795>.