

Amyotrophic Lateral Sclerosis and Frontotemporal Degeneration

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ORIGINAL ARTICLE

A case series of PLS patients with frontotemporal dementia and overview of the literature

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Abstract

Objective: Primary lateral sclerosis (PLS) is a rare form of motor neuron disease characterised by UMN degeneration leading to slowly progressive spasticity. Whether it is a separate disease or a subtype of ALS has been debated. In ALS comorbid frontotemporal dementia (FTD) is frequently seen ($\pm 15\%$). However, cognitive and behavioural changes are generally not considered to be a part of PLS. **Methods:** To report the clinical findings and frequency of PLS patients that developed FTD in a referral-based cohort and provide an overview of the literature. **Results:** In our cohort six out of 181 (3.3%) PLS patients developed FTD. In the literature a few cases of PLS with FTD have been reported and only a limited number of small studies have investigated cognition in PLS. However, when these studies are summarised a pattern emerges with FTD diagnoses in $\pm 2\%$ and frontotemporal impairment in 22% of patients. **Conclusions:** These findings suggest that PLS is part of the FTD-MND continuum and would favour viewing it as a subtype of ALS. It is, however, not a restricted (isolated UMN involvement) phenotype.

Keywords: Primary lateral sclerosis; cognition; frontotemporal dementia; dementia

Introduction

Primary lateral sclerosis (PLS) is a rare form of motor neuron disease (MND), characterised by the degeneration of upper motor neurons (UMN) leading to slow progressive spasticity. Whether it is a separate disease or a subtype of ALS has been debated. In ALS comorbid frontotemporal dementia (FTD) is frequently seen ($\pm 15\%$) (1) and up to 50% show signs of frontotemporal dysfunction without fulfilling formal diagnostic criteria (2). Parkinsonian features, sensory abnormalities and mild frontal lobe dysfunction have been reported in $\pm 10\%$ of PLS patients (termed PLS-plus) (3), but frank (frontotemporal) dementia is not

considered as part of PLS. Here we describe a case series identified through the review of electronic medical records of PLS patients that subsequently developed FTD, report the approximate frequency of PLS-FTD in a referral-based cohort and provide an overview of the literature.

Material and methods

Retrospective case series

The Academic Medical Centre (AMC Amsterdam) and University Medical Centre Utrecht (UMCU) form the national referral centre for MND and together we see 80% of MND patients in the

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Netherlands. Patients were seen between 2006 and 2016 at outpatient clinics and diagnosed with PLS by neurologists with extensive experience of MND. Patients were considered to have PLS when they fulfilled the diagnostic criteria for clinically pure PLS or PLS-plus according to the diagnostic criteria proposed by Gordon et al. (4), which in brief require evident and progressive upper motor neuron signs without focal muscle atrophy or visible fasciculations and no denervation on EMG four years from onset. The age at onset must be >40 years. Secondary and mimicking conditions must have been excluded, which in our cases was done through an extensive work-up (MRI imaging of the neuraxis, laboratory investigations (including metabolic disorders), serology (HIV, syphilis, Borrelia and HTLV1 and -2), CSF (if appropriate), genetic testing for hereditary spastic paraplegias (HSPs) and/or ALS and needle EMGs (to exclude LMN involvement)). Particular emphasis is placed on ruling out (1) UMN-predominant ALS by repeating EMGs, (2) HSP by taking detailed family histories, genetic testing and following patients over time (5,6) and (3) progressive supranuclear palsy; vertical gaze palsy, frequent falling within first year, proximal more than distal symmetrical akinesia or rigidity, abnormal neck posture (retrocollis) and early onset of cognitive impairment (7–9).

All patients suspected of having PLS were followed at one of our centres until a disease duration of four years (longer in the vast majority of cases), after which patients were referred to the nearest multidisciplinary specialised MND care team, which in some cases was not one of our centres.

During follow-up some patients were referred back because they had developed severe behavioural and/or cognitive changes. We had also observed this in some patients that had remained in our own care. In all of these patients we performed an additional work-up, which included imaging, laboratory investigations, serology, neuropsychological assessment, genetic testing and EMG. In all cases, it was the opinion of the treating physician that the behavioural/cognitive changes could be attributed to FTD.

We considered the observation that multiple patients had appeared to have developed FTD intriguing, as frank FTD is not listed in any of the proposed diagnostic criteria and multiple studies even report cognition and behaviour to be unaffected in PLS. We therefore retrospectively reviewed the electronic medical records of our patients with the objective of identifying all PLS patients that developed FTD and re-evaluated these cases against the current diagnostic criteria for bvFTD and primary progressive aphasia (PPA) (10,11). Review of medical records was carried out with the approval of the relevant medical ethics committees.

Literature overview

After having identified multiple cases of PLS with FTD, we performed a search of the literature (Figure 1) with the following objectives:

- (1) Providing an approximate frequency of published PLS cases with concomitant FTD or cognitive/behavioural changes. Based on the available data in the publications we evaluated the reported patients against current criteria for bvFTD or PPA (10,11) or classified them as PLS with cognitive impairment (ci), behavioural impairment (bi) or without cognitive impairment according to the Strong criteria (12).
- (2) Characterizing the cognitive profile of PLS by listing the affected cognitive domains as reported as well as by performing a meta-analysis. To be included in the meta-analysis studies needed to have a case-control design (matched for age and education or by applying age- and education-corrected standard scores) and report data from at least one validated neuropsychological test as mean and SD or raw or standardised test scores for both cases and controls. Studies had to report on unique cohorts and in the case of overlap the largest study was included. Data were categorised in 10 cognitive domains (ACE-R was included as a global measure of cognition), as described before (13), and extracted by two authors (BSdV, LMMR) in order to reduce extraction errors. Using Review Manager 5.3 we calculated the effect size of each cognitive domain per study expressed as Hedges' *g*. When multiple neuropsychological tests for one cognitive domain were used in a study, we calculated an average effect size so that each study only added one effect size to the final analysis. A random effects model was applied to obtain an average weighted effect size across the studies.
- (3) Summarizing imaging and neuropathology findings in PLS patients with comorbid dementia.

Results

Retrospective case series

Between 2006 and 2016, 181 patients were diagnosed with PLS. Interrogation of their medical records showed that concomitant FTD had been diagnosed in six (3.3%). All of these patients had developed severe behavioural changes or language deficits after years of having progressive, but isolated UMN signs. As frank FTD is not generally considered to be a feature of PLS an additional work-up was performed to rule out other causes (such as comorbid Alzheimer's disease, delirium, metabolic

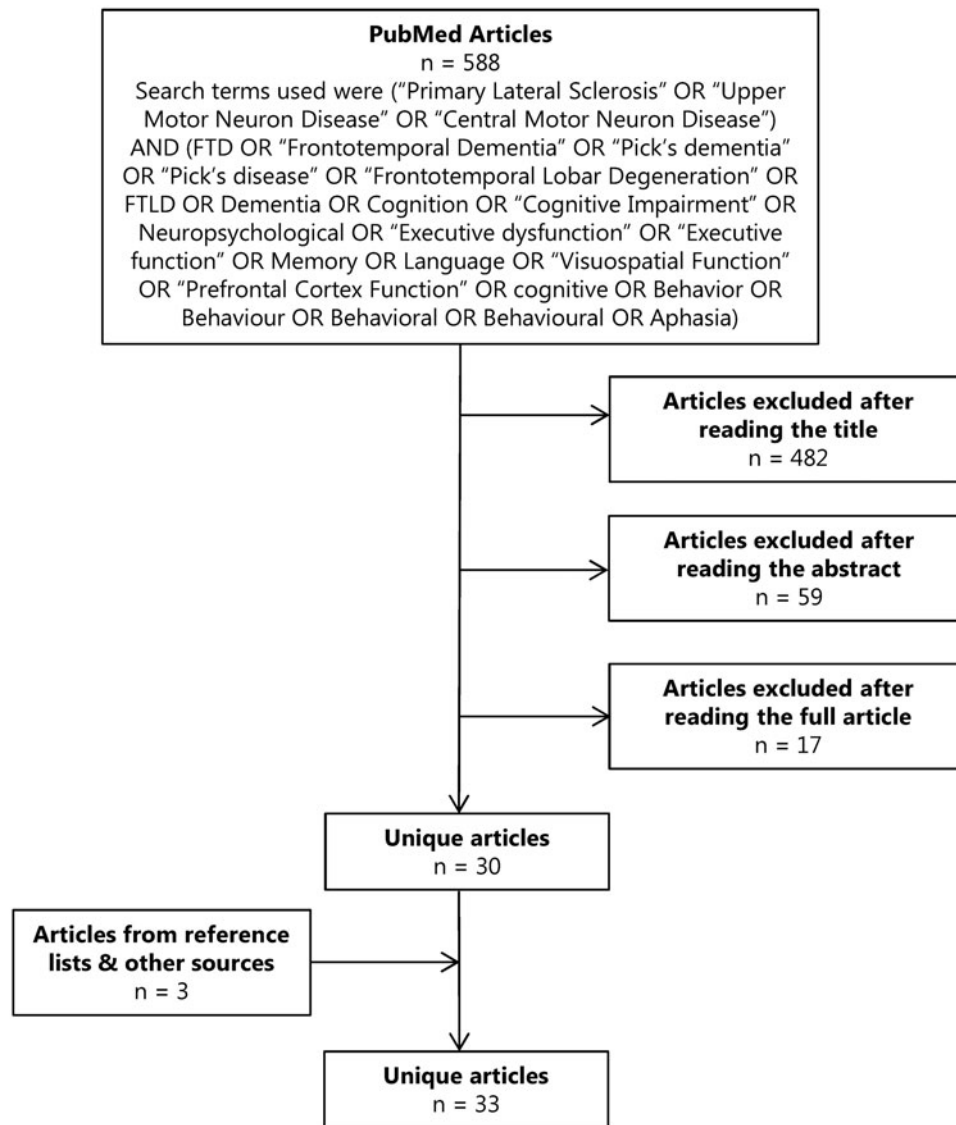


Figure 1. Summary of the results from our literature search. The search was performed using MEDLINE (via PubMed) on articles in English from July 1963 to January 2017 reporting on cognition and/or behaviour in PLS. Titles and abstracts were screened and relevant full text articles were retrieved. References were screened for additional studies and publications were also identified from the authors' literature collections. When overlap between studies was expected, corresponding authors were contacted for further details. Since the inclusion of the search term "PLS" led to a high amount of irrelevant hits (e.g. partial least squares, post ligation syndrome, parathyroid lesions, etc.) it was not included in our list of search terms. We included studies on PLS in which dementia, cognition or behaviour was mentioned.

disorders, mass lesions, etc.) through neuropsychological evaluation (behaviour, cognition), MRI imaging and laboratory investigations.

In five patients severe and progressive deterioration of behaviour (apathy, binge eating, loss of decorum, perseverative/stereotypical behaviour, diminished social interest or personal warmth) was the most prominent feature (bvFTD). In one patient progressive language deficits were the most prominent feature with impairment in confrontation naming, word comprehension, object recognition and emotion perception and empathy, while memory and visual spatial functions remained relatively spared. This patient was considered to have semantic dementia.

Repeated imaging in four out of these six cases showed progressive (asymmetrical) frontal and/or temporal atrophy (Figure 2). A summary of the clinical characteristics and full case descriptions are provided in Table 1 and Supplementary material.

Because we considered these cases unusual, we also re-evaluated the initial PLS diagnosis. None of the cases showed clinical or electrophysiological evidence of LMN involvement at the moment of re-evaluation (four to nine years after onset) excluding conversion to ALS-FTD. Moreover, genetic testing for *C9orf72* was negative. In the lower limb-onset patients we considered (complex) HSP to be highly unlikely because genetic testing was negative, onset was late, asymmetrical and all of them had

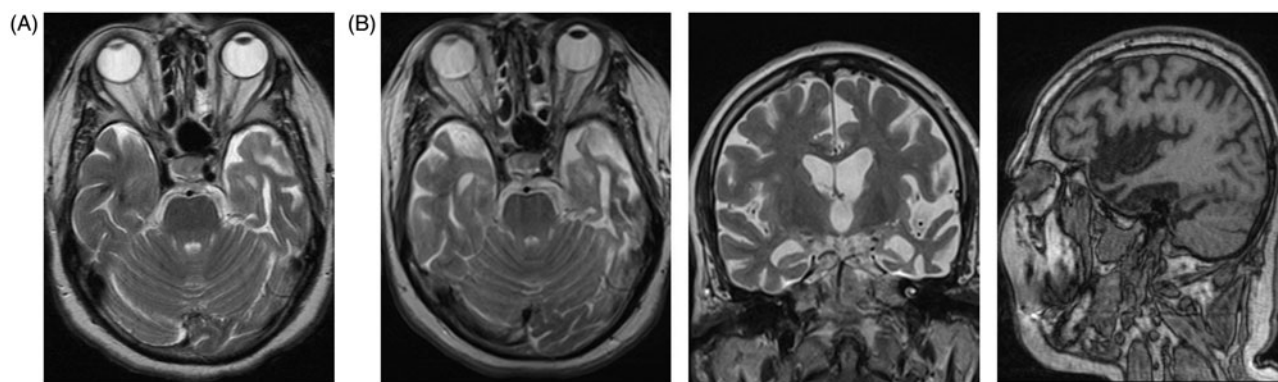


Figure 2. The initial axial T2 weighted MRI (A) showed left temporal lobe atrophy. The second scan made 2 years later (B) demonstrated bilateral temporal lobe and hippocampus atrophy (axial and coronal T2 weighted MRI), but more severe on the left side with a knife blade aspect of the temporal gyri while the general cerebral atrophy was limited (far right: sagittal T1 weighted MRI).

developed bulbar involvement within a relatively short time-frame. Saccadic eye movements, tremor or slight cogwheel rigidity was seen in three patients, but Parkinsonism was not a prominent feature in any of the cases and none had vertical gaze palsy. We therefore also considered PSP or other forms of Parkinsonism to be unlikely.

We did not detect evidence for another non-degenerative nervous system, medical or psychiatric disorder as cause for the observed cognitive and behavioural changes. Findings on neuropsychological examination were not considered to be consistent with Alzheimer's disease or any other type of dementia. Cases 1 and 3–6 fulfil the current criteria for bvFTD while case 2 meets criteria for semantic dementia (10,11).

Overview of the literature

We found 33 publications on cognition/behaviour in PLS reporting on a total of 307 patients, of which seven had concomitant FTD (2.3%). In 68 cases cognitive or behavioural changes were present, but which did not meet criteria for FTD (22.1%) (Table 2).

Cognitive profile: We identified a total of 19 studies in which some form of neuropsychological evaluation was performed in PLS patients. There were considerable differences with regard to the test batteries used, which in some studies was limited to simple screening instruments (e.g. MMSE), whereas others performed full neuropsychological examinations. Executive dysfunction was the most commonly observed impairment (reported in 12 out of 19 studies). Language deficits, memory impairment and behavioural change were also observed. The frequency of cognitive deficits was highest in studies that administered a full neuropsychological examination (14–23), which may suggest under-reporting in studies that only applied simple screening instruments (Table 2).

A total of four studies fulfilled the inclusion criteria for the meta-analysis encompassing 10 cognitive domains. Most cognitive domains were

only assessed in a single study and the maximum number of studies per cognitive domain was 2. Large effect sizes (Hedges' $g > 0.8$) were observed for executive function, delayed verbal memory, psychomotor speed and fluency. A large effect was also seen for the ACE-R, included as a global measure of cognition. The other domains did not demonstrate any significant effects. It must be noted that there is considerable heterogeneity and therefore these results should be interpreted with caution (Table 3).

Imaging: Diagnostic criteria for PLS include that brain imaging should be without structural abnormalities, although atrophy of the precentral gyrus is allowed (24). The corticospinal tracts may also appear hyper-intense on T2-weighted images, thought to be reflective of Wallerian degeneration. More advanced imaging techniques also demonstrate abnormalities of motor cortex and the corticospinal tracts. For instance, ^{18}F FDG-PET imaging may show a stripe of hypometabolism in the precentral gyrus (25) and diffusion tensor imaging (DTI) studies show reduced fractional anisotropy within the corticospinal tracts and mid-body of the corpus callosum (15,26,27). The number of imaging studies that also included PLS patients with cognitive disturbances is unfortunately limited (Table 4). Interestingly, these studies show that there may be more widespread involvement of the brain in PLS. In particular, DTI studies demonstrate white matter tract damage may be quite extensive affecting the basal ganglia, corpus callosum, frontal and temporal lobes (15,27). SPECT, CT-perfusion and fMRI studies confirm involvement of these non-motor regions (14,18,21). PLS patients with cognitive impairment predominantly had executive dysfunction and in some studies the severity of cognitive dysfunction correlated with the extent of frontal involvement (14,15). Memory impairment and/or hippocampal atrophy was not reported in these studies.

Neuropathology: In pure PLS there is prominent loss of pyramidal neurons, often complete absence

Table 1. Clinical characteristics of PLS-FTD patients.

Gender	Case 1 Male	Case 2 Female	Case 3 Female	Case 4 Female	Case 5 Female	Case 6 Male
Age at onset of PLS (yrs.)	53	62	67	68	57	59
Site of onset	Left Leg	Bulbar	Left leg	Left leg	Bulbar	Right Leg
Progression to other regions over time?	Bulbar	Arms & legs	Bulbar	Bulbar	No	Arms & legs
Decreased vital capacity?	No	No	No	No	No	No
Clinical or EMG evidence of LAMN involvement 4 or more years from onset?	Absent	Absent	Absent	Absent	Absent	Absent
Vertical gaze palsy	No	No	No	No	No	No
Frequent falling during 1st of symptoms?	No	No	No	No	No	No
Time from PLS onset to 1st cognitive/behavioural changes (mo.)	108	72	50	60	84	60
Most prominent feature	Behavioural changes	Language deficits	Language comprehension and apathy	Behavioural changes	Behavioural changes	Behavioural changes
FTD subtype	Possible bvFTD	Semantic dementia	Probable bvFTD	Probable bvFTD	Possible bvFTD	Probable bvFTD
Behavioural changes (consensus clinical criteria bvFTD) (12)	(1) Behavioural disinhibition (2) Apathy (3) Hyperorality and dietary changes	(1) Apathy (2) Behavioural disinhibition (3) Perseverative, stereotyped or compulsive/ritualistic behaviour	(1) Apathy (2) Diminished social interest (3) Executive dysfunction	(1) Apathy (2) Behavioural disinhibition (3) Perseverative, stereotyped or compulsive/ritualistic behaviour	(1) Apathy or inertia (2) Behavioural disinhibition (3) Loss of sympathy	(1) Behavioural disinhibition (2) Diminished social interest (3) Altered food preferences
Neuropsychological findings	Language deficits and executive dysfunction with relative sparing of memory and visual spatial tasks	Language deficits	Language deficits, executive dysfunction and to a lesser extent memory impairment	Mild memory impairment	Executive dysfunction and language	Language, fluency and executive dysfunction with relative sparing of memory and visual spatial tasks
Atrophy on MRI imaging	NA	Bilateral frontal atrophy and more pronounced of the anterior part of the temporal lobes	Bilateral temporal atrophy	Left temporal atrophy	NA	Bilateral frontal atrophy

(continued)

Gender	Case 1 Male	Case 2 Female	Case 3 Female	Case 4 Female	Case 5 Female	Case 6 Male
Time from first cognitive/behavioural changes to FTD diagnosis (mo.)	3	4	6	12	12	60
Development of parkinsonian features during follow-up	Tremor	Bilateral resting tremor	-	-	-	-
C9orf72 (wild type/expanded)	Wild type	Wild type	Unknown	Wild type	Unknown	Wild type

PLS; Primary lateral sclerosis; FTD: Frontotemporal dementia; bvFTD: Behavioural variant FTD; EMG: Electromyography; LMN: Lower motor neuron; MRI: Magnetic resonance imaging; NA: Not available.

of Betz cells, in the precentral gyrus with severe degeneration of the corticospinal tract, but with preservation of the motor nuclei in the brainstem and anterior horn cells in the spinal cord. Neurofibrillary tangles, senile plaques and Lewy bodies are absent and the observed protein aggregates are ubiquitin-positive, but tau-negative. As most of these studies predated the discovery of TDP-43 as the main component of aggregates within the MND-FTD spectrum, it is unclear whether these aggregates stain for TDP-43. However, Kosaka et al. report TDP-43-positive pathology in the motor cortex, frontal and temporal lobe in a PLS patient with frontotemporal lobar degeneration (28).

In the autopsies of PLS patients with comorbid dementia the hippocampus appears to be unaffected. The most severe pathology outside of the motor system is seen in the frontal and temporal regions (gliosis, white matter damage) which may be accompanied by neuronal loss (28–31). To a lesser degree atrophy of the basal ganglia (thalamus and striatum, but not substantia nigra) may also be seen (28–31). Again, without evidence for tauopathies, including AD or α -synucleinopathies (Table 5).

The only exception to these findings is the case reported by Engel et al. where there is only mild loss of neurons in the precentral gyrus that is not considered to be disproportionate to neuronal loss elsewhere in the brain (22). It appears UMN signs resulted from a prominent loss of myelinated axons in the spinal cord, which would be more consistent with HSP than PLS. The authors acknowledge this, but favour a diagnosis of PLS based on the late and asymmetrical onset combined with a negative family history. Similarly, the authors struggle to classify the cognitive changes in this patient. Clinically it was considered to be a frontal syndrome, but neuropathology shows amyloid-positive diffuse plaques and neurofibrillary tangles, which would suggest Alzheimer's disease. The most prominent pathology is, however, not seen in the hippocampus region, but rather in the orbitofrontal cortex and they even consider the possibility that the observed amyloid plaques could be attributed to normal aging. After consideration of all these observations, the authors consider this a disorder within the PLS-HSP spectrum with neuropathological features of AD. In this case there is no definitive clinical, genetic or pathological diagnosis and it is not clear whether we should consider this as PLS with dementia or perhaps HSP with comorbid AD.

Discussion

Studying PLS is challenging for many reasons. First it is a very rare disorder (2–5% of patients in adult neuromuscular clinics). Secondly, there is no diagnostic test that definitively demonstrates PLS, and

Table 2. Studies on PLS patients that interrogated cognition and/or behaviour.

No.	1st author, year (reference)	Overlapping studies*	PLS cases			Cognitive assessment	Affected cognitive domains
			n	FTD (n)	CI/BI (n)		
1	Russo, 1982 (42)		4	0	0	–	–
2	Sotaniemi, 1985 (43)		2	0	0	–	–
3	Pringle, 1992 (26)		8	0	0	–	–
4	Kiernan, 1994 (44)		8	0	0	–	–
5	Caselli, 1995 (16)		9	0	8	Full NPE	Executive function, Memory
6	De Konings, 1997 (21)		1	0	1	Full NPE	Mild frontal lobe deficits
7	Sugihara, 1999 (29)		1	1	0	HDS	–
8	Engel, 2000 (22)		1	0	1	Full NPE	Executive function
9	Forestier, 2001 (20)	9&15	20	0	9	Full NPE	Executive function
10	Kosaka, 2012 (28)	10&11	1	1	0	–	–
11	Tan, 2003 (30)	10&11	1	1	0	–	–
12	Mochizuki, 2004 (31)		1	1	0	–	–
13	Yoshida, 2004 (45)		2	2	0	–	–
14	Gordon, 2006 (4)		11	1	0	–	–
15	Piquard, 2006 (19)	9&15	20	0	17	Full NPE	Memory
16	Norlinah, 2007 (33)		5	0	1	–	Executive function, Memory
17	Tartaglia, 2007 (46)	17,18&23	43	0	0	–	Subcortical frontal systems
18	Murphy, 2008 (18)	17,18&23	18	0	4	Full NPE	–
19	Tomik, 2008 (47)		4	0	1	–	Executive function
20	Zago, 2008 (48)		16	0	0	Token test, RCPM, writing examination	Memory
21	Huey, 2010 (49)		19	0	1	MMSE+FAB	Spelling impairment
22	Gilbert, 2010 (50)		6	0	1	–	Executive function, Memory
23	Grace, 2011 (17)	17,18&23	18	0	7	Full NPE	–
24	Coon, 2012 (27)		3	0	0	MMSE, FBI, FAB	Executive function, Behaviour
25	Amato, 2013 (51)		10	0	0	Stroop Test	–
26	Canu, 2013 (15)	26&30	21	0	10	Full NPE	Executive function, Language
27	Kolind, 2013 (52)	27&32	7	0	0	ACE-R, TMT, VFI	–
28	Lobo, 2013 (23)		1	1	0	Full NPE	–
29	Meoded, 2013 (53)		23	0	6	DRS-2, D-KEFS	Executive function, Behaviour
30	Agosta, 2014 (14)	26&30	24	0	2	Full NPE	Executive function, Language
31	Misumoto, 2015 (54)		41	0	14	ALS-CBS, MMSE, FBI	Executive function, Behaviour
32	Proudfoot, 2015 (55)	27&32	7	0	0	ACE-R+TMT	Executive function
33	Wais, 2016 (56)		36	0	0	–	–

*Studies with confirmed overlap in PLS cases. The extent of overlap was mostly unknown. In order to make an estimate of the total unique cases in each of the three groups (total PLS, CI/BI and FTD), we only counted the largest number in each group of the overlapping studies. The resulting cumulative numbers were used to approximate the frequency of published PLS cases with concomitant FTD or cognitive/behavioural changes.

The number of cases with cognitive and/or behavioural deficits based on the opinion/observation of the author and/or the results of neuropsychological evaluation without fulfilling diagnostic criteria for FTD. FTD: frontotemporal dementia; CI: cognitive impairment; BI: behavioural impairment; NPE: neuropsychological evaluation; HDS: Hasegawa dementia scale; RCPM: Ravens Coloured Progressive Matrices; MMSE: Mini-mental state examination; FAB: Frontal assessment battery; FBI: Frontal behavioural inventory; ACE-R: Addenbrooke's Cognitive Examination Revised; TMT: trail making test; VFI: Verbal Fluency Index; DRS-2: Dementia Rating Scale-2; D-KEFS: Delis-Kaplan Executive Function System; ALS-CBS: ALS Cognitive Behavioural Screen.

Table 3. Pooled weighted effect sizes and heterogeneity statistics of cognitive domains.

Cognitive domains	Hedges' g^a	95% CI ^b	Studies (n)	Total subjects (n)	Heterogeneity between studies within cognitive domain (Q) ^c	$p(Q)^d$	I ² (%) ^e
Delayed verbal memory	1.62	(0.79, 2.45)	1	32	NA	NA	NA
Psychomotor speed	1.47	(1.06, 1.89)	1	39	NA	NA	NA
ACE-R	1.32	(0.64, 1.99)	2	64	0.97	0.32	0%
Fluency	1.24	(0.11, 2.36)	2	58	19.61	0.0002	85%
Letter fluency	1.07	(-0.40, 2.55)	2	58	5.06	0.02	80%
Category fluency	1.59	(-1.46, 4.63)	2	58	14.38	0.0001	93%
Executive functions	0.87	(-0.27, 2.02)	2	58	4.05	0.04	75%
Language	0.39	(-0.23, 1.02)	1	40	NA	NA	NA
Visuoconstructive functions	0.24	(-0.39, 0.88)	1	39	NA	NA	NA
Immediate verbal memory	-0.07	(-0.70, 0.55)	1	39	NA	NA	NA
Attention	-0.21	(-0.72, 0.24)	1	39	NA	NA	NA
Visual memory	0.24	(-0.39, 0.88)	1	39	NA	NA	NA

(a) Effect size is expressed as Hedges' g . A larger value indicate more impairment in PLS patients compared to healthy controls. A small effect size is represented as 0–0.2, a medium effect size as 0.2–0.5 and a large effect size as >0.8. (b) The effect size is significant when zero is not in the 95% confidence interval (95% CI), with a significance level of 0.05 (or 5%). (c) Q: Cochran's Q test is used to assess whether observed differences in results between the individual studies are compatible with chance alone. A high value corresponds with high heterogeneity. A large amount of heterogeneity means poor overlap between the results of the individual studies. (d) A low p -value (>0.05) indicate a large amount of heterogeneity. (e) I²: Test for quantifying inconsistencies between the results of studies. The variability in effect estimates due to heterogeneity is described as a percentage. A percentage of 0–40% indicates that heterogeneity might not be of importance, 30–60%: indicates moderate heterogeneity, 50–90%: indicate substantial heterogeneity and 75–100%: indicates considerable heterogeneity (57).

this is further complicated by the fact that different sets of diagnostic criteria have been proposed. Knowledge of the disease is therefore based on small and possibly heterogeneous cohorts. Despite these issues, PLS is a relatively well-defined clinical syndrome characterised by the progressive loss of UMN. In over half of cases, there is an insidious onset of symptoms in the legs, which slowly and relatively symmetrically ascends to the cervical and bulbar regions. In the remaining patients the disease is characterised by prominent bulbar symptoms with a patchier pattern of progression. Perhaps the most relevant debate with regard to PLS is whether it is a subtype of ALS. The most recent version of the El Escorial criteria considers PLS to be a restricted phenotype of ALS, meaning it is characterised by 'UMN deficits existing in isolation' (32). Keeping it as a subcategory was, however, considered desirable as patients with clinically pure UMN dysfunction have a more benign prognosis (survival >10 years to normal life expectancy). Seemingly contradicting the view of PLS as a pure UMN disorder is the fact that Parkinsonian features, sensory abnormalities and mild frontal lobe dysfunction are seen in $\pm 10\%$ of patients (PLS-plus) (4,20,33). This suggests more widespread involvement of the nervous system, at least in some cases.

Here, we report a case series of PLS patients that went on to develop FTD over the course of the disease. We considered this to be an intriguing finding, given that the commonly used Pringle criteria list cognition and behaviour to be normal in PLS and the Gordon criteria allow mild frontal

impairment, but none lists frank FTD (or dementia) as a disease feature (4,26).

We therefore aimed to provide an estimate of the frequency of dementia as well as to classify the type of dementia observed in PLS. Based on our own retrospective case series and the literature; we found that comorbid dementia occurs in 3% of PLS patients, which is clinically considered to be FTD by most authors. Our review of the literature indicates 22% of patients show cognitive deficits within the spectrum of FTD without fulfilling the formal diagnostic criteria.

We must however emphasise that this is a rough estimate that could be an overestimation as well as underestimation for several reasons: this is a retrospective study based on medical records (potentially incomplete, non-standardised follow-up, varying disease durations), referral bias (leading to more unusual cases presenting at academic centres) and publication bias (lack of publications on normal cognition in PLS).

In our meta-analysis on neuropsychological studies in PLS we could only include four studies and for many cognitive domains data were only available from one study (with a maximum of two studies for a single domain). The meta-analysis shows considerable heterogeneity and large confidence intervals indicating that these results should be interpreted with caution. It is, however, interesting to note that the meta-analysis shows a profile with deficits in the same domains as in the other studies (not included in the meta-analysis) when one simply lists the affected domains. Moreover, these

Table 4. Overview of neuroimaging findings in PLS.

Study (1st author, year, reference)	PLS (n)			Other groups (n)			Imaging Technique	Results	
	Total	co-morbid	FTD	CI/BI	ALS	PSP			Controls
de Koning, 1997 (21)	1	0		1	-	-	-	SPECT	Bilaterally reduced activity in the motor cortex and frontal lobes.
Murphy, 2008 (18)	18	0		4	-	-	7	CT-Perfusion	Increased CBV in the grey matter of the frontal and temporal lobes, basal ganglia and thalamus in the PLS-ci group compared to controls and PLS without cognitive impairment. Increased MTT in the grey and white matter of the frontal, parietal and occipital lobes, basal ganglia and thalamus in the PLS-ci group compared to controls. Cognitive impairment in PLS is associated with haemodynamic compromise.
Pringle, 1992 (26)	8	0		0	-	-	-	MRI (1.5T); structural MRI & [18]FDG PET	Atrophy of the precentral gyrus on structural MRI and diminished glucose uptake in the pericentral cortex on [18]FDG PET.
Kierman, 1994 (44)	8	0		0	11	-	49	MRI (1.5T); Cortical surface measurements	25% reduction in mean cortical surface area of the precentral gyrus and 15% reduction in the frontal lobes in PLS patients compared to ALS and controls (no differences seen between ALS and controls).
Coon, 2012 (27)	3	0		0	-	10	20	MRI (3T); DTI on regions of interest (CST (pons), body of the CC and superior cerebellar peduncle (decussatio))	Reduced FA in superior cerebellar peduncle and corpus callosum in PLS and PSP compared to controls. FA reduction in the corticospinal tracts only seen in PLS.
Kolind, 2013 (52)	7	0		0	23	-	7	MRI (3T); mcDESPOT protocol (in vivo myelin imaging: SPGR, bSSFP, IR-SPGR)	Cerebral myelin water fraction reductions in PLS, but not in controls and ALS.
Canu, 2013 (15)	21	0		10	-	-	35	MRI (3T); DTI	Increased MD and radD in the CST, corpus callosum, brainstem, anterior limb of internal capsule, superior and inferior longitudinal fasciculi, fornix, thalamic radiations, and parietal lobes, bilaterally in PLS-ci compared to PLS without cognitive deficits and controls. Executive and language test scores correlated with extent of WM damage.
Meoded, 2013 (53)	17	0		4	13	-	17	MRI (3T); structural & DTI	Reduced grey matter volume in the right motor cortex in PLS patients. Wide spread white matter involvement in both

(continued)

Study (1st author, year, reference)	PLS (n)		Other groups (n)			Imaging Technique	Results
	Total	co-morbid FTD	CI/BI	ALS	PSP		
Agosta, 2014 (14)	24	0	2	-	-	26	ALS and PLS, but no correlation with cognitive performance. Increased functional connectivity in PLS spanning sensorimotor, medial, and dorsal frontal, insular, and superior temporal regions. Level of functional connectivity within the frontal network is correlated with executive dysfunction. More severe cognitive abnormalities in PLS cases, but test results did not correlate with fMRI results.
Proudfoot, 2015 (55)	7	NR	NR	61		39	MRI (3T); resting state fMRI

PLS: primary lateral sclerosis; FTD: frontotemporal dementia; CI: cognitive impairment; BI: behavioural impairment; ALS: amyotrophic lateral sclerosis; PSP: progressive supranuclear palsy; SPECT: single-photon emission computed tomography; CBV: cerebral blood volume; PLS_{Sci}: PLS with cognitive impairment; MTT: mean transit time; MRI: magnetic resonance imaging; PET: positron emission tomography; CST: corticospinal tract; DTI: diffusion tensor imaging; CC: corpus callosum; FA: fractional anisotropy; SPGR: sagittal spoiled gradient recalled echo; bSSFP: balanced steady state free progression; IR-SPGR: inversion-recovery-prepared SPGR; MD: mean diffusivity; radD: radial diffusivity; WM: white matter.

results are also similar to the neuropsychological findings in the patients from our case series, suggesting consistent findings in the cognitive profile of PLS with deficits in executive function, delayed verbal memory, psychomotor speed and fluency.

It is of note that memory was never affected in isolation, principally or as the most prominent feature, suggesting this is not comorbid Alzheimer's disease. This seems to be reinforced by findings from imaging and neuropathological studies. Imaging studies report abnormalities outside of the motor system, in particular in fronto-temporal brain regions, characterised by atrophy, white matter tract damage, decreased connectivity, metabolism and perfusion. Neuropathological studies report atrophy of frontal and temporal lobes, white matter damage in frontal regions, with preservation of the hippocampus. Intra-neuronal ubiquitin-positive inclusions are observed, in one case also staining for TDP-43, without evidence for amyloid, tau or α -synuclein pathology. Based on these findings it is our opinion comorbid FTD may develop in PLS. This places PLS within the MND-FTD continuum and perhaps provides further evidence for a link to ALS, but also demonstrates that PLS is not a disorder characterised by UMN deficits existing in isolation (restricted phenotype).

These observations also have consequences for the clinical management as it has been shown in ALS that cognitive/behavioural impairment is associated with non-compliance with treatment recommendations, negatively impacts survival and significantly increases care-giver burden (34). We would therefore recommend that PLS patients undergo cognitive screening at regular intervals. In the reported cases, cognitive and behavioural changes developed after years of isolated UMN signs. As very few natural history studies have been performed in PLS and nearly all published studies are cross-sectional, it seems likely that cognitive involvement in PLS is under-reported.

From a scientific point of view characterising PLS as a subtype of ALS may also be very relevant. Survival in ALS is highly variable, ranging from a few months to >15 years, and therefore many studies looking for (genetic) modifiers have been undertaken. In these studies, fast progressing ALS patients are compared to those with slow disease progression. Perhaps including PLS patients in these studies would increase power to find such associations, as these are the slowest progressors. Further study of PLS may also provide insight into the mechanisms underlying the spread of disease as the relatively slow rate of progression might facilitate longitudinal (imaging, biomarker, other) studies, which are often complicated in ALS due to the severity of the disease. Finally, in three of our cases we observed years of slow motor decline that

Table 5. Overview of neuropathological findings in PLS.

Study (1st author, year, reference)	n	Phenotype	Cognitive/behavioral changes	Gross inspection	Motor Cortex (UMN)	Spinal cord and brainstem (LMN)	Frontal and temporal cortices	Miscellaneous (cerebellum, basal ganglia, etc.)	Descending axonal pathways.
Pringle, 1992 (26)	1	PLS . Spinal onset (L leg) late fifties, progressing to the bulbar region, no LMN signs, survival 15 years.	None	Cortical atrophy, esp. central sulcus	Loss of large pyramidal cells, with complete absence of Betz cells, in the precentral gyrus.	Motor nuclei in the brainstem and anterior horn cells in the spinal cord were preserved and did not contain Bunina bodies or skein-like inclusions.	No abnormalities (no neurofibrillary tangles, pick bodies or Lewy bodies)	No abnormalities in basal ganglia including substantia nigra.	Myelin pallor.
Sugihara, 1999 (29)	1	PLS with dementia . Spinal onset (legs), late thirties, progressing to the bulbar region, no LMN signs, survival 17 years.	Moderate dementia (not otherwise specified 10 yrs. after onset) progressing to severe dementia over years.	Diffuse cerebral atrophy, particularly of the frontal lobe and precentral gyrus.	Loss of large pyramidal cells, with complete absence of Betz cells, in the precentral gyrus.	Motor nuclei in the brainstem were unaffected. Anterior horn cells in the spinal cord were well preserved and did not contain Bunina bodies or ubiquitin positive inclusions. Unusual ballooning of dendrites of anterior horn cells.	Senile plaques and neurofibrillary tangles were absent. Tau staining was negative. Severe dissociate gliomyelinique in frontal lobes and to a lesser degree in the temporal lobe.	Atrophy striatum and thalamus. Preservation of the substantia nigra and no evidence of Lewy bodies. Unusual ballooning of dendrites of Purkinje cells.	Intense pyramidal tract degeneration extending down into the spinal cord.
Engel, 2000 (22)	1	PLS with dementia . Spinal onset (L leg) late fifties, progressing to the bulbar region, no LMN signs, survival 12 years.	Concrete thinking, perseveration, and impaired executive function (7 years after onset) without memory or visuospatial impairment.	Mild, generalised atrophy.	Mild loss of neurons in all parts of the cerebral cortex, but not more prominent in the motor cortex compared to other regions.	Spinal cord motor neurons were preserved. Midbrain, pons and medulla were normal.	Beta/A4 amyloid plaques in all layers of the cortex, but most prominent in orbitofrontal cortex.	Loss of neurons and astrocytosis parahippocampal gyri. Neurofibrillary tangles and Hirano bodies were seen in the hippocampus and parahippocampal gyrus.	Bilateral loss of myelinated axons in the corticospinal tracts in the spinal cord, but did not extend rostrally into the brain stem.
Tan, 2003 (30)	1	PLS with dementia . Bulbar onset, mid-seventies, with progression	Dementia not otherwise specified. Imaging showed bilateral	Striking atrophy of the precentral gyrus with marked atrophy	Marked neuronal loss with complete absence of Betz	Lower motor neuron nuclei in the brainstem were well	Pronounced decrease in neuropil area, without obvious	Mild neuronal loss and gliosis was noted in the	Severe degeneration of the corticospinal tract (myelin pallor, gliosis,

(continued)

Study (1st author, year, reference)	n	Phenotype	Cognitive/behavioral changes	Gross inspection	Motor Cortex (UMN)	Spinal cord and brainstem (LMN)	Frontal and temporal cortices	Miscellaneous (cerebellum, basal ganglia, etc.)	Descending axonal pathways.
		of UMN signs to the limbs, no LMN signs, survival 7.5 years.	frontotemporal-predominant cerebral atrophy.	of the frontal and temporal lobes bilaterally.	cells. Ubiquitinated positive round- or crescent-shaped inclusions in the remaining neurons.	preserved. In the spinal cord, the anterior horn cells were well preserved at all cervical, thoracic, lumbar and sacral levels.	neuronal loss and gliosis. No evidence for a tauopathy or synucleinopathy. Ammon's horn, including the dentate granule cells, and amygdaloid nucleus were well preserved.	neostriatum and thalamus.	and scattered macrophages) at the level of the internal capsule, brain stem and spinal cord.
Mochizuki, 2004 (31)	1	PLS with FTD and Parkinsonism. Bulbar onset, late fifties, progression to limbs, rigidity and bradykinesia 5 years after onset, survival 9 years.	Apathetic and severely uncooperative. Imaging: Symmetrical and severe atrophy of frontal and temporal lobes.	Marked atrophy of the frontal and temporal lobes including the precentral and superior temporal gyri. Moderate atrophy of the neostriatum.	Marked neuronal loss in the precentral cortex with complete absence of Betz cells. Ubiquitinated positive but tau-negative intraneuronal inclusions	The hypoglossal nucleus appeared preserved. Anterior horn cells were well preserved.	Neuronal loss and gliosis in the frontal and temporal cortices, most accentuated in the superior temporal cortex. Myelin pallor and gliosis in frontotemporal cortices. The hippocampus and dentate gyrus were relatively preserved. No Lewy bodies, Pick bodies, neurofibrillary tangles, or senile plaques were present.	Moderate neuronal loss and gliosis in the neostriatum. Severe neuronal loss with gliosis of the substantia nigra.	Marked degeneration with gliosis through the internal capsule, medulla oblongata, the lateral and anterior corticospinal tracts of the spinal cord.
Kosaka, 2012 (28)	1	PLS with dementia. Bulbar onset, late seventies, with progression of UMN signs to the limbs, no LMN signs, survival 7 years.	Communication became impossible (language). Frontotemporal cerebral atrophy was evident on MRI.	Atrophy of frontal lobe, especially the precentral gyrus. Additionally there was atrophy of the anterior	Severe neuronal loss with a complete absence of Betz cells. Ubiquitinated positive neuronal cytoplasmic inclusions.	Good preservation of the lower motor neuron nuclei in the brainstem and spinal cord.	Ammon's horn, especially the CA1-subiculum border zone, were unremarkable. No pathological features of tauopathies, including	Neuronal loss was also noted in the neostriatum. The substantia nigra was intact.	Degeneration of the corticospinal tracts in the medulla oblongata and spinal cord with advanced, marked atrophy

(continued)

Table 5. Continued

Study (1st author, year, reference)	n	Phenotype	Cognitive/behavioural changes	Gross inspection	Motor Cortex (UMN)	Spinal cord and brainstem (LMN)	Frontal and temporal cortices	Miscellaneous (cerebellum, basal ganglia, etc.)	Descending axonal pathways.
				Gross inspection and medial temporal lobes.	pTDP-43 positive.		AD or a-synucleinopathies were observed. pTDP-43 positive aggregates.		with dense fibrillary gliosis.

PLS: primary lateral sclerosis; UMN: upper motor neuron; LMN: lower motor neuron; FTD: frontotemporal dementia; pTDP43: phosphorylated 43-kDa TAR DNA-binding protein; AD: Alzheimer's disease.

remained slow although cognitive deterioration was very rapid and severe. That motor and cognitive decline occurred at a very different pace may suggest that these are different pathophysiological processes.

In this study we aimed to characterise the nature of cognitive and behavioural changes in PLS by re-evaluating our own and published cases against current diagnostic criteria for dementia, which show that roughly 3% of PLS patients fulfil criteria for FTD and a further 22% show some degree of frontotemporal impairment. One may, however, also argue that attempting to label these cases within existing classification systems is overly rigid. Perhaps the take home message of this paper is that pathology in PLS first seems to spread within the motor cortex and subsequently to functionally related areas of the brain (frontal and temporal lobes). These observations are similar to findings in ALS, where TDP-43 pathology appears to be propagated along axonal pathways with more frontotemporal involvement in advanced stages (35). Similarly, FTD patients may develop clinical or histopathological evidence of UMN involvement later in the disease, which has been labelled as FTLT-PLS (36–41). Therefore it has been proposed that ALS and FTD should be considered the phenotypic extremes of a spectrum, the MND-FTD continuum. Here, we provide evidence that PLS should also be viewed as part of the MND-FTD continuum with highly similar neuropsychological, imaging and histopathological findings to ALS, but that PLS is not a restricted phenotype (limited to upper motor neurons). Further studies of PLS are relevant to diagnosis, management and prognosis of PLS and may further provide insight into mechanisms underpinning the pathophysiology of the FTD-MND continuum.

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