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Progression in Primary Lateral Sclerosis: a prospective analysis

Mary Kay Floeter, M.D., Ph.D.* and Reversa Mills, M.D.

Electromyography Section National Institutes of Neurological Disorders and Stroke

Abstract

Objective—To determine whether rates and patterns of progression differ among Primary Lateral Sclerosis (PLS) patients.

Methods—50 patients fulfilling clinical criteria for PLS were classified on initial presentation into 3 subtypes: ascending, multifocal, and sporadic paraparesis (PLS-A, PLS-M or PLS-SP). Patients were surveyed annually. Measures of movement speed, clinical rating scales, and transcranial magnetic stimulation were re-assessed at 1–5 years intervals for spread to additional body regions and progression of severity within affected regions.

Results—Forty-seven patients continued to fulfill criteria for PLS over a mean follow-up of 6.6 years, with a mean disease duration > 14 years. PLS-A patients had more predictable progression to additional body regions. Severity progressed faster in newly affected regions followed by stabilization in PLS-A or PLS-M subtypes.

Conclusion—Clinical progression in PLS does not occur steadily, but has periods of faster decline upon spreading to a newly affected region. Classification of PLS patients by subtype is more relevant to predicting the spread of disease, but not progression of severity.

Keywords

primary lateral sclerosis; motor neuron disorders; spasticity; upper motor neuron syndrome

Introduction

Motor neuron disorders consist of several diseases with different degrees of lower motor neuron and corticospinal or upper motor neuron (UMN) degeneration. Primary lateral sclerosis (PLS) lies at one end of the spectrum, with clinical signs of progressive corticospinal dysfunction and clinical sparing of lower motor neurons.^{1, 2} There is no specific diagnostic test for PLS, but clinical criteria were proposed³ that exclude ALS and other disorders known to cause progressive spasticity. PLS is a relatively rare condition, comprising 1 – 4% of patients followed in ALS clinics^{4–7} and only a few reports contain significant numbers of PLS patients.^{4, 5, 7–9} We previously reported that 25 patients who fulfilled the clinical criteria for PLS were heterogeneous, with noted a few subtypes with histories of distinct patterns of symptom progression⁸. In slightly more than half of patients, symptoms began in the legs and slowly ascended (PLS-A), whereas another subtype had varying regions of onset and patterns of symptom progression, which we termed multifocal (PLS-M). We speculated that subtypes may have different underlying etiologies. However, our subtype classification was retrospective, based upon history at initial presentation. In another study reviewing charts of 29 patients whose initial presentation in an ALS clinic was

*For correspondence Mary Kay Floeter M.D. Ph.D. 10 Center Drive, Bld 10 CRC, Room 7-5680 Bethesda MD 20892-1404 floeterm@ninds.nih.gov 301-496-7428 301-402-8796 (fax).

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consistent with PLS, Gordon and colleagues found that 13 patients subsequently developed an upper motor neuron predominant form of ALS, most within four years after onset of symptoms.⁴ The first objective of this study was to determine if the application of the clinical criteria proposed by Pringle, including symptom duration of at least three years³ identified PLS patients who continued to fulfill those criteria when followed prospectively.

A second objective was to determine whether clinical symptoms progressed in a predictable pattern in different subtypes of PLS patients. Survival is a key feature that distinguishes PLS from ALS, with median survival time of more than a decade in PLS.⁵ Although PLS is generally considered to be a progressive disease, it is not known whether progression occurs at a steady pace or if progression continues throughout the lifetime. Progression has at least two components: spread of the disease to different regions of the nervous system and worsening of severity within an affected regions. As has been noted for ALS, patients with PLS will only be identified after disease begins, and future treatments are likely to focus on arresting disease progression. Understanding the time course of disease and symptom progression also has implications for selecting patients appropriate for clinical trials^{10, 11} Among the factors known to affect survival in sporadic ALS, older age and bulbar onset of symptoms have been associated with shorter survival times in numerous studies.^{11–14} Certain phenotypic variants of ALS have been associated with longer survival times.^{15, 16}

Methods

Identification of cohort

Between 2000–2008, medical records from 121 patients referred by physicians to NIH with a presumptive diagnosis of primary lateral sclerosis were reviewed. Patients were excluded from further consideration if the records indicated that symptoms were present for less than 3 years, or if there were additional disorders of the nervous system, a history of spine surgery, denervation on needle EMG studies, a family history of progressive spasticity, or an inability to travel by commercial or personal vehicle. Eighty-three patients underwent a multi-day evaluation visit at the NIH Clinical Center in Bethesda, Maryland under a screening protocol approved by the Institutional Review Board (NCT00015444). The evaluation visit included a history, neurological examination, and diagnostic physiological and serological studies as noted in Table 1. Lumbar punctures, and MRI of the brain, cervical and thoracic spine were obtained if these had not previously been done and reported in the referring records. Transcranial magnetic stimulation (TMS) was carried out to measure resting cortical thresholds and central motor conduction times using a 90-mm round coil with a MagStim 200 stimulator (Jali Med, NJ) in single pulse mode, as previously described.⁸ Patients with implanted pumps or pregnancy were excluded from TMS studies. EMG was carried out if indicated on clinical examination, or if it had not been performed at least three years after symptom onset and within 3 years prior to enrollment. Enrollment EMG studies included those from referring physicians that assessed at least two clinically affected segments.

Patients who fulfilled the diagnostic criteria for PLS proposed by Pringle³ were included in the cohort for prospective follow-up. A detailed history of symptom onset and progression prior to the evaluation visit was used to classify each patient into one of three PLS subtypes - ascending, multifocal, or sporadic spastic paraparesis - as previously described.⁸ Following the initial evaluation visit, questionnaires were mailed annually to patients in the cohort asking about changes in their medical and functional status. Patients who reported progression of symptoms were seen for follow-up visits. Additionally, patients with a relatively short duration of disease (less than 5 years), were generally seen at 1–2 year intervals, and patients with long-standing or stable disease were seen at 3–5 year intervals.

If the follow-up neurological examination showed clinical signs of lower motor dysfunction, an EMG was performed.

Clinical Ratings

On each visit, manual muscle strength was rated for 7 muscles in each limb using the 5-point MRC scale.¹⁷ Ankle spasticity was graded using the modified Ashworth scale¹⁸ and hyperreflexia was graded using the NINDS myotactic reflex scale.¹⁹ Vibratory sensation was assessed using the Rydel-Seiffer tuning fork.²⁰ Measures of gait and finger tapping speed were made on each visit. Three repetitions of timed gait for a distance of 20 feet were videotaped and measured, permitting patients to use their usual assistive devices. Finger tapping rate was measured for three 15-s epochs on a computer keyboard using custom software (LabView, National Instruments). Averages of the 3 trials were used. Spontaneous speech and repetition of standard sounds were videotaped, and the presence or absence of dysarthria was noted.

Clinical history

On initial and follow-up visits patients were queried about the dates when they required the use of canes, walkers, or wheelchairs within and outside their home and whether they had stopped working.

Results

Demographics

Fifty of the 83 patients examined were found to fulfill the proposed diagnostic criteria for PLS³ on initial evaluation. Among the 50 PLS patients, there were 20 women and 30 men, predominantly Caucasian. There were two patients of Hispanic ancestry and one African-American. The mean age at study entry was 54.7 ± 8.2 years; the mean age of symptom onset was 46.9 ± 9.0 years, ranging from age 29 to 65. Only 4 patients were younger than age 35 at the onset of symptoms. At the initial visit, 24 patients were classified as having an ascending pattern of symptom progression, 14 were classified as having a multifocal pattern of progression, and 12 patients had only lower extremity symptoms, either spastic paraparesis or leg monoparesis. We had initially termed such patients as “uncertain”, but in this report will refer to them as PLS-SP, because they resemble the description of “apparently sporadic spastic paraparesis”.²¹ The mean and range of the age of onset and the duration of symptoms prior to entry into the study was similar for the three subtypes (Table 2 and Figure 1, light grey bars).

Clinical Follow-up

Forty patients returned for one or more follow-up visits; ten patients provided follow-up information by questionnaire only. To date, three patients have been lost to follow-up and one patient is known to have died. No autopsy was obtained. The mean length of follow-up after the initial evaluation was 6.6 years (range 1 – 10 years), and the mean duration of disease from the onset of the first symptom was similar for the three groups, approximately 14 years (Table 2). Duration of disease was inversely correlated with age of onset ($r^2 = 0.22$; $p = 0.001$), without differences among the three subtypes.

Misclassification

There were 3 of the 50 patients who fulfilled criteria for PLS on study entry who later developed evidence of a different neurological diagnosis: multiple sclerosis in one patient, multisystem atrophy in another patient, and ALS in the third patient. In two of these three patients, the symptoms had only been present for about three years at the time of the initial

evaluation, and new signs leading to the alternative diagnosis became apparent within 18 months. One of these two patients had presented with a monoparesis of the leg and the other with spasticity of both legs. The patient who developed ALS had a fairly rapid course of progression, from an ambulatory condition to dependent care over the next 3 years. The examination at 5 years from the onset of the first symptoms was typical of sporadic ALS, with marked weakness, muscle atrophy, and widespread acute denervation on the needle EMG examination. The third patient had a 6-year history of progressive gait and balance problems followed by dysarthria. The examination showed relatively mild spasticity and we classified this patient as the multifocal subtype at his initial evaluation. However, by the following year, he had developed a supranuclear gaze palsy, considerable cortical atrophy, and no progression of spasticity.

In addition, two patients who were initially classified as having a sporadic paraparesis or monoparesis at the first visit subsequently developed spasticity in the arms and slowing of speech that was more compatible with an ascending pattern of progression. In the discussion below, the three patients who were later given a different diagnosis are excluded, and the two patients who evolved to an ascending pattern will be included with the ascending subtype. Consequently, the remaining cohort consists of 47 patients, of whom 26 had an ascending pattern, 13 were multifocal, and 8 remained with spastic paraparesis.

Progression of symptoms in PLS – ascending subtype—Patients with the ascending subtype gave a history of steady progression of symptoms from legs to upper extremities to cranial regions. By history, the rate of spread to rostral regions differed among individuals, but generally occurred over several years. The median interval between the onset of leg symptoms and upper extremity symptoms was 3.5 years and the median interval between the onset of leg symptoms and changes in speech was 5.0 years (range 1–15 years). During the prospective follow-up, only 4 of 26 patients exhibited progression of UMN signs to a previously unaffected region. However, within affected regions, the severity of motor impairment increased over time. Finger tapping rates tended to decline relatively quickly in the first few years after developing upper extremity spasticity, but many patients reached an asymptotic level of tapping (Figure 2 A, B). The finger tapping rate rarely declined to less than 2/s. The time to walk 20 feet also tended to increase over time, but was a more variable measure than finger tapping (Figure 3A). Self reported declines in gait were accompanied by greater use of canes and walkers, the use of which increased over time (Figure 4).

Slowing of the rate of speech typically preceded dysarthria. Some speech remained intelligible in all but three patients in the PLS-A group. Other pseudobulbar symptoms included excessive startle, pseudobulbar affect, and choking or coughing when swallowing. However no episodes of aspiration were reported.

Progression of symptoms in PLS – multifocal subtype—The multifocal subtype of PLS had an asymmetric or patchy pattern of symptom spread by history.⁸ Of the 13 patients classified as PLS-M, four had bulbar-onset of symptoms with later limb symptoms, four had an initial progressive hemiparesis fitting with the description of Mills syndrome,^{22, 23} and five had limb-onset symptoms, often mild, that spread to bulbar regions before all limbs were involved. The time course of the spread of symptoms reported prior to enrollment was variable, although several patients had reported long periods of stability between progression of symptoms from one region or limb to another. During the years of prospective follow-up, one patient in the multifocal group died, and one patient developed symptoms in a previously unaffected limb, as will be described below. For about half of the PLS-M patients, symptoms had been present 5 years or less. In these patients, as in the PLS-A patients, severity had a relatively rapid decline over the first few years of follow-up, as seen in the finger tapping rate (Figure 2, middle panels) and timed gait (Figure 3B).

Thereafter, clinical signs were more symmetric and remained relatively stable. Similarly, in patients with relatively recent onset of bulbar symptoms, dysarthria was noted to decline markedly in the first years of follow-up.

The sole PLS-M patient whose symptoms spread to a previously unaffected limb reported that the new symptoms developed over a short period of time following a period of greater than usual physical exertion in the 13th year after symptom onset. When seen the following year, measures of timed gait and finger tapping rate were not greatly changed from enrollment, which had been in the 8th year after disease onset, nor from the follow-up visit in the 12th years after disease onset. Nevertheless, motor strength had declined in the previously strong limb and motor evoked potentials could no longer be elicited, which differed from the finding of normal cortical thresholds and central motor conduction times on the previous visits. EMG showed no active denervation.

Progression of symptoms in PLS – sporadic paraparesis—Of the 12 patients classified as sporadic paraparesis on initial evaluation, only 8 retained this designation during follow-up, as two evolved into PLS-A and two were later diagnosed with other disorders. The mean age of onset in PLS-SP patients was similar to other PLS subtypes (Table 2), although four had symptom onset before age 40. On enrollment all had a fairly symmetric spastic paraparesis. Clinically these patients often had a marked scissoring gait, more so than PLS-A patients, and more commonly had mild to moderate weakness of ankle and hip flexors and mildly reduced vibration in the feet (Table 2). These findings were not associated with abnormalities of tibial somatosensory evoked potentials in the 5 patients in whom they were obtained. Although we did not carry out genetic testing for all known mutations for hereditary spastic paraparesis (HSP), none had a family history. Testing for the SPG-4 mutation had been done in four patients and was negative.

Central motor physiology—Transcranial magnetic stimulation (TMS) to assess cortical thresholds for motor evoked potentials (MEPs) in hand muscles was carried out at enrollment except when contraindicated. In patients in whom MEPs were obtained on the initial evaluation, TMS was repeated on follow-up visits. In the PLS-A group, MEPs in hand muscles were unobtainable in 19 of the 22 patients who were tested. In the other 3 PLS-A patients, thresholds for evoking MEPs and central motor conduction times were initially normal. Two of these patients had no UMN signs above the legs and had originally been classified as PLS-SP. As the clinical spread of symptoms to upper extremities occurred, the thresholds for evoking MEPs became elevated and MEPs were eventually unobtainable.

In the PLS-M group, MEPs were obtainable, with normal or borderline elevated thresholds, from at least one side in 7 of 12 patients tested on the initial visit. Central motor conduction times were normal. This group included the patient who later died and another who was lost to follow-up. TMS was repeated in 4 patients who returned for subsequent testing, and over time cortical thresholds became elevated and MEPs unobtainable. In three of those patients the finger tap rate had also declined; the fourth patient, has been described above, who developed symptoms in an unaffected limb.

In the PLS-SP group, thresholds for evoking MEPs were normal in the 7 of 8 patients tested on initial evaluation. TMS was repeated on subsequent visits in 4 patients and the thresholds for evoking MEPs and central motor conduction times remained normal.

Conclusion

Our findings affirm that the clinical criteria proposed by Pringle and Brown³ are accurate in identifying patients with persistent UMN dysfunction that does not progress to the clinical

picture of classic ALS. All but three of the fifty patients who fulfilled the clinical criteria on entry to the study still met those criteria over a mean follow-up longer than 6 years and disease duration greater 14 years. We also confirm observations made in several retrospective reports describing clinical experience with PLS patients followed in large ALS clinics: that waiting until 4 years after symptoms begin assures greater accuracy in distinguishing PLS patients from ALS patients with upper-motor neuron dominant symptomatology⁴ and that the median duration of survival after the onset of symptoms is longer than 15 years⁵, considerably longer than in sporadic ALS. When PLS patients were classified into subtypes according to their initial presentation, there were no detectable differences in survival, age of onset or disease duration.

Clinical progression includes the spread of symptoms to previously unaffected regions as well as worsening severity. Progression of motor dysfunction differed among the three subtypes primarily in the spread of symptoms. PLS-A patients had a relatively predictable spread of UMN symptoms and signs from one region to the next, with a longer interval between the advance from lower to upper extremities than from upper extremities to cranial regions. We have previously suggested that this tempo would be compatible with a smoothly progressive dying-back axonopathy of the corticospinal tract.⁸ PLS-M patients had a much less predictable spread of symptoms from one region to the next. About half of the patients reported periods of arrest of symptom progression. Interestingly, however, in both PLS-A and PLS-M subtypes, the severity progressed rapidly once symptoms began in a limb. We found that in the first years after an arm or leg became affected, the rate of finger movements or gait had a steep slope of decline. Thereafter, motor function reached a stable plateau in many PLS-A and PLS-M patients. Interestingly, the plateau differed between patients, and thus is not just the minimum function preserved in the absence of corticospinal input. In all but a few patients, transcranial magnetic stimulation showed elevation and loss of corticospinal excitability when the first clinical signs and declines in motor ratings appeared in a limb. The loss of corticospinal excitability was consistent across PLS-A patients. In PLS-M patients occasional exceptions occurred with preserved corticospinal excitability in an impaired limb. Progression in PLS-SP patients could not be characterized, as many exhibited only minor slowing of gait during the follow-up period.

The relationship between clinical measures of progression and the progression of the underlying disease process remains to be established. The way in which disease progresses in PLS will depend on its underlying biology. In ALS, clinical manifestations suggest that disease progresses by contiguous spread from one region to another, independently at the spinal cord and cortical levels.²⁴ Because corticospinal neurons projecting to opposite limb motor neurons are in opposite hemispheres and not contiguous, this mode of spread seems unlikely for PLS-A and PLS-SP, which affect the two sides of the body relatively symmetrically. On the other hand, the PLS-M subtype is heterogeneous, and probably comprises a variety of conditions, some of which, such as the Mills variety,²² may progress in a fashion more compatible with contiguous spread within the cerebral cortex. Clinical measures reflect the progression of severity within affected regions to a great extent. PLS appears to be punctuated by periods of relatively rapid decline in motor function in newly affected regions, as has also been observed in some patients with ALS.²⁵ Thus clinical measurements alone may be an inaccurate indicator of the anatomical spread of the underlying disease. A dissociation between clinical measures and disease progression is particularly pertinent for assessing effects of interventions in clinical trials¹⁰ and highlights the need for biomarkers that measure the extent of central nervous system involvement to complement measures of clinical status.^{26–28}

The hypothesis that clinical subtypes of PLS have different etiologies remains to be carefully evaluated. Several biological processes that have been proposed to cause or

contribute to the development of ALS, including oxidative stress, mitochondrial dysfunction, aggregation of misfolded proteins, defects in axonal transport, growth factor deficiency, glutamate excitotoxicity, and alterations in RNA processing,²⁹ are also candidates for the pathogenesis of PLS. Some of these are likely to have intermittent modes of progression, whereas others are likely to progress in a smooth fashion. Experimental models of ALS also point to a role of non-neuronal cells in modulating disease progression after onset.³⁰ Our finding that both PLS-A and PLS-M subtypes have similar rapid progression in newly affected regions suggests that it is premature to separate these two clinical subtypes in investigations into the etiology of PLS. However, there may be other ways to classify patients that would be related to etiology. For example, differences in axonal and neuronal pathology in PLS patient groups with different etiologies may be detectable in vivo using advanced imaging methods²⁸, or with CSF markers, such as TDP-43³¹.

We did not test whether our PLS patients had mutations in genes known to cause familial ALS,^{32, 33} PLS,^{34, 35} juvenile PLS,³⁶ or hereditary spastic paraplegia.³⁷ Other studies have not found mutations in ALS-2, the gene for juvenile PLS, in patients presenting with adult-onset PLS.³⁸ However, mutations in SPG4 and SPG7, genes that cause HSP, were recently reported in about 10% of Dutch PLS patients presenting with leg spasticity,³⁹ whose clinical description matches our PLS-SP subtype. Thus it is likely that some of our PLS-SP patients represent the sporadic occurrence of HSP. Because PLS-A patients progress through a phase in which only legs are spastic, clinical differentiation is not reliable, and genetic testing for known mutations may be useful to distinguish patients with sporadic HSP from patients with PLS. In our cohort, patients with PLS-SP had slightly reduced vibratory sensation and strength compared to PLS-A patients, but these differences were often subtle, and more apparent on group averages than in individual cases. In the family histories, none of the PLS patients reported family members with PLS or HSP, but other neurodegenerative disorders were seen in some first degree relatives and more distant relatives, a finding that may suggest genetic susceptibilities to neurodegenerative diseases.

Our finding that relatively few PLS patients developed ALS differs from reports showing substantial involvement of lower motor neurons in PLS and progression to ALS.^{4, 9} This difference could reflect selection bias. Unlike previous studies, our cohort of patients were not selected from within a large ALS clinic, but were recruited specifically for research studies in PLS and spasticity. Thus it is likely that they represent a healthier population than in a general neuromuscular clinic. Additionally, PLS patients were specifically excluded if EMG studies showed denervation. The lower motor neuron findings described in other studies included subclinical and transient EMG findings that would not have been appreciated without repeated EMG, which was not part of our routine testing. The classification of patients as “clinically pure PLS” also stipulates normal EMG studies of limb, thoracic and cranial muscles four years after disease onset⁴, which is more extensive than in this study. Non-invasive studies of motor unit number estimation⁴⁰ show substantial preservation of lower motor neurons in hand muscles of PLS patients who fulfilled the clinical criteria of Pringle³ who had a disease duration of greater than three years.

In summary, these data show that progression in PLS is punctuated by periods of more rapid decline and stabilization. Measures of clinical severity do not decline continuously and may not accurately reflect the anatomical extent of the disease process. These findings highlight the need for developing better markers of upper motor neuron degeneration to complement clinical measures as outcomes in clinical trials. Classification of PLS patients into clinical subtypes on presentation may have some limited usefulness for prognostication, primarily for predicting the spread of clinical signs in the PLS-A subtype, and selecting candidates from PLS-SP for genetic testing of HSP genes. The PLS-M subtype of patients had the least

predictable clinical course. However, in the absence of differences in age of onset, duration, survival or risk factors, there is little rationale at this time to search for different etiologies between PLS subtypes.

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Figure 1. Onset and disease duration of individual patients

Horizontal bars indicate the lifespan of each of the 47 PLS patients in the final cohort. The onset of symptoms is indicated by light grey shading, and black shading indicates the time each was followed prospectively for this study. The three subtypes classified by pattern of progression are grouped: ascending (PLS-A), multifocal (PLS-M) and sporadic paraparesis (PLS-SP). Patients lost to follow-up are indicated by (+), and (++) indicates deceased.

Figure 2. Measures of finger tapping speed

Finger tapping speed is plotted separately for the right and left hands for the three PLS subtypes. Symbols represent individual patients, and follow-up visits are connected by lines within the plot. Horizontal dotted lines represent laboratory norms for healthy subjects.

Figure 3. Measures of gait speed

Timed gait for a 20-ft walk, with assistive devices allowed. Symbols represent individual patients and follow-up visits are connected by lines.

Figure 4. Progression in use of gait assistive devices

Use of canes, walkers, and wheelchairs is plotted in PLS-A patients according to the duration of disease. Points representing individual patients who progressed from one device to another over time are interconnected.

Table 1

Diagnostic testing carried out to exclude other disorders in PLS patients

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Imaging studies

Brain MRI

Cervical spine MRI or myelogram

Chest X-ray

EMG

Needle EMG showing no denervation at least 3 years after symptom onset

Serological studies

Serum chemistry, Vitamin B12, and Vitamin E levels

Sedimentation rate

Serology for syphilis, HTLV 1 and 2

Fasting very long-chain fatty acids

Paraneoplastic antibody screen

Serum protein immunofixation

Table 2

Clinical characteristics of the three subtypes of PLS patients

	Ascending (PLS-A) N=26	Multifocal (PLS-M) N=13	Sporadic Paraparesis (PLS-SP) N=8	p value
Age at first symptom	45.4 ± 9.0	48.0 ± 8.5	43.8 ± 8.5	ns
Duration of disease	14.0 ± 5.7	13.8 ± 8.8	13.6 ± 4.3	ns
Length of NIH follow-up	6.5 ± 3.3	6.5 ± 2.9	6.4 ± 2.4	ns
Motor score lower limbs [*] (max = 70)	68.5 ± 1.8	67.0 ± 5.5	53.4 ± 20.5	.0004 ^{**}
Vibration feet [*] (max= 16)	14.2 ± 2.5	13.4 ± 2.9	10.8 ± 5.1	0.034 ^{***}
Vibration index fingers [*] (max= 16)	15.2 ± 1.8	15.2 ± 1.3	15.3 ± 0.9	ns

Data expressed as mean ± SD.

^{*} Sum of scores from both sides;^{**} ANOVA, Significant post hoc contrast: PLS-SP < PLS-A, PLS-M;^{***} ANOVA. Significant post hoc contrast: PLS-SP < PLS-A.