

Amyotrophic Lateral Sclerosis and Frontotemporal Degeneration

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Preface: promoting research in PLS: current knowledge and future challenges

Hiroshi Mitsumoto , Martin R. Turner , all Delegates of the PLS Conference, Senda Ajroud-Driss , Patricia Andres , Jinsy Andrews , Estela Area Gomez , Juan Marcos Solano Atehortua , Suma Babu , Richard Barohn , Peter Bede , Michael Benatar , Sheena Chew , Robin Conwit , Philippe Corcia , Merit Cudkowicz , Frank Davis , Mamede de Carvalho , Vivian Drory , Lauren Elman , Pam Factor-Litvak , Jose Americo M. Fernandes , Dominic Ferrey , Eoin Finegan , John Fink , Mary Kay Floeter , Christina Fournier , Angela Genge , Raghav Govindarajan , Volkan Granit , Georg Haase , Orla Hardiman , Matthew Harms , Ghazala Hayat , Terry Heiman-Patterson , Bryan Hill , Annemarie Hübers , Edward Huey , Omar Jawdat , Osamu Kano , Kristen Kau , Matthew Kiernan , Yasushi Kisanuki , Jerome Kurent , Justin Kwan , Dale Lange , Albert Ludolph , Ian Mackenzie , Giovanni Manfredi , David Marren , and Family, Mitsuya Morita , Jennifer Murphy , Sharon Nations , Bjorn Oskarsson , Sabrina Paganoni , David Pellerin , John Ravits , Kourosh Rezaia , Guy Rouleau , Stephen Scelsa , Teepu Siddique , Nailah Siddique , Vincenzo Silani , Zachary Simmons , Jeffrey Statland , Bryan Traynor , Marka van Blitterswijk , Leonard van den Berg , David Walk , Deborah Warden & James Wymer



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Preface: promoting research in PLS: current knowledge and future challenges

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Primary lateral sclerosis (PLS) is a condition that most neurologists will never personally diagnose. For the estimated several thousand people living with PLS globally, while it may not be life-shortening in comparison to the far commoner amyotrophic lateral sclerosis (ALS), it brings a very high level of life-long disability and discomfort. Neurologists speculate on why PLS is so rare and why we do not have a clear understanding of its pathogenesis, the latter similar to the current position in all neurodegenerative disorders. A quick search on the number of PLS-specific papers in the PubMed database yielded a more than 200-fold difference in comparison to ALS (Figure 1).

Within an ever-broadening clinical syndrome encompassed by the term motor neuron disease (MND), there are perhaps 10% of individuals who

present initially with a clinically upper motor neuron-predominant (UMNp) dysfunction, and with no currently detectable signs of lower motor neuron (LMN) degeneration. While the diagnosis of PLS may be suspected in someone of a younger age (compared to the mean age of onset of ALS), especially in the presence of generalized spasticity, most UMNp cases will eventually progress to clinical LMN involvement within the spectrum of ALS. An unsettling waiting period of several years before making a firm diagnosis of PLS has resulted, causing great frustration for patients and their physicians. With a confirmed diagnosis, those living with PLS are then excluded from the many and growing number of therapeutic trials being undertaken in ALS. As more is understood about PLS, we believe that the disease may hold an important key to

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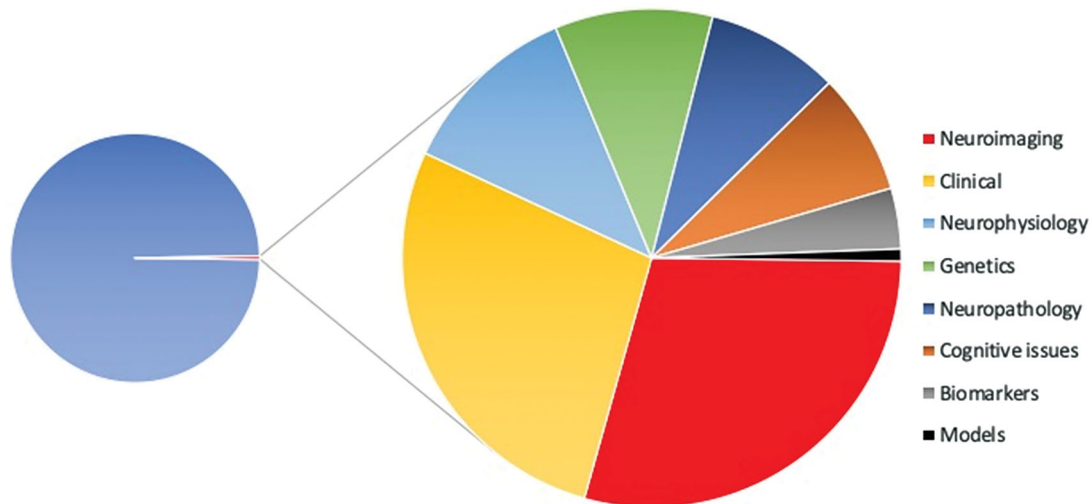


Figure 1. Search of PubMed publications focused on both ALS and PLS. Left panel: ALS versus PLS total. Right panel: PLS publications by main topic of focus.

understanding the pathological mechanisms of MND more widely.

The first international PLS conference was organized by Teepu Siddique (Northwestern University, USA) in 2004 followed by a UK study day for patients and carers held in 2015 by Martin Turner (University of Oxford, UK). Led by Hiroshi Mitsumoto (Columbia University, NY, USA), several volunteers came together to organize a second international conference on PLS: Nazem Atassi (Sanofi-Genzyme, formerly Mass General Hospital, USA), Lauren B. Elman (University of Pennsylvania, USA), Mary Kay Floeter (National Institute of Neurological Diseases and Stroke-NINDS, USA), Sabrina Paganoni (Massachusetts General Hospital, USA), and Teepu Siddique (Northwestern University, USA). They acquired generous meeting support from NINDS (R13 conference grant), Spastic Paraplegia Foundation (SPF), ALS Association, MND Association, Mitsubishi-Tanabe Pharma, and Biogen Pharmaceuticals. Furthermore, Mr. David Marren and family also provided a kind donation to support this conference. The meeting took place on 3–4 May 2019 in Philadelphia, PA, USA. More than 70 individuals from many countries attended the conference, including patient representatives, advocacy groups, clinicians, and pure scientists.

The meeting aims were to: (1) review cutting-edge research, (2) stimulate goal-oriented research, (3) define PLS with greater precision to develop useful diagnostic criteria, and (4) foster an international collaboration for a prospective PLS Registry and biorepository. The Editor of

Amyotrophic Lateral Sclerosis and Frontotemporal Degeneration, Orla Hardiman, agreed to publish this supplement summarizing the discussions from the conference, with the kind support of Biogen Pharmaceuticals and SPF. Hiroshi Mitsumoto took responsibility for editing the supplement and Martin Turner accepted his kind request to serve as coeditor and to take on the separate task of leading an update of the diagnostic criteria for PLS through a consensus among the assembled experts.

The papers that make up this supplement offer a unique, expert-led distillation of the latest scientific and practical understanding of PLS. It covers various topics, including clinical aspects, neuroimaging, neurophysiology, genetics, and neuropathology. The cellular neurobiology of PLS is an emerging and exciting area covered and, furthermore, individualized patient care and management, therapeutic trials, and their outcome measures are also discussed.

We are deeply grateful for all the authors and contributors of the supplement, and the generous support and enthusiasm we have received for the conference and the preparation of this supplement. We thank the conference staff: Georgia Christodoulou, who traveled from Los Angeles to assist with proceedings, and members of the Columbia research team, Madison Gilmore and Marie-France Likanje.

We hope this supplement will catalyze an improved therapeutic landscape for those living with PLS, those yet to be diagnosed, and all those who care for them.