Archives Italiennes de Biologie, 149:1-4, 2011.

Introducing Amyotrophic Lateral Sclerosis

V. SILANI[1], V. MEININGER[2], F. FORNAI[3,4]

[1] Department of Neurology and Laboratory of Neuroscience, "Dino Ferrari" Center, University of Milan, IRCCS Istituto Auxologico Italiano, Milan, Italy;
[2] Centre Référent Maladies Rares, APHP, UPMC, Hôpital de la Salpêtrière, Paris, France;
[3] Department of Human Morphology and Applied Biology, University of Pisa, Italy;
[4] Neurobiology of Movement Disorder Unit INM IRCCS Neuromed, Pozzilli (IS), Italy

ABSTRACT

Introducing ALS at present times leads to re-define the concept of motor neuron selectivity which characterizes this disorder. In fact, multiple systems including skin, liver, and bone marrow are altered in ALS patients. The motor neuron is still the focus of the disorder and the extended pathology did not modify the concept of ALS as a devastating disorder based on motor neuron loss. Nonetheless, the involvement of non-motor neurons as well as areas outside the central nervous system leads to a different perspective to understand the causes, pathophysiology and therapy of ALS. For this reason a specific issue is dedicated to understand whether intersecting basic, pre-clinical and clinical knowledge of ALS may lead to a coherent novel scenario allowing to translate basic findings into clinical practice. Several pre-clinical issues described in this volume appear robust enough to indicate that we should modify a number of approaches when designing future therapeutic strategies. Similarly, novel investigations based on altered cell to cell communication are needed to further progress in understanding amyotrophic lateral sclerosis.

Key words

Charcot • Multi-system degeneration • Frontotemporal dementia • Neuronal inclusions • Misfolded proteins

Amyotrophic lateral sclerosis (ALS) was firstly described as a clinico-pathological entity by Jean Martin Charcot in 1869 and in subsequent articles in 1874. Originally defined as motor system disease primarily affecting the final common motor pathways in the spinal cord and brain, ALS is today recognized to be a complex disorder involving other "non motor" regions of the Central Nervous System (CNS) and organs like the skin, liver, and, more recently, bone marrow (Bossolasco et al, 2010), and the enteric nervous system (Wakabayashi et al., 2010). This new prospective of ALS, a disease with involvement of multiple neuronal and non-neuronal cell populations and also of different organs outside the CNS must have unpredictable consequences on future therapeutical strategies not merely restricted to the rescue of degenerating motoneurons but simultaneously directed to multiple organs.

Since the first description of the disease, the discovery in 1993 that mutations in SOD1 occur in certain families with ALS has been particularly important: several other genes have been isolated in selective families and functional studies have identified possible mechanisms of disease (Rosen et al., 1993). Probably one of the major advancement in the definition of the disease has been the discovery of the frontotemporal involvement: in 2006, the notion that pathological TDP-43 is involved in neurological diseases was proposed when it was discovered to be the major disease protein in frontotemporal

Corresponding Author: Francesco Fornai, MD, PhD, Department of Human Morphology and Applied Biology, University of Pisa, via Roma 55, 56126 Pisa, Italy - Tel.: +39 050 2218611 - Fax: +39 050 2218606 - Email: francesco.fornai@med.unipi.it

dementia (FTD) with ubiquinated inclusions, FTD with motor neuron disease (FTD-MND), and ALS (Neumann et al., 2006). Therefore, a common pathogenesis linked to TDP-43 abnormalities in these disorders has been suggested and further confirmed. This scheme reflects the considerable overlap of clinicopathological features between all neurodegenerative diseases. In fact, ALS and FTD may be situated at different points along one continuous and broad clinicopathological spectrum of a multisystem degeneration. Detailed reviews on the significance of clinical overlap and transition forms between ALS, FTD-MND, and FTD-U have recently been published and the consensus criteria on the diagnosis of frontotemporal cognitive and behavioural syndromes in ALS have emerged (Strong et al., 2009).

The information provided by genetic studies toward the understanding of the pathogenesis of ALS both in sporadic and familiar forms (FALS) has been invaluable, so far. Identification of novel cellular pathways involved in motor neuron degeneration has been achieved, providing potential therapeutic targets. The discovery of novel FALS-associated genes has dramatically enlarged the knowledge of ALS pathogenesis but unfortunately, only one third of the genetic variability in FALS has been explained so far. After identification *TARDBP* and *FUS*, other genes have been reported such as *VCP* (Johnson et al., 2010) and, more recently, the *FUS* homolog *TAF15* (Ticozzi et al., 2011). Family-based linkage studies have identified genes that contribute to FALS. By contrast, the cause of most cases of sporadic ALS remains unknown. Studies other than Genome-wide association studies (GWAS), such as candidate-gene association studies, have been used to identify genetic risk factors involved in sporadic ALS; however, replication of these associations in different populations has often failed. GWAS, which have no a priori hypothesis about disease gene function, have been done in sporadic ALS and have identified several candidate susceptibility genes, including *ITPR2 FGGY*, *DPP6,* and *UNC13A*. However, the odds ratios associated with the risk alleles identified in these studies were low and the results have rarely been replicated in independent studies. Recently two independent GWAS studies in Europe identified a linkage disequilibrium block in the chromosome 9p21locus, suggesting that a variant in this genomic interval might have a role in sporadic ALS and possibly FTD (Laaksovirta et al., 2010; Shatunov et al., 2011). After new gene identification, the consequent engineering of animal models of ALS has been reached, providing essential tools for validating drugs efficacy.

ALS patients inevitably develop disability despite currently available medical therapies. Accordingly, a neuroprotective therapeutical strategy that slows or stops disease progression is an urgent requirement. While there are many promising candidate agents based on laboratory studies, the translation of a novel study intervention into a viable disease-modifying therapy has proven to be extremely difficult to achieve. To date, no agent has been determined to be neuroprotective by either regulatory authorities or physicians. Among the limiting factors are uncertainty as to the aetiology and pathogenesis of cell death in ALS and what precisely to target, a reliable animal model in which to test putative neuroprotective therapies, a method for accurately determining the optimal dose range to employ clinical trials, and a clinical outcome measure that accurately reflects the status of the underlying disease state. There is some optimism that we are beginning to be able to overcome some of these obstacles. While we don't yet know the precise cause of ALS, genes associated with familial cases of the disease have implicated mitochondrial defects and/or proteolytic stress, with increased production or impaired clearance of misfolded proteins being at the heart of the disease. These genes have led to discovery of a host of novel candidate targets for putative neuroprotective agents. While no satisfactory animal model currently exists, it is not unreasonable to consider that gene mutations that have been or will be discovered will eventually increase the number of ALS animal models. Determining the dose levels to study in a clinical trial of a putative neuroprotective agent is currently a problem, but it should be solvable with a concerted effort. Finally, there remains the issue of how to measure the impact of a protective agent on disease progression. The study designs used to date need to be enriched of measures with the assumption that the intervention may have a disease-modifying effect. There is an intensive search for a biomarker of disease progression that could be used as a surrogate marker, but at present, none has been delineated. The need to substantiate the early clinical diagnosis with neurophysiological findings

represents matter of a continuous process with new and updated electrophysiological criteria.

The desperate need of biological markers has been unsuccessful at the moment but with the realisation that ALS has a consistent cerebral component to pathology, notwithstanding marked clinical and prognostic heterogeneity, neuroimaging has been able to generate potential biomarkers of both corticospinal tract and extra-motor cerebral pathology (Agosta et al., 2010). A range of MR modalities have been developed that can potentially track other disease-related cerebral effects, including white matter integrity (diffusion imaging), and metabolite changes using MR spectroscopy), which is highly sensitive but has lacked standardisation and specificity to date.

In the last few years there have been major advances in our understanding of ALS: it must now be determined if some of the mechanisms of disease described above can be finally translated into effective treatment strategies that will improve survival and quality of life for ALS patients.

Summary

The complex and new scenario of an old disease changing features inspired the Meeting held on 23 October 2009 at the IRCCS Neuromed in Pozzilli, Italy. The Meeting covered many new aspects of the disease, tackling the problem from different angles both in the pre-clinical and clinical perspective. The final goal of any study has to be the definition of the most adequate therapy and, for ALS, this is still an unsolved task. In keeping with this, the present special issue encompasses several features which characterize ALS aiming to provide an updated perspective of the disease ranging from the analysis of motor neuron survival due to genetic and acquired environment to relevant clinical outcomes involving disease definition and novel treatment options.

Acknowledgements

We thank IRCCS Neuromed-Ricerca Corrente Finalizzata Min. San. 2011-2013 on “Fisiopatologia e meccanismi di sopravvivenza nel motoneurone” to provide research funds.

References

Agosta F., Chiò A., Cosottini M., De Stefano N., Falini A., Mascalchi M., Rocca M.A., Silani V., Tedeschi G., Filippi M. The present and the future of neuroimaging in amyotrophic lateral sclerosis. *Am. J. Neuroradiol.*, doi: 10.3174/ajnr.A2043.

Bossolasco P., Cova L., Calzarossa C., Servida F., Mencacci N.E., Onida F., Polli E., Lambertenghi Deliliers G., Silani V. Widespread metalloproteinase alterations in amyotrophic lateral sclerosis. *J. Mol. Med.*, **88**: 553-564, 2010.

Johnson J.O., Mandrioli J., Benatar M., Abramzon Y., Van Deerlin V.M., Trojanowski J.Q., Gibbs J.R., Brunetti M., Gronka S., Wuu J., Ding J., McCluskey L., Martinez-Lage M., Falcone D., Hernandez D.G., Arepalli S., Chong S., Schymick J.C., Rothstein J., Landi F., Wang Y.D., Calvo A., Mora G., Sabatelli M., Monsurrò M.R., Battistini S., Salvi F., Spataro R., Sola P., Borghero G.; ITALSGEN Consortium, Galassi G., Scholz S.W., Taylor J.P., Restagno G., Chiò A., Traynor B.J. Exome sequencing reveals VCP mutatioons as a cause of familial ALS. *Neuron*, **68**: 857-864, 2010.

Laaksovirta H., Peuralinna T., Schymick J.C., Scholz S.W., Lai S.L., Myllykangas L., Sulkava R., Jansson L., Hernandez D.G., Gibbs J.R., Nalls M.A., Heckerman D., Tienari P.J., Traynor B.J. Chromosome 9p21 in amyotrophic lateral sclerosis in Finland: a genome-wide association study. *Lancet Neurol.*, **9**: 978-985, 2010.

Neumann M., Sampathu D.M., Kwong L.K., Truax A.C., Micsenyi M.C., Chou T.T., Bruce J., Schuck T., Grossman M., Clark C.M., McCluskey L.F., Miller B.L., Masliah E., Mackenzie I.R., Feldman H., Feiden W., Kretzschmar H.A., Trojanowski J.Q., Lee V.M. Ubiquitinated TDP-43 in frontotemporal lobar degeneration and amyotrophic lateral sclerosis. *Science*, **314**: 130-133, 2006.

Rosen D.R., Siddique T., Patterson D., Figlewicz D.A., Sapp P., Hentati A., Donaldson D., Goto J., O’Regan J.P., Deng H.X., Rahmani Z., Krizus A., McKenna-Yasek D., Cayabyab A., Gaston S.M., Berger R., Tanzi R.E., Halperin J.J., Herzfeldt B., Van den Bergh R., Hung W.Y., Bird T., Deng G., Mulder D. W., Smyth C., Laing N.G., Soriano E., Pericak-Vance M.A., Haines J., Rouleau G.A., Gusella J.S., Horvitz H.R, Brown R.H. Jr. Mutations in Cu/Zn superoxide dismutase gene are associated with familial amyotrophic lateral sclerosis. *Nature*, **362**: 59-62, 1993.

Shatunov A., Mok K., Newhouse S., Weale M.E., Smith B., Vance C., Johnson L., Veldink J.H.,

Van Es M., Van Den Berg L., Robberecht W., van Damme P., Hardiman O., Farmer A.E., Lewis C.M., Butler W.L., Abel O., Andersen P.M., Fogh I., Silani V., Chiò A., Traynor B.J., Melki J., Meininger V., Landers J.E., McGuffin P., Glass J.D., Pall H, Leigh PN, Hardy J, Brown R.H. Jr., Powell J.F., Orrell R.W, Morrison K.E., Shaw P.J., Shaw C.E., Al-Chalabi A. Chromosome 9p21.2 in sporadic amyotrophic lateral sclerosis in the UK and seven other countries: a genome-wide association study. *Lancet Neurol*., **9**: 986-994, 2010.

Strong M.J., Grace G.M., Freedman M., Lomen-Hoerth C., Woolley S., Goldstein L.H., Murphy J., Shoesmith C., Rosenfeld J., Leigh P.N., Bruijn L., Ince P., Figlewicz D. Consensus criteria for the diagnosis of frontotemporal cognitive and behavioural syndromes in amyotrophic lateral sclerosis. *Amyotroph. Lateral Scler*., **10**: 131-146, 2009.

Ticozzi N., Vance C., LeClerc A.L., Keagle P., Glass J.D., McKenna-Yasek D.M., Sapp P.C., Silani V., Bosco D.A., Shaw C.E., Brown R.H. Jr, Landers J.E. Mutational Analysis reveals the FUS homolog *TAF15* as a candidate gene for familial amyotrophic lateral sclerosis. *Am. J. Med. Genet. Part B Neuropsychiat. Genet*., doi: 10.1002/ajmg.b.31158.

Wakabayashi K., Mori F., Tanji K., Orimo S., Takahashi H. Involvement of the peripheral nervous system in synucleinopathies, tauopathies and other neurodegenerative proteinopathies of the brain. *Acta Neuropathol*., **120**: 1-12, 2010.