Clinical trial readiness for Calpainopathies

Date: September 15 - 17, 2017
Workshop number: 233
Location: Naarden, The Netherlands

Organizers:
Dr. Isabelle Richard (Evry, France), Dr. J. Andoni Urtizberea (Hendaye, France)

Description of the workshop:
The 233rd ENMC workshop entitled “Clinical trial readiness for Calpainopathies” took place from the 15th to the 17th of September 2017 in Naarden, The Netherlands. A multidisciplinary group of 20 persons from 9 countries (France, Germany, Italy, Denmark, Spain, UK, Japan, Brazil and USA) attended the workshop, including 18 clinical and basic science researchers, and two representatives of patient organizations (Associazione Italiana Calpaina 3, Italy and Coalition to Cure Calpain3, USA).

Background:
Calpainopathy or Limb-Girdle Muscular Dystrophy type 2A is due to mutations in CAPN3, a gene encoding an enzyme named calpain 3. This disease is characterized by slowly progressive muscle weakness affecting selectively the musculature of both girdles. There is no treatment for this disease to date. The emergence of novel therapeutic approaches in the field, like gene therapy, has prompted a much awaited discussion between physicians and researchers about the readiness for clinical trials in calpainopathy.

Discussions and achievements:
After an invigorating historical introduction of the topic by Michel Fardeau, the discussion was divided in 5 sessions, encompassing the following topics: 1) Overview of LGMD2A 2) Patient landscape, databases and registries 3) Outcomes measures including natural history of LGMD2A 4) CAPN3 function, models and therapies; biomarkers and 5) workplan for future actions.

In most countries, it appears that LGMD2A is usually the most frequent form of LGMD. Most of the patients present a classical clinical phenotype with a significant, selective involvement of the posterior compartment of the thigh. Unusual presentations of calpainopathy with pseudo-metabolic or important joint contractures, benign forms or non-conventional mode of transmission (autosomal dominant) have been presented and discussed. Respiratory function may be compromised in a proportion of patients. Although it seems to be rarely severe in LGMD2A, assessment and monitoring of respiratory function should be part of the standards of care. Cardiac issues are rarely observed and are probably coincidental. The disease course is usually slow. Muscle imaging could be as well used as a monitoring tool to follow the progression of affected muscles.

Diagnosis is achieved by gene sequencing. The molecular diagnosis of calpainopathy is complicated by the fact that, in a number of cases, the protein level is preserved in Western Blot or when a decrease is observed, it may be caused by secondary deficiencies. A possible correlation between protein expression – type of mutation and disease severity has been reported but collaborative studies are required for a full understanding of the mechanism. Experts highlighted the value of muscle biopsies for diagnosis and research purposes. Despite the introduction of Next Generation Sequencing in the
diagnostic algorithm of primary calpainopathy, biopsy analysis can be of tremendous help for a better understanding of the correlation between protein expression and clinical course.

The discussion pointed out that for now, no specific clinical outcomes have been clearly defined, highlighting the need of additional data on the clinical evolution of LGMD2A in preparation of future clinical trials. The importance of patient registries whatever their scope and process (more centralized, patient self-reported or not) was also discussed. LGMD2A specific registries exist in few countries and there is an international database handled by Coalition to cure Calpain3. A global European database would be of great interest while a global worldwide register seems out of reach at this point due to divergent policies regarding data protection across the Atlantic.

In the last session, and among other therapeutic options, an AAV-mediated gene transfer approach was presented with promising results. Nevertheless, it is clear that more fundamental studies are still needed at a time when the function itself of calpain 3 is not fully understood yet.

Participants:
Alicia Alonso (Barcelona, Spain); Robert-Yves Carlier (Garches, France); Vincent Carson (Lancaster, PA, USA); Bruno Eymard (Paris, France); Michel Fardeau (Paris, France); Marie-Laurence Gourlay (Evry, France); Michela Guglieri (Newcastle, UK); Jean-Yves Hogrel (Paris, France); Bruno Kullmann (Milan, Italy); Jennifer Levy-Keiser (USA); William Lostal (Evry, France); Yasuko Ono (Tokyo, Japan); Helene Prigent (Garches, France); Isabelle Richard (Evry, France); Amets Saenz (San Sebastian, Spain); Claudio Semplicini (Padova, Italy); J. Andoni Urtizberea (Hendaye, France); Mariz Vainzof (Sao Paulo, Brazil); John Vissing (Copenhagen, Denmark); Maggie Walter (Munich, Germany).

A full report of this ENMC workshop will be published in Neuromuscular Disorders.