271st ENMC International Workshop

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Title: Third ENMC meeting on SBMA: Towards a unifying effort to fight Kennedy's disease
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Background and aims of the workshop

On October 20-22, 2023, in the Netherlands, 26 scientists from academia, healthcare, and industry representing 11 countries (Denmark, France, Germany, Israel, Italy, Portugal, Spain, Switzerland, United Kingdom, USA, and Japan) gathered with four patient representatives from AIMAK, KDUK, and KDA. This workshop, led by Maria Pennuto, Gianni Sorarù, Linda Greensmith, and Pierre-Francois Pradat, focused on advancements in research and clinical practices related to Kennedy's Disease (KD), also known as Spinal and Bulbar Muscular Atrophy (SBMA).

SBMA, a rare X-linked neuromuscular disorder, primarily affects males due to a mutation in the Androgen Receptor (*AR*) gene, which binds the male sex hormones, androgens. This mutation causes slowly progressive muscle fatigue, weakness, and atrophy, especially in the limbs, face, and neck, and can lead to extra-neurological symptoms such as breast enlargement and metabolic issues. In the last years, significant progress has been made in understanding SBMA's pathological mechanisms and its clinical spectrum, as well as in developing tools for clinical evaluation - all vital for conducting therapeutic trials.

The workshop aimed to consolidate knowledge and collaborations among experts and patient representatives, align on trial designs and outcome measures, and promote participative medicine, thereby enhancing the chances of developing effective treatments for SBMA.

Preclinical Research

The first part of the workshop focused on preclinical research, where research scientists shared their latest findings, including results on new molecular mechanisms leading to toxicity, as well as alternative strategies for intervention in SBMA patients. It has now been several years since SBMA began to be viewed as a neuromuscular disorder rather than a pure motor neuron disease. In support of this view, new findings presented at this workshop pointed towards the importance of investigating both the neuronal and muscular counterparts of the motor unit in SBMA preclinical studies, ultimately suggesting muscles as a valuable target for novel therapeutic intervention.

Scientists also presented new findings on novel mechanisms of action of the AR and how mutations in the AR lead to toxicity. Several new angles of investigation and novel approaches were presented, including i) an assessment of the biophysical properties of the AR, with results showing that the AR has a decreased ability to change its physical status when mutated, ultimately leading to aberrant function of AR; ii) an investigation of the direct downstream targets of the AR in a single-molecule fashion in normal and mutated ARs; and iii) a study of the aberrant equilibrium between the proteasome and autophagy in mutated AR conditions, which ultimately impairs the clearance of damaged proteins and toxic aggregates.

Novel therapeutic strategies were proposed during the workshop, including strategies aimed at modulating AR activity by targeting of AR co-activators, AR synthesis, post-translational modifications and degradation and clearance of mutant toxic AR. In addition, several tools to deliver therapeutic interventions were proposed and discussed. Further studies on this matter need to be performed to find the best strategy to be undertaken.

The scientific discussion during this session highlighted the urgent need for the discovery of new biomarkers of disease and target engagement, as these will be crucial for the understanding the impact of any therapeutic intervention on disease in both animal models as well as patients in clinical trials.

Clinical Research

Updates from the clinical research session revealed that progress is being made in identifying biomarkers and disease outcome measures for SBMA, such as muscle MRI and biochemical measurement of Troponin T, which are crucial for detecting disease progression and efficacy in clinical trials.

Discussions regarding symptom management highlighted the need for multidisciplinary management and evidence-based guidelines for SBMA. This is particularly relevant for the potential benefits of exercise, which has proven to be safe for patients with neuromuscular diseases. Moreover, participants acknowledged the importance of patient-reported outcomes alongside performance assessments.

New trial designs benefit from advances in genetics and treatment strategies, yet SBMA's rarity and heterogeneity complicate patient stratification and recruitment. The workshop attendees agreed that International protocol sharing and standard of care implementation could accelerate trial implementation. Clinical trials could be streamlined by reducing in-person visits and utilizing local centres, along with remote monitoring techniques and patient-reported outcome measure.

The International SBMA Registry, leveraging the Italian National Registry, is gathering data on around 700 patients from 9 countries, aiding epidemiological understanding, biomarker discovery, and clinical trial recruitment.

Impact on the patients and their families

The final day of the workshop featured a session from the patients' perspective, highlighting their diagnostic experiences, daily life with the disease, and aspirations for a cure. A critical issue raised by the patient representatives and patient associations was the medical community's limited awareness of SBMA, leading to diagnostic delays and inadequate management. Patient associations were agreed to be a vital support for those with SBMA as well as strong liaisons with healthcare professionals and researchers.

Next steps

The workshop concluded with a commitment to reinforce ongoing collaborations, emphasizing the importance of multidisciplinary approaches. Future international events are planned in collaboration with patient associations to better disseminate scientific findings to the SBMA community and involve them in the research process.

Short-term objectives include strengthening international data collection and collaborating with patients to establish guidelines that streamline clinical trials. Long-term goals focus on deepening the understanding of KD's pathology to develop targeted treatments.

A full report will be published in Neuromuscular Disorders (PDF).