The role of brain dystrophin in muscular dystrophy; **Implications for clinical care and translational research**

NOVEMBER 2019

THE ROLE OF BRAIN DYSTROPHIN IN MUSCULAR DYSTROPHY

- **Location** Hoofddorp, The Netherlands
- **Title** 249th ENMC workshop on The role of brain dystrophin in muscular dystrophy: implications for clinical care and translational research
- **Date** 29 November - 1 December 2019
- **Organisers** Dr J. Hendriksen (the Netherlands), Dr. M. Thangarajh (USA), Dr H.E. Kan (the Netherlands) and Prof F. Muntoni (UK)
- **Workshop report by** The European Neuromuscular Centre (ENMC)
- **Participants** Dr Y. Aoki (Japan), Dr P. Collin (the Netherlands), Dr M. Colvin (USA), Dr N Doorenweerd (the Netherlands), Prof A. Ferlini (Italy), Dr A. Goyenvalle (France), Dr J. Hendriksen (the Netherlands), Dr J. Hoskin (UK), Dr H.E. Kan (the Netherlands), Mr F. Lamy (France), Dr K. Maresh (UK), Prof F. Muntoni (UK), Dr E.H. Niks (the Netherlands), Prof U. Schara (Germany), Prof D. Skuse (UK), Prof V. Straub (UK), Prof S. Takeda (Japan), Dr M. Thangarajh (USA), Dr N. Truba (USA), Prof S. Tyagarajan (Switzerland), Dr C. Vaillend (France), Dr M. van Putten (the Netherlands), Prof J. Vissing (Denmark), Dr E. Vroom (the Netherlands).

Thanks to the European NeuroMuscular Centre, last November a workshop on the role of brain dystrophin in muscular dystrophy; Implications for clinical care and translational research took place. The ENMC kindly gave us permission to publish the lay report of this meeting on the WDAD website. The workshop report of the 249th ENMC workshop on brain dystrophin is now online as journal pre-proof. The DOI of the article is: 10.1016/j.nmd.2020.08.357.

This lay report is currently translated into several languages including German, French, Italian, Danish and Dutch. We generously thank the ENMC for hosting this workshop and the translators of the report: Prof U Schara, Dr C. Vaillend, Prof. A. Ferlini, Prof J. Vissing, Dr M. van Putten and Dr N. Doorenweerd for their general contribution to making information more accessible to the global muscular dystrophy community.

Source: https://www.enmc.org/download/the-role-of-brain-dystrophin-in-muscular-dystrophy-implications-for-clinical-care-and-translational-research/

The 249th ENMC workshop was held from the 29th of November to the 1st of December 2019, and brought together 24 representatives of patients, neuromuscular, neuropsychology, and psychiatry experts from Europe, the United States, and Japan. The topic of this workshop was the brain comorbidities in Duchenne and Becker muscular dystrophies (DMD and BMD respectively).

The molecular basis of the brain involvement present in patients with DMD and BMD is increasingly being unravelled. We now appreciate that cognitive, behavioural, and psychiatric symptoms may affect up to approximately 50% of individuals with DMD, and recent evidence indicates a high prevalence of brain comorbidities in patients with BMD, as well. This finding is related to the deficiency of multiple dystrophin variants, also called isoforms, during brain development in different brain locations.

These central nervous system (CNS) symptoms have important clinical implication for the affected individuals and their full participation in life; more importantly, these CNS symptoms are often not well recognised and managed adequately in clinical settings. Moreover they are not addressed by the genetic therapies under development, as these treatment approaches mainly aim to improve skeletal and heart muscle function and do not target the brain of the patients.

EXPERIMENTAL AND CLINICAL TOPICS DISCUSSED

Regarding experimental and preclinical aspects, we discussed:

- The genetic regulation of the various forms of dystrophin in the brain, and their distribution in different brain regions, drawing attention to similarities and differences between the human and mouse models;
- Which are proteins that interact with the different forms of dystrophin in different areas of the brain;
- Which are the behavioural and structural correlates in different mouse models with genetic changes that differently disrupt the different forms of dystrophin in the brain and how does this change over time;
- The effect of restoring different forms of dystrophin after birth using different genetic therapies.

Regarding the clinical topics, we discussed:

- What is the frequency and severity of brain related symptoms in DMD/BMD;
- What can brain imaging telling us about the features of dystrophin deficiency (both in DMD and BMD patients));
- What can the human symptoms teach us to direct the deeper assessment of the mdx mouse models deficient in the various forms of dystrophin, and vice-versa, what are emerging features from the studies in the mice that should be explored further in patients;
- What are the recommended standards of care for the assessment and management of CNS symptoms; v) what are the treatment options to improve the outcome of DMD/BMD patients in whom neuropsychiatric symptoms occur?

Source: https://www.enmc.org/download/the-role-of-brain-dystrophin-in-muscular-dystrophy-implications-for-clinical-care-and-translational-research/

The representatives from patient advocacy groups' elegantly articulated how common and significant the cognitive symptoms are in affected individuals, and highlighted the extra burden for the families that these symptoms cause. Too often the neuromuscular specialists concentrate exclusively on the muscle and heart complications, with little attention to the early diagnosis and intervention for the brain problems. It is encouraging that at least some of the behavioural aspects of DMD can be improved by medication, but these therapies are not systematically utilised; and much more research to investigate the underlying mechanisms for the CNS symptoms is required, in order to find more specific interventions.

The participants' agreed to collaborate further regarding patient registries, experimental models, and clinical studies on these topics and specific working groups were formed to address specific areas. This collaboration will also be facilitated by the recently awarded European Union H2020 grant to address the **Br**ain **I**nvolvement i**N** **D**ystrophinopathies (**BIND**) which will begin in January 2020. A full report of the conference is currently under preparation and will be published in Neuromuscular Disorders.

CONTACT

MANAGING DIRECTOR

Dr. A. Breukel
ENMC

+31 35 54 80 482 / +31 631901121
breukel@enmc.org

OPERATIONAL MANAGER

A. Zittersteijn
ENMC

+31 35 54 80 481 / +31 651838224
enmc@enmc.org

The European Neuromuscular Centre (ENMC) was founded in 1992 by a group of European patient associations that dedicated itself to bring leading researchers and clinicians from all over the world together. To achieve this goal, ENMC applies a concept unique in the scientific world, which consists of organising and financing workshops on application basis. Topics of the workshops vary from outcome measures, clinical trial readiness and preclinical studies, to diagnosis and care for all neuromuscular diseases.

Source: https://www.enmc.org/download/the-role-of-brain-dystrophin-in-muscular-dystrophy-implications-for-clinical-care-and-translational-research/