1. Introduction

This workshop hosted a group of 19 clinicians and basic scientist from 5 countries (France, USA, Canada, Denmark and The Netherlands). Recent research developments and possible collaboration in advancing therapies for oculopharyngeal muscular dystrophy (OPMD), a late onset, rare and progressive neurodegeneration disorder were discussed in this meeting.

The disease is caused by alanine expansion mutations in the gene encoding for poly(A)-binding protein nuclear 1 (PABPN1), resulting in accumulation of mutant PABPN1 in the cell nucleus and the formation of insoluble aggregates. Therefore, OPMD is categorized together with neurodegenerative disorders that are caused by single amino acid repeats. While the genetic cause for those disorders is often recognized, the molecular basis for symptoms is still obscure. PABPN1 is ubiquitously expressed and it is not known why symptoms develop only after midlife and initially only in subsets of skeletal muscles [1,2].

While the genetic cause for OPMD was reported in 1998 and good surgical treatments exist for major early symptoms, there are currently no medical options for the more general skeletal muscle involvement, no validated biomarkers and no clinical severity scale.

We suggest that therapeutic developments in OPMD could be boosted by international coordination and collaborations between clinical and research groups. The 191st ENMC-OPMD workshop represents the initial step.

In common with many other neuromuscular disorders, OPMD is a rare disorder, with the exception of a few founder populations like the French-Canadians and Bukhara Jews. The prevalence of OPMD outside these populations has only been estimated in France (1:100,000). Also for this reason, it is highly relevant that OPMD research should be coordinated as an international effort.

The objectives of this workshop were to provide an update on both the clinical and basic research aspects of OPMD and to promote more collaborative actions. Key topics were explored, including clinical diagnostic difficulties and clinical approaches for OPMD (Sessions 1), recent advances in understanding PABPN1 function (Sessions 2 and 3), molecular mechanisms in OPMD (Sessions 4 and 5), molecular and cellular models for OPMD and therapeutic approaches (Session 6 and 7) and finally, the need for coordinated and collaborative research (Session 8) in order to promote translational research.

2. Session 1: Introduction to OPMD

2.1. Nomenclature for OPMD – recommendation

A definitive nomenclature to describe PABPN1 mutations in OPMD is lacking. This has stemmed largely from the original description of PABPN1 mutations as...
pure (GCG) expansions [2]. It is now recognized that in OPMD patients a broad spectrum of mutations have been reported. All mutations consist of cryptic triplet repeat (GCN) codon expansions, or point mutations, that always code for alanine and lead to a lengthening of the wildtype (GCN)10 N-terminal domain. The length of the alanine expansions ranges from +1 to +7. We suggest that a new ENMC Nomenclature for PABPN1 mutations should be adopted and this would be (GCN)11–17/Ala11–17 for the patient mutations, and (GCN)10/Ala10 for the wild type allele. When available, it is encouraged that the full sequence of the mutation be reported.

In addition, we recommend a uniform nomenclature for the intra nuclear inclusions found in OPMD and in different cellular and animal models. These should be referred to as aggregates.

2.2. Clinical aspects of OPMD

In OPMD primary symptoms are observed in the oropharyngeal (dysphagia), levator palpebrea (eyelid ptosis), and proximal limb muscles limiting greatly the applicability of previously validated muscle performance scales or quality of life assessment to grade its severity. Bernard Brais’s (McGill, Canada) group reported an unpublished study performed between 2004 and 2006 on 43 OPMD patients and 13 controls to define clinical, biochemical and dysphagia outcome measures that could distinguish cases according to the severity of symptoms. OPMD patients were separated into groups with either “classical” or severe presentation if they had early proximal limb symptomatic weakness. Severe cases were defined according to the age-dependent criteria (Table 1). This pilot study showed that average CK and serum myoglobin levels where higher in the more severe cases compare to “classical” with a similar age distribution (CK: 756 compare to 357 U/L; and myoglobin 183 compare to 66 µg/L). However, both fall when patients become less active as the condition progresses, limiting their use as biomarkers.

Two Dutch OPMD cases were reported by Baziel van Engelen (Radboud University Nijmegen, The Netherlands) with brain (frontal dementia) and minimal muscle involvement (except for ptosis) and an unusual genotype: one compound heterozygote for a recessive (GCN)11/Ala11 and a dominant (GCN)15/Ala15 mutation, and one patient with the longest expansion reported to date (GCN)17/Ala17 mutation. MRI of the brain showed nonspecific sub cortical white matter abnormalities. These cases led to a discussion on the full clinical spectrum of OPMD. All agree that except in homozygote cases for two dominant mutations [3], dementia was not a frequent finding in an OPMD cohort. Based on the above mentioned cases and the few OPMD cases described to date with dementia that carry predominantly the larger mutations or are compound heterozygotes [4,5]. Therefore, because of lack of evidence at this time, all agreed that dementia should not be seen as a more frequently associated feature of OPMD or even place patients at a higher risk for their age.

Baziel van Engelen also reported on a phenotype-genotype study comparing clinical, histological, genetic and transcriptome data in 39 Dutch OPMD patients, 6 pre-symptomatic OPMD patients and 12 controls. From this they concluded the following: considering that PABPN1 regulates genome-wide mRNA expression, they suggest that progressive changes in genome-wide mRNA expression but not aggregate formation lead to OPMD.

Guy Rouleau (Université de Montréal, Canada) addressed the lack of a complete description of the full clinical spectrum of OPMD. He underlined that the association of peripheral neuropathy and dementia in OPMD are still anecdotal and will require the study of larger multiple mutation sizes cohorts to be settled. The influence of mutation size on clinical severity will also require a larger study to be settled prior to the validation of an OPMD severity scale. At this time, the only large cohort base study on penetrance of the disease, was the one published by his group that reported the following decade penetrance for (GCN)13/Ala13 carriers: 1% (<40 years), 6% (40–49), 31% (50–59), 63% (60–69), 99% (>69) (Brais et al. S70–S74). Reporting on the Quebec experience with upper oesophageal sphincter dilatation with Maloney bougies did not lead to benefits past three months post-procedure in most cases for the dysphagia [6], whereas surgery has been shown to bring lasting benefits with low post-operative morbidity and mortality [7]. With the recent use of synthetic material frontal suspension for eyelid ptosis correction under local anesthesia has become the golden standard.

2.3. Clinical scales for OPMD

Bernard Brais reported that combined MRC values for deltoid and psoas muscles (the easiest muscles to assess using a Chatillon dynamometer K-MSC-500 (Ametek)), was correlated with the severity status as expected considering that proximal weakness was a key variable in defining severity (Table 1). However, a fair amount of inter observer variability was documented supporting that the use of such a dynamometer requires observer

<table>
<thead>
<tr>
<th>Criteriaa</th>
<th>Age of onset</th>
</tr>
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<tbody>
<tr>
<td>Limitation of the ocular movements accompanied by lower limbs weakness (MRC score ≤5, on a scale of 0–5)</td>
<td>&lt;60 years</td>
</tr>
<tr>
<td>Proximal weakness of upper limbs MRC ≤5</td>
<td>&lt;70 years</td>
</tr>
<tr>
<td>Proximal weakness of lower limbs MRC ≤3</td>
<td>≤70 years</td>
</tr>
<tr>
<td>Proximal weakness of lower limbs MRC ≤4</td>
<td>≤60 years</td>
</tr>
<tr>
<td>Proximal weakness of lower limbs MRC ≤5</td>
<td>&lt;50 years</td>
</tr>
</tbody>
</table>

a To meet one of the criteria was sufficient to be labeled affected by a severe form of OPMD. Number of patients is 43.
training in the context of a trial. Quality of life and symptomatic dysphagia questionnaires did not discriminate between severity groups. Lastly, a dysphagia testing assay, using a nuclear medicine swallowing test, was very sensitive to evaluate OPMD associated dysphagia [8]. This test consisted in the swallowing of a standard 20 ml of water which contains 0.5–1.0 mCi of Tc-99m sulfur isotope that has been thicken to honey texture. Images are taken every 15 s for 2–5 min and computer analyses speed and completeness of swallowing. These results suggest that it is a good test monitoring response to treatment and scoring the dysphagia. It is recommended to include this test, with some variations, as universal measure for OPMD severity and as part of any OPMD trial protocol.

MRI has been reported recently by various groups as a possible unbiased means to assess OMPD severity. Baziel van Engelen reported that muscle quality can be quantified with MRI. An MRI study of lower limbs on 8 Dutch cases supports the conclusion of a Swiss group [9] that quantitative MRI using T1 weighted images correlate well with the degree of clinical involvement. These studies show that fatty infiltration preceded clinical features, including muscle weakness measured by the MRC or hand held dynamometry. The value of MRI to assess disease onset and progression was discussed. However it is still unclear which muscles are the most pertinent for MRI in OPMD. In particular, it was discussed if the tongue, knowing it is involved in early symptomatic cases, could be explored by imagery as an anatomical structure to address evolution or even local treatment. Baziel van Engelen discussed the many generic measures of outcome that have been validated in other neuromuscular disorders; but deplored that for OPMD a validated specific severity assessment protocol is still unavailable. It was agreed in this workshop that in order to initiate drug trials, a validated clinical scale for OPMD must be developed that could include adapted generic quality of life scales such as INQol or SF36.

Clear criteria have been reported for muscle weakness and for swallowing but not for drooping eyelids. It is recommended to apply these criteria as part of OPMD trial protocols.

2.4. Clinical approaches in OPMD and considerations for future trials

John Visning (Rigshospitalet Copenhagen University, Denmark) reviewed the choice of the appropriate ophthalmological treatment by discussing 14 Danish cases of OPMD. He stressed the importance of raising the awareness by ophthalmologists of OPMD as a cause of late-onset ptosis, because the aponeurotic approach (before a diagnosis of OPMD had been reached) showed a poor functional and cosmetic result, whereas a subsequent frontal brow suspension was successful in the Danish OPMD population. It was suggested that in French-Canada the diagnosis was probably made earlier because of the larger families, the much higher prevalence and the greater awareness of the clinicians. All groups confirmed that there was no obvious cardiac involvement in OPMD.

Jean Lacau St Guily (Hôpital Tenon, Paris, France) reported ongoing phase 1 clinical trials of myoblast autograft therapy associated with cricopharyngeal (CP) myotomy in OPMD patients with dysphagia. The protocols involved grafting of autologous myoblasts isolated from limb muscles into the pharyngeal muscles with the aim of improving both swallowing and contractile function. A prospective trial in 12 patients with OPMD and dysphagia who underwent both myoblast autograft and CP myotomy (national PHRC) was achieved with good tolerance; after completion of this first trial, another trial with 15 patients is currently running. These trials are firstly safety studies of both autograft and surgical procedures, but the autograft may improve the swallowing disorder and life-threatening complications in OPMD induced by aspiration and weight loss, resulting in a potential individual benefit. Myotomy of the CP upper esophageal sphincter was carried out at the same time as the myoblast transplantation into the dystrophic pharyngeal muscles, since this surgery is already validated to lead to a significant although often transient improvement in swallowing. The advantage of this autograft strategy is that focal treatment is indicated in OPMD and there is no risk of rejection. To date the procedure had been well tolerated with no adverse or unexpected events. Significant improvements in swallowing and QoL scores have been observed, and a further case-controlled study is planned. Several issues should be addressed to improve the design of clinical trials in OPMD:

- Tools to follow the grafted myoblasts in the pharyngeal musculature.
- Evidence of increased physiological strength of the grafted muscle.
- Long-term follow-up (beyond 2 years) to assess effects on the high rate of post-myotomy secondary deterioration.
- Comparative trial designs with grafted and non-grafted arms. Further research is also required to improve assessment of muscle morphology, muscle function, swallowing processes, and magnetic resonance imaging in the muscles of the pharynx.

3. Session 2: PABPN1 function

PABPN1 is the gene mutated in OPMD, and, therefore, to understand how the mutated PABPN1 protein leads to muscle weakness in OPMD it is important to explore the perturbation of its normal function caused by the expansion of its polyalanine domain. In this section we
discussed recent studies on PABPN1’s functions, with an emphasis on skeletal muscle specificity, and how the polyalanine expansions and protein aggregation contribute to the pathophysiology.

Though PABPN1 is ubiquitously expressed, OPMD mutations clearly have a more dramatic impact on skeletal muscle than other tissues raising the question as to why this tissue is more vulnerable to mutated PABPN1. Recent work has started to explore the role of PABPN1 in myogenesis to establish whether OPMD mutations influence some components of this fundamental process that could be a key to disease pathophysiology. Myoblasts from OPMD pharyngeal and limb muscle have statistically less differentiation potential than age-matched control group [10], suggesting that expression of mutant PABPN1 could negatively impact muscle regeneration. Though dominant PABPN1 mutations have been largely thought to cause pathology through a gain of function mechanism [11] there is growing evidence that a loss of function of PABPN1 through decreased availability of soluble PABPN1 could play a role in the disease [12–15]. To explore this possibility and the role of PABPN1 in myogenesis, Grace Pavlath and Anita Corbett (Emory University, USA) have examined the consequences of PABPN1 depletion in primary mouse myoblasts from extraocular, pharyngeal and limb muscles [16]. PABPN1 knockdown significantly decreased cell proliferation and myoblast differentiation during myogenesis in vitro. At the molecular level, PABPN1 depletion in myoblasts led to a shortening of mRNA poly(A) tails, demonstrating the molecular function of PABPN1 in polyadenylation control in a mammalian muscle cell. Depletion of PABPN1 also caused nuclear accumulation of poly(A) RNA, confirming that PABPN1 directly or indirectly, perhaps by shortening tail length, is required for proper poly(A) RNA export from the nucleus. Whether such molecular defects are detected in muscle tissue affected in patients remains to be determined as one previous study that measured poly(A) tail lengths in myoblast lines derived from heterozygotes and one homozygote case showed no significant difference in poly(A) tail length [17].

Given the possibility that a loss of PABPN1 function could contribute to muscle pathology in OPMD, one potential approach would be to enhance the function of the existing pool of PABPN1 protein. To achieve such a goal would require an understanding of how PABPN1 function is regulated in muscle cells. Corbett and Pavlath presented initial studies aimed at determining whether PABPN1 could be regulated by post-translational modification. This work reveals that PABPN1 is phosphorylated in muscle cells. Furthermore, the phosphorylation status of PABPN1 changes over the course of myogenesis as does bulk poly(A) tail length, suggesting that phosphorylation of PABPN1 could regulate its function in polyadenylation. Future studies will define the role of specific modified residues within PABPN1.

Although progress has been made in defining the role of PABPN1 in the muscle cells affected in OPMD, how perturbation of myogenesis contributes to OPMD pathophysiology still needs to be established. A specific subset of skeletal muscles may be more sensitive to PABPN1 depletion, which could begin to explain why these specific muscles are most affected in the disease.

Elenora de Klerk (Leiden University Medical Center, The Netherlands) presented a role for PABPN1 in dictating the site of 3′-end cleavage and polyadenylation. A decrease in PABPN1 expression was found to cause a genome-wide shortening of the 3′ untranslated region, and thus a more frequent use of the proximal alternative cleavage site [18]. This often causes an increase in the accumulation of transcripts. Such a preference in the proximal alternative cleavage site usage was also identified in the OPMD mouse model A17.1 PABPN1 [15,18]. In myogenic cell cultures expressing mutant PABPN1 at similar levels to wild-type PABPN1 a correlation was found between levels of soluble PABPN1 and a preference for the proximal alternative cleavage site usage [15]. This study suggests that in fused muscle cells an increase in proximal alternative cleavage site usage results from decrease levels of soluble PABPN1, which is more pronounced in cells expressing mutant PABPN1. However, how this contributes to the disease still needs to be explored.

4. Session 3: Molecular mechanisms in OPMD

For the development of specific and targeted therapeutic approaches for OPMD it is highly relevant to identify the molecular mechanisms underlying the disease. Three complementary research approaches have been discussed: genome-wide expression profiles, genetics and cell biology.

4.1. Cross-species transcriptome studies in OPMD

To start addressing the molecular mechanisms underlying OPMD, a powerful approach consisting in the comparison of OPMD transcriptomes in patients and in OPMD animal models was undertaken in a collaborative efforts [19] and was presented by Vered Raz (Leiden University Medical Center, The Netherlands). The rationale behind this approach was 1—OPMD is a rare disease and obtaining sufficient patient muscles for expression studies in not trivial. Therefore, comparing expression profiles between OPMD models and patients’ material will enable to increase confidence in the variation observed. 2—Expression of mutant PABPN1 in different model systems and at different expression levels may trigger different molecular mechanisms. With a cross-species study it would be possible to identify common molecular pathways that are consistently affected between models and patients, and deregulation in
the different species would point out to the most relevant deregulated pathways. Mouse and Drosophila models of OPMD were used in addition to patient biopsies and the deregulation of the ubiquitin–proteasome system (UPS) was identified as the predominant molecular defect in OPMD [20,21]. Vered Raz also reported that whereas the UPS was consistently deregulated in all species, other pathways involved in protein degradation, autophagy and lysosome were not, thus reinforcing the specific role of the UPS in OPMD. She also reported that in a myotube model of OPMD, PABPN1–Ala16 had a slower turn-over than normal PABPN1 [22], proposing a model where decreased proteasome activity during aging would contribute to slower turn-over of alanine expanded-PABPN1 leading to the formation of aggregates which in turn would further affect proteasome activity through the recruitment of UPS components.

In a fly model of OPMD, presented by Aymeric Chartier (IGH, Montpellier, France), expression of mutant PABPN1 in muscles causes a progressive muscle weakness and degeneration and can be recognized by functional approaches (flight and wing positioning) and microscopy techniques [23]. This model also reproduces the formation of PABPN1 nuclear aggregates. This model is amenable to genetic screens which have revealed the implication of several pathways including poly(A) tail length control, potentially relevant to the abnormal alternative polyadenylation site cleavage discussed above. The fly model has also been useful to explore the ubiquitin–proteasome dysfunction and perform successful drug screens [22,25].

4.2. The role of aggregates in OPMD pathogenesis

Janet Davies (Kings College London, UK) who has developed a mouse model of OPMD together with David Rubinsztein [26] asked whether oral treatment of OPMD mice with anti-aggregation drugs would reduce OPMD symptoms. She has identified three drugs, doxycycline, trehalose and cystamine that show beneficial effects (reviewed in: [27]). The protein anti-aggregation activity of these drugs as the basis for their positive effect remained uncertain.

Several lines of evidences suggest that the presence of PABPN1 aggregates per se might not be pathogenic, whereas the process of aggregate formation might be [13]. Consistent with this, Aida Abu Baker (University of Montréal, Canada) reported on one of her earlier study showing that the toxic form of expanded-PABPN1 in a cell model of OPMD was soluble [12]. PABPN1 toxic form might indeed correspond to intermediate steps in the formation of aggregates, such as oligomers. Oligomer-like structures of PABPN1 have been identified using life cell imaging techniques [13]. Abu Baker also reported that additional pathways that are affected in OPMD cell models such as histone acetylation and the Wnt signaling pathway could be targeted by drugs.

5. Session 4: OPMD and aging

In OPMD symptoms are typically developed only during midlife, albeit the ubiquitous expression of PABPN1. In humans, aging is associated with a gradual decline in muscle mass and quality, which has been referred to by many authors as sarcopenia. These changes first become evident in the fifth decade of life at about the same time as the clinical onset of OPMD. Therefore, it was noted in this meeting that it is important to take into consideration aging-regulated modifications when studying late-onset disorders, like OPMD. Gillian Butler-Browne (Institut de Myologie, Paris, France) discussed the question as to whether OPMD onset appears because of aging or OPMD pathophysiology is due to premature aging? Muscle aging is multifactorial and is associated with deregulation of many of the cellular processes necessary to maintain muscle homeostasis. Recently, it has been shown that both the proteasome activity and autophagy become down regulated with age leading to an accumulation of damaged proteins and damaged mitochondria [28]. Deregulation of the proteasome is also most prominent in OPMD [19]. In OPMD there is the continual production of mutant aggregated PABPN1, but during the first 4 decades of life this protein has no evidence of toxicity. Vered Raz discussed the possibility that age-regulated changes in PABPN1 levels may contribute to symptoms, and the consequence of an age-regulated decline in protein homeostasis in OPMD has been discussed. It was suggested that aging-associated modifications may tip the balance to trigger OPMD pathogenesis.

6. Session 5: Animal and cellular models in OPMD

The aim of this session was to have an overview of the different cell and animal models available for OPMD and to emphasize on what they can teach us with respect to disease pathogenesis, molecular mechanisms and to develop therapeutic approaches.

6.1. Mouse models to OPMD

Capucine Trollet (Institut de Myologie, Paris, France) presented a detailed physiological and histological analyses on the muscles of the A17.1 mice [29] and compared this mouse model to human OPMD muscles, based on histological analysis on muscle biopsies. She highlighted several similarities including INIs, muscle fiber atrophy, affected and less-affected muscles, pathological features (such as splitting fibers, vacuoles and internalized nuclei) and fibrosis.
Janet Davies described the rationale behind the development of this transgenic muscle-specific OPMD mouse model: (1) the assumption of a toxic gain of function of mutated PABPN1; (2) tissue specific pathology and phenotype; (3) progressive disease; (4) onset of the disease.

In addition to the muscle-specific over expression of expanded-PABPN1 in the A17.1 mouse, three mouse models were generated by ubiquitous expression of Ala13- or Ala17- PABPN1 [30,31]. More recently, ubiquitous expression of expanded-PABPN1 in mice was generated with an inducible expression system by Mankodi et al. [31]. In this model muscle pathology is induced by over expression of expanded-PABPN1. This model enables to study of the effect of expanded-PABPN1 in adulthood and aging.

6.2. A Drosophila model to OPMD

In the Drosophila OPMD model developed in the laboratory of Martine Simonelig a mutated mammalian Ala17 PABPN1 is expressed specifically in muscles using a (Mhc: myosin heavy chain)-Gal4/UAS system [23]. A genome wide genetic screen has been made using this model to identify suppressor genes capable of suppressing the wing posture phenotype that should reveal molecular pathways involved in OPMD pathophysiology and highlight potential therapeutic strategies.

6.3. A nematode model to OPMD

Christian Neri (INSERM, Paris, France) developed a nematode OPMD model where Ala13 PABPN1 is co-expressed with a nuclear-localized GFP specifically in body wall muscle cells using the myo3 promoter [32]. Nematodes movements were quantified and revealed that the OPMD nematode model showed defects in motility together with a progressive loss of muscle cells. These defects were specifically induced by mutant PABPN1 expression while expression of wild type PABPN1 showed no movements’ defects. This model has revealed A role for the sirtuin-FOXO longevity pathways was studied in this model [32].

6.4. Cell models

Capucine Trollet summarized the cell models that have been generated. Aggregation has been intensively studied in non-muscle mitotic cells using transient transfection with high overexpression of expanded-PABPN1, and often induces cell death (reviewed in: [11]). More recently, PABPN1 was studies in low overexpression conditions. In this condition, cell death is not induced by expanded-PABPN1 expression, but pre-aggregated structures of expanded-PABPN1 were reported [13]. As pre-aggregated structures were not found in wild type PABPN1 expressing cells, it was suggested that pre-aggregated structures could represent toxic structures [13].

More relevant to OPMD is the effect of expanded-PABPN1 in muscle cells. High over expression of expanded-PABPN1 or knock-down of PABPN1 causes myogenic defects [16,31]. In myotube cultures that were stably transfected expanded-PABPN1 at low over expression levels myogenic defected were not found [14]. Due to the effect of PABPN1 expression levels on protein aggregation, it is, as yet, not conclusive how expanded-PABPN1 causes myogenic defects.

7. Session 6: From bench to therapy in OPMD

The animal model systems for OPMD are useful to develop therapeutic strategies for OPMD (summarized in Table 2).

7.1. Screens for drug discovery in OPMD

Christian Neri presented drug-screening data (+2000 compounds tested) in nematodes based on automated whole-animal fluorescence-based imaging at high resolution. These data suggest that PABPN1 nematodes are useful to identify active compound families. Christian Neri also shared knowledge acquired with Huntington’s disease research networks, and he emphasized the value of performing drug discovery within the frame of molecular-profiling/disease-modeling studies. He suggests this would provide strong guidance to target drugs and to speed up trials.

7.2. Drug discovery in an OPMD mouse model

George Dickson (London) provided an overview of potential gene and drug therapy strategies for OPMD including knockdown of mutant PABPN1, over expression or augmentation of wild-type PABPN1, boosting of muscle physiology, reduction and dispersal of Table 2

| Overview of potential strategies towards a drug, gene or cell therapy for OPMD. |
|---|---|
| Therapeutic aim | Therapeutic strategies |
| Knockdown of mutPABPN1 | RNA interference (shRNA/siRNA) |
| | Antisense inhibition |
| | Gene disruption (e.g. ZFNs) |
| | Vectorise & overexpress PABPN1 |
| | Express pathway enzymes (e.g. PAP) |
| Augmentation of wtPABPN1 Activity | Inhibition of myostatin |
| Muscle “boosting”/atrophy compensation | Activation of mIGF |
| | Ubiquitin proteasome system modulation |
| | Apoptosis modulation |
| | FOXO pathway inhibitors |
| INI Reduction or Dispersal | Small drugs (e.g. guanabenz, doxycyclin, cystamine) |
| | Intrabody strategies (VHH-3F5) |
| Muscle precursor cell autograft | Myoblasts, mesoangioblasts, etc. |
aggregates, and stem or precursor cell autografting (Table 3). He presented studies evaluating prevention of muscle atrophy and recovery of locomotor function in the context of the A17.1 and A10 OPMD mouse models following gene therapies for (i) PABPN1 knockdown and replacement, (ii) myostatin inhibition and (iii) expression of lama antibody (intabody) that specifically binds PABPN1 [13]. In addition, building on the prior studies of Martine Simonelig in the Drosophila-OPMD model [24], Dickson presented a study on the chronic effect of using the authorized medicine, guanabenz (Wytensin) to treat the A17.1 OPMD mouse.

8. Closing session: Discussion and plans for future collaborative efforts

Despite progress on many levels, the group concluded that there are still important unanswered questions: Does the size of the mutation influence disease severity? What is the natural history of OPMD? What would be the best clinical outcomes to follow OPMD patients in therapeutic trials? Is MRI a valuable tool to follow disease? Can we identify valuable biomarkers for OPMD?

The participants concluded that defining appropriate outcome measures for OPMD drug trials should be a top international priority. Furthermore, the need for an OPMD registry, standardized clinical outcome measures and development of non-invasive biomarkers are required as a preliminary step prior to setting up such trials.

As for a registry, the, participants agreed to encourage groups to follow the parameters listed in Table 3 in patients to generate a first multicenter data set to serve as a building block for such an international registry.

List of participants

- Dr. A. Abu Baker, Canada
- Prof. B. Brais, Canada
- Dr. J.F. Briand, France
- Dr. G.S. Butler Browne, France
- Dr. A. Chartier, France
- Dr. A. Corbett, USA
- Dr. J. Davies, United Kingdom
- Prof. G. Dickson, United Kingdom
- Prof. B. van Engelen, The Netherlands
- Dr. T. Gidaro, France
- Dr. E. de Klerk, The Netherlands
- Prof. J. Lacau St. Guily, France
- Dr. C. Neri, France
- Dr. G. Pavlath, USA
- Dr. V. Raz, The Netherlands
- Dr. G. Rouleau, Canada
- Dr. M. Simonelig, France
- Dr. C. Trollet, France
- Prof. J. Vissing, Denmark

Acknowledgements

This workshop was made possible by the financial support of the European Neuromuscular Centre (ENMC) and its main sponsors: Muskelsvindfonden (Denmark), Association Française contre les Myopathies (France), Deutsche Gesellschaft für Muskelkrankheit (Germany), Telethon Foundation (Italy), Schweizerische Stiftung für die Erforschung der Muskelkrankheiten (Switzerland), Princes Beatrice Spierfonds (The Netherlands), Spierziekten Nederland (The Netherlands), Muscular Dystrophy Campaign (UK), – Finnish Neuromuscular Association (Finland), and a special generous support of the Dutch ZonMw.

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