1. Introduction

A workshop entitled Illuminating CNS and Cognitive Issues in Myotonic Dystrophy, sponsored by the Marigold Foundation, was held in Toronto in May, 2012. Participants included 24 clinicians, scientists and patient representatives from six countries and from diverse fields of myotonic dystrophy type 1 (DM1) research. The purpose was to promote a more accurate understanding of DM1 pathology [1], to highlight specific areas and focus efforts on understanding CNS dysfunction as a critical area of investigation for DM1 research, with the overarching aim of reducing the heavy burden that CNS dysfunction places on DM1 patients and families.

DM CNS dysfunction and cognitive impairment is a challenging area of study due to the disease's complex pathophysiology and the diversity and variability of the clinical presentation, coupled with our limited understanding of brain function. Cognitive function in myotonic dystrophy type 2 (DM2) has similarities, though reportedly less acute than in DM1. A discussion-based forum explored numerous topics summarized below, and yielded a consensus list of action items and research areas needing development.

1.1. Theme 1: Understanding the DM patient experience; Chair: Dr. Housman

While the majority of DM1 research to date has focused on the neuromuscular aspects of the disease, DM1 patients and families report that the CNS and cognitive issues are often the most troubling and difficult to deal with. Symptoms are typically progressive, highly variable, and include executive dysfunction, cognitive impairment, apathy, fatigue/over-sleeping, often leading to severe difficulties in maintaining employment and active social participation. CNS-based aspects of DM1 must be better characterized in terms of causation for therapeutic CNS targets to be identified. It was suggested that much can be learned from research on other diseases (like Huntington’s disease and Alzheimer’s disease) that have ongoing clinical trials directed at alleviating CNS symptoms and deficits.

1.2. Theme 2: Perspective of the European DM CNS Task Force; Chair: Dr. Meola

The accomplishments of the European DM CNS Task Force meetings (2010, 2011) highlighted the importance of understanding DM as a brain disorder. DM1 shows deficits in executive functions and particularly in childhood DM1 onset there is IQ deficit problems and attention deficit hyperactivity disorders. Although there are many CNS-related symptoms, little is known about the neuropathology of DM. Despite this gap in knowledge, it is known that there are tau abnormalities and neurofibrillary tangles in DM patients that differ from neurological disorders exhibiting similar brain pathology to brains of individuals affected with Alzheimer’s disease, and yet also show some similarity to other neurological diseases, such as fronto temporal dementia.

DM1 appears as a “continuum” of different clinical subtypes, particularly in the childhood-onset cases. It was agreed that there should be a further systematic breakdown in classification when diagnosing children (congenital, early onset childhood, classical childhood, and juvenile), with distinct ages-at-onset. Each form should also have a severity measurement, from mild to severe,
allowing clinicians and researchers to more easily correlate symptoms with imaging results, genotype (repeat lengths), and other biomarkers or health indexes.

The pathomolecular mechanisms underlying the neurological dysfunctions are not clear. The study of potential biomarkers is equally as difficult, as the availability of tissues from pathological sites is either lacking or are end-stage. Knowing which, if any, biomarkers could be assessed early-on in disease (optimally pre-symptomatic) could aid in management and the type of therapy offered. Biomarkers could potentially differentiate between the various DM1 subtypes, given that the absolute length of the CTG repeat is not always a good indicator of disease onset, progression or severity.

It was agreed that more longitudinal studies must be performed to better understand and correlate the diverse symptoms in DM1 cases, especially childhood onset. Such studies have begun, however this approach must be more universally instigated. It was also noted that registries for adult patients are generally good but adding children to registries usually involves a considerable lag time. More accurate registries would permit longitudinal studies, which is necessary for raising funds for therapeutic research and testing.

1.3. Theme 3: Neurodevelopmental, neurofunctional, or neurodegenerative?; Chair: Dr. Housman

It is unclear whether CNS dysfunction in DM1 patients is neurodevelopmental, neurofunctional, and/or neurodegenerative. There is currently insufficient clinical evidence (due to a paucity of longitudinal studies) to conclude that DM1 is in part neurodegenerative. Progressive dysfunction of the CNS could potentially account for cognitive decline, rather than true neurodegeneration per se. Most agreed that childhood onset cases are likely to show CNS dysfunction due to neurodevelopmental issues, which could lead to functional deficits. There is a need for a greater research focus on the CNS in DM to illuminate these issues.

1.4. Theme 4: Characterizing cognition in DM1 patients; Chair: Dr. Winblad

Most DM1 individuals have aspects of non-verbal disability, apathy, and fatigue, although the degree of these deficits varies. Important issues that need to be addressed are: the causes of each cognitive defect; what the deficits entail; and, most importantly, the consequences of each deficit to the individual in terms of quality of life. A better understanding of each cause would lead to more appropriate interventions.

We need to define the cognitive domains relevant to each onset age, and identify the best tests to characterize them. For example, are IQ tests important to use in adult-onset patients? Longitudinal observational studies could be more useful in such assessments. Will a more substantial natural history of each patient help assess patient cognitive impairment? Many tests used to assess DM1 patient cognition were developed for other disorders. A more accurate and DM1-targeted set of standardized tests are needed for comparability and a more effective definition of deficits faced by DM1 patients. It is important to reduce both administrator bias as well as user burden, as patients can become fatigued by lengthy tests. Convincing drug companies to focus on medicinal interventions for CNS issues will require reliable, validated, and reproducible tests that indicate cognitive aspects as ‘targets’.

1.5. Theme 5: Neuroimaging in DM1/DM2; Chair: Dr. Kornblum

Neuroimaging in DM1 individuals and models can determine if morphological changes occur during the disease course. The most frequently applied techniques are morphological MRIs, with a few studies using functional MRI [2]. There appears to be, depending upon the MRI techniques and various clinical parameters, anything from diffuse brain atrophy to white matter affection, as well as global or focal gray matter reduction. DM2 patients have shown similar but less pronounced changes. Myotonic dystrophies are predominant white matter diseases, linking them to the growing group of brain disconnection disorders [3].

The correlation of structural brain abnormalities to clinical and/or genetic findings is highly variable [3–5] – indicating a need for further research. To this end, the need for brain banks and tissue repositories was reiterated. Additional longitudinal neuroimaging studies will permit determining the natural history of the CNS affection and help differentiate between developmental defects, neurodegeneration, and age-related lesions. Standardization of software or, at the very least of analysis methods, is an important consideration – allowing comparison of imaging and clinical data on CNS affection across centers. A comparison of the longitudinal imaging with neuropsychological data will help correlate any decline in cognitive functioning with a change in brain morphology. Creation of an animal model displaying matching clinical presentations of the DM CNS attributes would prove invaluable in explore this uncharted territory.

1.6. Theme 6: Molecular basis of CNS dysfunction; Chairs: Drs. Ranum and Swanson

DM is known predominantly as an RNA gain-of-function disorder, with RNA sequestering proteins from their normal functions. One of the sequestered proteins, MBNL1, regulates alternative splicing and within the CNS, the altered splicing patterns of certain genes may cause a neurological developmental disorder, in that the neonatal splicing pattern persists through development. Mice knocked-out for Mbnl2, which is also sequestered by the expanded CUG, show a clear CNS presentation [6], and its gene targets are now
an obvious source to further understanding DM CNS pathology. Therapeutic targets include the expanded DM RNA, the somatic expansion of the DNA, and various mis-regulated transcripts. It is unclear which genes are mis-spliced within the CNS in patients, and which of these leads to specific CNS attributes. Further research including laser capture micro-dissection for specific cell types as well as tissue banking will clarify the role of mis-splicing within the CNS. With this data, targeted therapies directed at alleviating CNS symptoms may be possible. Moreover, the utility of DM mouse models for mirroring the DM CNS dysfunction must be more fully studied.

A further challenge is that mis-splicing itself may not contribute directly to the pathology of the disease in every tissue. Given this, therapies targeting mis-splicing should be evaluated with caution, and only after strong links between pathophysiology and splicing defects are established for each symptom and/or tissue. With this in mind, therapeutics designed for molecular targets other than mis-splicing may be a more viable approach to treatment. Additionally, any therapies that are currently being designed and tested based upon their efficacy to treat muscle symptoms should also be monitored for any potential effects on the CNS.

The additional complexity of repeat-associated non-ATG (RAN) translation [7,8] should also be considered when assessing DM pathogenesis. RAN translation occurs when expanded RNA transcripts, are translated into homopolymeric proteins in the absence of an ATG initiation codon. This process produces polyGln proteins in myoblasts, muscles and blood of DM1 patients as well as in the cardiac myocytes and leukocytes of DM1 transgenic mice [7]. Although some RAN translation proteins, such as polyGln, are known to be toxic in other disorders (e.g., Huntington’s disease) it is not yet clear if these unusual proteins are pathogenic in DM1. Further studies on the toxicity of RAN translation products are warranted and may illuminate new pathways for therapy.

1.7. Theme 7: Disease models of myotonic dystrophy; Chair: Dr. Gomez-Pereira

There are many DM mouse models available that recreate some aspects of DM in humans [9]. Given the strong consensus that more neuroimaging must be conducted in DM1 patients to better understand potential correlations between repeat length, RNA/protein deficits, and CNS structural abnormalities, the topic of structural studies in appropriate mouse models was discussed. DM1 mouse models are variable and have not been fully characterized, either in terms of complete analogy to the human condition or in comparison to each other. A more extensive characterization of both humans and existing DM1 mouse models is needed to accurately gage which, if any, is a suitable enough mimic of the human phenotype. Carrying out imaging requires expertise from outside the current DM research community and lies within the mouse behaviorist and imaging fields. Production of more CNS-focused DM mouse models is worth considering. Much information can be gained from studying the DM1 disease mouse model of the CNS, as they are readily available and can be monitored for CNS effects during treatment. Standardized guidelines for testing behavior and pathophysiology among DM1 mouse models between labs would be useful for comparison across centers. Also, a close collaboration between clinicians and mouse behavioralists will be critical to gain an accurate picture of which mouse behaviors, phenotypes, or physical CNS changes are the most relevant and representative of the disease neuropathology. For instance, it is unclear whether typical DM1-associated deficits in executive functioning (specifically Theory of Mind) can be assessed in existing DM1 mouse models. Any therapies to alleviate CNS symptoms will be difficult to assess in model systems, without better understanding them in humans and in mice. Collaborative efforts between DM experts and mouse behavioralists is essential and recruiting. Appropriate mouse behavioral experts is key.

1.8. Theme 8: Linking molecular basis to clinical manifestations & biomarkers; Chair: Dr. Sergeant

There is known tau pathology in several patient brains, as well as neurofibrillar degeneration, however the tau pathology does not seem to correlate either with repeat length in the most pathological areas, nor with patient concerns, suggesting that the tau pathology remains infra-clinical [10,11]. It is also unclear whether the lesions that have been observed are related to DM1 pathology since they are clinically silent. Therefore, further correlative studies between a prospective neuropsychological assessment and post-mortem neuropathological examination would be needed to address those questions. However, tau pathology and neurofibrillary degeneration is often observed in the brain of DM1 patients, and therefore DM1 is considered to belong to the entity of Tauopathies. The usefulness of an international tissue and brain bank to address these and other complex questions in the DM CNS was reiterated. Important questions raised in the session include: whether DM1 patients are at risk of developing a neurodegenerative disease with aging; whether current animals models of DM accurately mirror the CNS aspects of the disease; whether there are non-imaging biomarkers, inflammatory markers or early immune system activation useful for early detection or as a predictor of age-of-onset, disease severity and potential therapeutic treatment.

1.9. Theme 9: Clinical research and preparedness; Chair: Dr. Day

To be of the most use to patients and families, clinical research must determine several things: which patients to
study (which ages of onset for example), when to study them (and how often to re-test), where to study (multi-center?) and what specific pathological features should be followed? There is a clear degeneration of CNS-related features such as stamina, sleepiness, pain, and systemic disease during the lifetime of a patient, however the question remains whether this is due to neurodegeneration, neurofunctional deficits, or a combination with neurodevelopmental delays that lead to functional deficits. Additionally, it is not known if there is a specific rate of decline based upon repeat size, age-at-onset, various biomarkers, or some other as yet unknown variable. Researchers must attempt to de-convolute CNS and systemic features of myotonic dystrophy for the most accurate investigations, comparisons, and treatment strategies.

2. Conclusions and discussion

Based upon meeting discussions, a short list of critical action items includes (i) an urgent need for a centralized repository, or at the very least, a more up-to-date database of available human tissues; (ii) more longitudinal natural history studies with CNS measures (including neuroimaging when possible) to better understand the patterns of progression and long-term decline in DM; and (iii) the need to design better (i.e., more applicable and more accurate) universally adopted patient questionnaires and clinical neuropsychological evaluations to more clearly understand what faculties of the CNS are affected throughout the life of the individual. Table 1 provides a complete listing of items that were generally agreed to be important and identified as next steps aimed at increasing our knowledge and overall understanding of the CNS issues faced by patients and how best to go about addressing and researching those issues. It is important to move forward with the understanding that DM1 is also a brain disorder, not just a disease of the muscles and heart, and that research focusing on the CNS aspects of DM has the potential to have significant, positive impact on the lives of patients and their families.

Table 1
Important areas of action.

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<th>Action Items</th>
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<td>1. Hold another DM CNS workshop within the next year to continue scientist/clinician dialog.</td>
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<td>2. Increase interactions between basic scientists and clinical investigators.</td>
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<td>3. Organize subgroups to find a consensus for neuroimaging, neuropathology, tissue collection, and model systems.</td>
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<td>4. Write a protocol on tissue collection that should be used more universally within the field.</td>
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<td>5. Establish consensus on which cognitive domains are most severely affected in DM (behavior, neuropsychological/psychiatric).</td>
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<td>6. Establish consensus on how best to measure the severely affected cognitive domains by establishing a subgroup of neuropsychological experts, and mouse investigators to have a proper comparison across patients and animal models.</td>
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<td>7. Coordinate multi-center, longitudinal studies to better understand the basis (i.e. neurodegeneration?) behind DM cognitive decline.</td>
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<td>8. Establish consensus for neuroimaging measures and protocols (i.e. the measurement of white matter and grey matter changes as well as CNS imaging data), include individuals that have been instrumental in developing a consensus for other neurodegenerative diseases (i.e. Huntington’s and Alzheimer disease).</td>
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<td>9. Increase collaborations with mouse imaging specialists and mouse behaviorists to improve understanding of CNS/brain decline in DM mouse models.</td>
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<td>10. Increase characterization of existing mouse lines (i.e. histopathology, imaging, behavior) to understand what CNS issues are accurately represented and appropriately measured in mouse models.</td>
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<td>11. Review feasibility and necessity of performing a comparison of all DM1 mouse models (as was done for Huntington’s disease mice) to determine which mouse lines are best for certain disease symptoms (or best as overall models).</td>
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<td>12. Establish requisition and distribution protocols for existing and future DM specimens such as proteins, RNA, DNA and tissue repositories.</td>
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<td>13. Define critically affected brain regions so that DM CNS tissue samples can be properly collected, stored and retrieved.</td>
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<td>14. Include a comprehensive clinical evaluation in autopsy and specimen collection protocols to better inform the research conducted using the material.</td>
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<td>15. Define relevant CNS biomarkers for appropriate follow-up as diagnostics in clinical studies.</td>
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<td>16. Establish more universal nomenclature for the variable childhood DM age-at-onsets (i.e. from mild to severe congenital, as well as juvenile and childhood).</td>
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<td>17. Include pediatric patients in DM patient registries.</td>
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<td>18. Investigate methods of establishing more accurate DM prevalence estimates to improve the case for investment in DM.</td>
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<td>19. Determine the usage of a generalized health index to better evaluate the significance of any differences detected in neuroimaging and neuropathology during the lifetime of a patient.</td>
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<td>20. Investigate whether RAN-translation has a pathogenic effect in DM and its usefulness as a therapeutic target.</td>
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Acknowledgements

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Appendix Workshop. participants

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References


