

Workshop report

Behavior patterns in Duchenne muscular dystrophy: Report on the Parent Project Muscular Dystrophy behavior workshop 8–9 of December 2006, Philadelphia, USA

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1. Introduction

Eighteen participants representing clinicians, scientists, parents, industry, and public health agencies involved in the assessment and treatment of children with Duchenne muscular dystrophy (DMD) from Australia, Canada, the Netherlands, the UK and the USA met in Philadelphia on December 8–9, 2006 to attend a workshop addressing behavioral issues among children and young adults with DMD. The workshop, sponsored by Parent Project Muscular Dystrophy (PPMD–USA), was organized in response to parent and clinician concerns regarding behavior associated with DMD, and its subsequent impact on patient and family quality of life. For the purposes of clarification, in this report the term “behavior” is defined as readily observable external actions and responses, as well as internal affective/emotional states. The aims of the workshop were to (1) evaluate current findings and determine whether characteristic behaviors occur among boys and young men with DMD, (2) examine etiological factors contributing to behavior patterns in DMD, and (3) develop recommendations for research and intervention strategies.

DMD is a genetic disorder occurring in approximately one in 3300 live male births. Mutations in the dystrophin gene result in an absence of dystrophin or a non-functional dystrophin protein. The different types and locations of the mutation are highly variable across individuals, and it is

unclear to what extent this has an impact on the phenotype. However, in all cases progressive muscle degeneration ensues, with morbidity typically occurring in the second or third decade of life. Muscle degeneration has understandably been the primary focus of research and treatment, and much less emphasis has been placed on behavioral functioning. There is, however, emerging evidence of central nervous system (CNS) involvement resulting in cognitive and neurobehavioral disorders. In addition, because of the debilitating and fatal nature of the disorder, significant psychosocial factors must also be considered. Behavioral functioning has a significant impact on quality of life and can also directly affect medical care, in particular as it is related to things like treatment adherence and behavioral response to medication. Research to date is limited, and studies have typically focused on one component of physiological, cognitive, or emotional functioning in DMD. The complex interactions between these various factors have not been clearly defined. As such, greater understanding of these interactions is necessary for appropriate patient care and treatment planning.

2. Physiological bases of behavior

2.1. Dystrophin in the central nervous system

John Morley (Australia) began the workshop by reviewing the role of dystrophin in the brain. In the non-DMD CNS, clusters of dystrophin are most abundant on the soma and proximal dendrites of pyramidal cells in the cerebral cortex and hippocampus, and of Purkinje cells in the cerebellum. In particular, dystrophin is localized at

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postsynaptic densities of GABAergic inhibitory synapses, and is also colocalized with dystrobrevins in Purkinje cells of the cerebellum [1,2].

The *mdx* mouse, which lacks the full-length (427 kDa) dystrophin, is a widely used animal model of DMD. In cerebellar Purkinje cells of the *mdx* mouse there is a marked decrease in the number of GABA_A receptor clusters immunoreactive for $\alpha 1$ and $\alpha 2$ subunits at the postsynaptic density [1]. Wallis and colleagues [3] reported no difference in expression of the gene for GABA_A receptor $\alpha 1$ subunit in the cerebellum of young (3–4 months old) *mdx* mice compared to wild-type controls. Dr. Morley's lab measured the expression of the GABA_A receptor $\alpha 1$ subunit in *mdx* and littermate control cerebellum using Western blot analysis and found no significant difference in the overall expression of GABA_A receptor $\alpha 1$ subunit in the membrane fraction preparation (unpublished observations). These findings support the suggestion that the absence of full-length dystrophin leads to a disruption in the targeting or stabilization of the receptors at the postsynaptic membrane, resulting in a reduced number of GABA_A receptor clusters.

Although this may have broad implications, the reduction in GABA_A receptor clusters at inhibitory synapses has been specifically shown to have a functional impact in two regions of the CNS. In the cerebellum, the amplitude and frequency of spontaneous miniature inhibitory postsynaptic currents (mIPSCs) in Purkinje cells of the *mdx* mouse are significantly lower than in littermate controls, with the reduction being more marked for large compared to small amplitude mIPSCs, which is consistent with a reduction in the number of postsynaptic GABA_A receptor clusters. Interestingly, those channels located appropriately at the postsynaptic sites appear to function normally [4]. Synaptic plasticity is also disrupted in cerebellar Purkinje cells of the *mdx* mouse, as demonstrated by a substantial reduction in long-term depression (LTD). The blunting of LTD occurred in the presence of pharmacological blockers of GABA, indicating that the consequences of an absence of dystrophin are not restricted to GABAergic-related functions [5]. An impairment of calcium homeostasis is a compelling candidate underlying the disruption in cerebellar long-term plasticity in *mdx* mice, and could be due to a direct impact of the dystrophin-deficiency on membrane transport of calcium, or possibly by disrupting the phosphorylation of calcium by enzymes normally localized at the postsynaptic density. In contrast, there is a marked enhancement of both short-term and long-term synaptic plasticity and of neuronal excitability in the hippocampus of the *mdx* mouse compared to littermate controls, possibly resulting from the reduced number of GABA receptor clusters lowering the threshold for NMDA receptor activation [6].

Although the specific role of dystrophin in the CNS remains unclear at this time, current hypotheses speculate that an absence of dystrophin alters neuronal function by disrupting ion channel localization, which in turn disrupts

the electrophysiology of neurons with downstream consequences for calcium homeostasis and synaptic plasticity. This disruption of neuronal function may lead to potential changes in cognition, behavioral functioning, sleep patterns, and response to medication.

While research has focused predominantly on the impact of deficient dystrophin in the cerebellum and hippocampus, it is important to remember that dystrophin is also distributed throughout other cortical and subcortical regions. Dr. Morley also pointed out that some boys with DMD are not only lacking the full-length dystrophin protein, but also one or more of the five smaller dystrophin isoforms that are localized in the CNS to a greater or lesser extent. Study of the genotype–phenotype relationship in boys with DMD, especially in regard to behavior and cognition, coupled with investigation using appropriate animal models is essential if we are to understand the role of dystrophin in the CNS.

3. Neurocognitive bases of behavior

3.1. Cognitive functioning in DMD

It has long been known that cognitive difficulties are associated with DMD, and the workshop reviewed how cognition might impact behavior. Sue Cotton (Australia) described her meta-analysis of 32 studies examining age, IQ, and disease severity among 1224 individuals with DMD [7,8]. Her results showed that full-scale IQ scores were shifted down about one standard deviation from the normative population. The mean full-scale IQ value was 80.2 with a standard deviation of 19.3. Thirty-five percent of the children in the DMD sample had IQ scores in the mental retardation range (scores ≤ 70), which is greater than in the general population (approximately 2%). However, it is notable that there is a continuum of intellectual ability in DMD, with scores ranging from impaired (≤ 70) to very superior (scores ≥ 130), and that the majority of children perform within normal limits.

Comparison of verbal and performance IQ scores did not fully support the commonly held belief that verbal scores are always depressed when compared to performance (nonverbal) scores among children with DMD. The group mean for performance IQ (PIQ) was about five points higher than for verbal IQ (VIQ), but examination of individual VIQ–PIQ discrepancy scores showed a wide and variable range of presentations, with some children clearly excelling on the verbal tests in comparison to nonverbal. Thus, although on average children with DMD show relative verbal weakness, this may have limited clinical significance for individual children. Dr. Cotton emphasized the need for more specific profile analyses and noted that children who took the Wechsler intelligence tests were particularly susceptible to doing poorly on the Vocabulary, Arithmetic and Digit Span subtests.

Dr. Cotton also compared children with DMD of different ages in a cross-sectional analysis, which suggested that

full-scale and performance IQ scores generally remained constant across the age groups, but that verbal IQ may increase with age. Her data showed that children 11 years and below had poorer logical verbal abstract reasoning, language development, mathematical/computational ability, general knowledge, and appreciation of social norms and practices when compared to older children. Longitudinal studies measuring intellectual functioning are needed to show whether verbal skills of children with DMD improve over time.

Based on her results, Dr. Cotton concluded that the classification of an individual child with DMD as either mentally retarded or not is of limited value when considering his daily behavior and function. The variability in IQ subtest scores observed in group studies of DMD indicates that more comprehensive neuropsychological assessments are necessary to gain insight into the cognitive factors contributing to behavioral functioning in individual patients. The general trend toward improvement in VIQ scores with age has interesting implications for behavior, as issues may evolve over time; younger children may manifest more difficulties with neurodevelopmental issues such as language comprehension and expression, while older children may struggle more with problems arising from their progressive physical abilities and medical complications.

3.2. Verbal span

Veronica J. Hinton (USA) discussed studies of more specific neuropsychological skills among children with DMD and how they may be related to relevant behavioral concerns. She reviewed her work showing that among 81 children with DMD whose IQ was above 70, performance on particular tests (including Digit Span and Story Recall), was selectively weak regardless of general intellectual level [9]. Moreover, when children with DMD were compared to their unaffected siblings of comparable age and receptive vocabulary level, selective deficits were found on the same tests, as well as on other measures that required the children to listen to verbal information [10]. They did not significantly differ on tests of visual-spatial skills, rote memory, or abstract reasoning. Further data from a follow-up study comparing children with DMD to their unaffected siblings on a range of verbal and memory tasks demonstrated the children with DMD were weaker on tasks of sentence recall or following verbal directions, yet their other language and verbal rote memory skills were not significantly different from their siblings [11].

This pattern of poorer immediate verbal memory span has generally been consistent across research studies examining this skill in DMD, although there are varying interpretations as to what such a deficit might reflect – including language, attention and/or memory deficits. Dr. Hinton proposed that children with DMD have a core deficit of limited verbal span, such that their ability to listen to and process verbal information lags behind their peers. She discussed a number of theoretical constructs that might

form the basis of this deficit including limited storage space in the hypothetical phonological loop, compromised cortico-cerebellar circuitry, and/or imperfect ability to “chunk” information. Although the basis is unknown, the idea is operationalized by simple tasks requiring processing of increasing amounts of verbal information. To this end, Dr. Hinton presented cross-sectional data of 112 children ages 5–12 with DMD and compared them to sibling controls and normative data on different levels of the Token Test for Children. The boys with DMD accurately completed tasks involving short verbal instructions, yet lagged behind their peers about two years on tasks involving longer verbal instructions (unpublished observations).

Dr. Hinton hypothesized that such a developmental lag might be particularly problematic among younger children, where the effects may be more generalized and may present as early language delays. Among school age children the effects might not be readily obvious, yet could have broad impact on daily life and behavior. Children with a weakness in immediate verbal memory span may be described as non-compliant, inattentive or forgetful. Deficits in this area may indirectly affect behavior and emotional adjustment, in that behavioral problems that start upon entry into formal schooling may be the result of the child’s difficulty understanding and encoding novel academic information and teacher expectations [12].

3.3. Learning disabilities in DMD

Jos Hendriksen (Netherlands) concluded session one by providing an overview of academic strengths and weaknesses in DMD. Dr. Hendriksen proposed that children with DMD have particular difficulty with automatization, placing them at increased risk for developing a specific learning disability. Substantial research has confirmed this, finding that boys with DMD are at a higher risk of developing reading problems [13,14], with 20% of them having serious reading problems and another 20% having moderate reading problems. Although fewer studies have been published on other academic skills, there is also evidence that shows that children with DMD have poor math and writing skills and that their performance in these academic areas is as compromised as their performance on reading tests [12,15].

Thus, children with DMD are at increased risk for the three types of specific learning disabilities: dyslexia (reading disorder), dyscalculia (mathematics disorder), and dysgraphia (disorder of written communication). It is generally agreed upon that automatization of skills is one of the core deficits in these learning difficulties: automatization of phonemes (sound-symbol relationships) and words in dyslexia, automatization of numbers and procedures in dyscalculia, and automatization of sizes and shapes in dysgraphia. Failure in the process of automatization leads to inaccurate, inefficient, and dysfluent academic skills. The cerebellum has been theorized to play an important role in this process. Moreover, the cerebellum has been

hypothesized to be involved in dyslexia [16] and its involvement in DMD might explain the higher incidence of reading problems in DMD.

Dr. Hendriksen emphasized that for all children language arts (reading and writing) become increasingly important methods of obtaining new academic material and demonstrating competence as they matriculate, and weaknesses can be cumulative over time. Dr. Hendriksen also discussed how behavior problems frequently occur conjointly with specific learning disabilities and that struggling to learn will impact on any child's quality of life and emotional adjustment. Early detection of and interventions for learning disabilities are therefore important and all boys with DMD should receive screening at a young age. He showed how early intervention strategies in his clinic, aimed at training and improving phonological skills, helped boys with DMD develop more adequate reading skills and self esteem (unpublished observations).

4. Behavior patterns in DMD

4.1. Psychosocial adjustment/coping

The goal of the second session was to review what is currently known about specific patterns of behavior among boys with DMD. This includes behaviors that are a response to disease-associated variables (e.g., stressors, medical interventions), as well as behaviors that might be considered neurodevelopmental in nature. Jos Hendriksen (Netherlands) began this session by discussing psychosocial adjustment. Psychosocial adjustment is a general term referring to emotional, behavioral, and social functioning, and is believed to be a central aspect of quality of life. Although psychosocial adjustment can be sensitive to stressors that are not disease specific, it provides a good estimate of how a child is coping with DMD. Dr. Hendriksen noted that the psychosocial adjustment of boys with DMD occurs within the context of normative development as well as declines in physical functioning. Therefore, their behavior should be assessed from a developmental perspective, in which there are normal stressors (e.g., first bad grade at school) and illness related stressors (e.g., falling down and becoming wheelchair dependent).

Studies examining psychosocial, behavioral, and emotional functioning in boys with DMD have been relatively sparse. Results have been equivocal, but there is evidence that some boys with DMD are at increased risk for experiencing depression [17]. Dr. Hendriksen reported the results of the largest study to date on psychosocial adjustment in boys with DMD [18]. The psychosocial adjustment of 351 boys with DMD was assessed by a parent-completed rating scale, the Psychosocial Adjustment and Role Skills Scale (PARS-III) [19]. This scale proved to be reliable and valid for the DMD population. Results indicated that most boys with DMD cope relatively well with the disorder, but a minority (approximately 17%) are at increased risk for psychosocial problems. Further analysis indicated that boys

with DMD ages 8–10 years of age have significantly poorer total adjustment scores when compared to other boys with DMD. Dr. Hendriksen speculated that this may be a response to stressors associated with decreases in physical functioning leading up to the loss of ambulation (which typically occurs around this age). In general, total adjustment scores improved with age, suggesting that the boys grow into better adjustment. There was one exception, however; peer relations were negatively correlated with age – suggesting that peer relations become more problematic as the boys grow older. It was hypothesized that decreases in physical functioning and health may result in reduced access to social and recreational opportunities.

Dr. Hendriksen reported that, in light of the higher risk for maladjustment in this population, parents may need practical recommendations for building self esteem and teaching their children with DMD how to deal with stressful and emotional issues. He recommended using a strategy known as “Emotion Coaching” [20] that involves: (1) being aware of the child's emotions (2) recognizing emotions as an opportunity for intimacy and teaching (3) listening empathically and validating the child's emotions, (4) helping the child to verbally label emotions, (5) setting limits while helping the child to solve the problem.

Dr. Hendriksen also referred to recent research showing that parents of DMD boys are at an increased risk for depression and stress [21,22]. Although the exact implications have not been documented in this population, it is likely that this can have an impact on the parent-child relationship, resulting in an indirect effect on the child's psychosocial adjustment.

4.2. Social behavior

Kate Bushby (UK) presented data from a study of 82 children with neuromuscular disease [23]. Among the responders, parents of 37 boys with DMD and 8 boys with Becker muscular dystrophy (BMD) answered questions about their child's behavior, communication and social skills. The results indicated that DMD/BMD boys had unexpectedly high levels of social and communication difficulties, both when compared to the general population and to children with other neuromuscular disorders. In this sample, 18% of boys with DMD and 50% of boys with BMD were identified by their parents as having poor social interactions, while 30% with DMD and 43% with BMD were identified as having problems with communication. Of note is that 5% of DMD and 37% of BMD cases reported having a preexisting diagnosis of an autism spectrum disorder. These findings suggest that social interactions and communication are areas of weakness for boys with DMD/BMD, even if they do not have autism. Further, the children who were identified as having significant behavioral concerns were all more likely to be identified as having learning disabilities. The possibility of the behaviors being reactive responses to the challenges children may face in their school was discussed, along with the possibility that

these behaviors are part of the phenotypic presentation of the disorders.

Veronica J. Hinton (USA) reported that the above findings were similar to those from a study of parent ratings of behavior in a sample of 181 boys with DMD [24]. Her group found that about a third of the boys were reported to have significant social problems (e.g., being immature, having poor peer relationships) and these rates were significantly higher than the normative sample, unaffected sibling controls and a comparison group of children with cerebral palsy. Notably, the younger children with DMD were more likely than the older children to have increased social problems. Further, within the DMD group, approximately a quarter of the sample had significant problems with being withdrawn and having poor attention.

4.3. *Autism spectrum disorders*

Veronica J. Hinton (USA) then reviewed the literature examining autism spectrum disorders in DMD. The term “autism spectrum disorders” collectively refers to a group of diagnoses that have similar behavioral presentations including Autistic Disorder, Asperger’s Disorder, and Pervasive Developmental Disorder – Not Otherwise Specified. Case studies describing children with DMD and autism have been published [25,26], and there is emerging evidence that the prevalence of autism spectrum disorders among boys with DMD is higher than expected in the general population. Dr. Hinton presented data showing that boys with DMD tend to have greater difficulty identifying facial affect compared to controls [27], a characteristic often associated with autism spectrum disorders. She then discussed an ongoing study of 65 children with DMD or BMD, in which 26% of the children with DMD (but none of the control children) scored above the cut-off on a screening measure of autistic behaviors [28]. For those who scored above the cut-off, Dr. Hinton administered a comprehensive structured interview to each child’s mother and found that up to 16% of the children met criteria for an autism spectrum disorder. These children were all described by their mothers as having significant qualitative abnormalities in reciprocal social interactions and communication, along with restricted or repetitive behaviors, all presenting before the age of 3 years. Thus, this study also indicated that DMD is associated with higher than expected rates of autistic disorder. The possibility of sample bias inflating the rates was discussed, as was the fact that most children with DMD are not autistic.

During discussion, participants reported concern that boys with DMD may demonstrate problems with “theory of mind”. This term, which has been theorized to be one of the core deficits in autism, refers to the ability to take another’s perspective, understand the connection between external factors and emotional state, and apply this knowledge to social problem solving. Dr. Hinton suggested that language difficulties, the tendency of being withdrawn, avoiding eye contact, having difficulty reading facial affect,

and problems with theory of mind are a constellation of behaviors that may fall on a continuum in DMD. The number of children on the extreme end of this continuum results in an increase in the prevalence of autism spectrum disorders observed in DMD. There may also be a number of DMD boys on the milder end of the continuum who do not meet diagnostic criteria, but who still have weaknesses in these areas to varying degrees.

4.4. *Sensory processing disorder*

Laura Case (US) reported on behaviors observed in DMD boys that may indicate problems with sensory processing. Although the definition and application of sensory processing disorder (SPD) has been inconsistent in the past, SPD is currently used to describe impairment in a child’s ability to detect, modulate, interpret, and/or respond appropriately to sensory stimuli (in the absence of an obvious physical sensory impairment such as blindness or deafness) [29]. SPD purportedly explains problems of apparent hyper- or hyporeactivity in response to auditory, visual, tactile, olfactory, oral, or vestibular sensory information. Although it is expanding, research examining SPD is still at an early stage, and it has not yet been included as a diagnosis in the International Classification of Diseases (ICD-10) [30] or the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) [31]. Although there are no studies addressing this particular issue in boys with DMD, some parents report that their children with DMD present with features characteristic of children with SPD. They report children who are hypersensitive to tactile stimulation and complain about seams or wrinkles in their socks, socks that are not on straight, or tags in their shirts. Other parents report that their sons are aversive to “messy play” or may be “picky eaters” regarding certain tastes, consistencies, and textures. Others report that their child cannot regulate their emotions easily, or have difficulty tolerating noisy environments. In some cases, children are reportedly hyporeactive and may be non-responsive when spoken to, or may seek out stimulation through excessive activity or by smelling or chewing on objects.

Sensory interventions employ a variety of different techniques and will not be summarized in this report. The interventions are typically aimed at specific sensory modalities or processing of multiple modalities, after individual assessment has identified altered behavior with regards to that aspect of processing. These treatment strategies are hypothesized to elicit cortical reorganization and subsequent behavioral change. Research studies examining outcomes of sensory interventions, most commonly conducted with children who have autism and other developmental disabilities, have yielded equivocal results [32].

While sensory-related behaviors may be minor inconveniences for some children and families, they can be significantly problematic for others and can have an impact on education, social functioning, and medical/health issues

such as treatment adherence (e.g., ability to tolerate ankle-foot orthotics while sleeping). Thus, despite the complications surrounding diagnosis and treatment, sensory processing disorders have important clinical implications and further research is warranted. Because of the potential for multiple determinants of behavioral problems and comorbidities, SPD assessment, typically performed by occupational therapists, should occur in conjunction with behavioral/emotional evaluation conducted by a mental health professional.

4.5. Attention-deficit/hyperactivity disorder and obsessive-compulsive disorder

James Poysky (USA) presented on attention-deficit/hyperactivity disorder (ADHD) and obsessive-compulsive disorder (OCD) in DMD. In this report, ADHD is used to collectively refer to disorders characterized by inattention, with or without hyperactivity/poor impulse control. Similar to other neurological disorders, anecdotal accounts by clinicians indicate that ADHD is one of the most commonly observed comorbidities among boys with DMD; however, there are limited research studies documenting the prevalence and impact of this type of behavior in DMD. A recent study by Hinton and colleagues indicates that approximately 1 in 4 boys with DMD have significant problems with attention [24]. Hendriksen, Poysky, and Vles (unpublished observations) found that 12% of survey respondents reported their child with DMD had been diagnosed with ADHD. These children were also rated as having significantly poorer psychosocial adjustment when compared to boys with DMD without diagnoses of ADHD.

Cognitive findings provide modest evidence of ADHD in DMD. Complex attention and verbal fluency may be problematic [33], and some studies have found deficits in executive functioning [34] and concept formation [12], while others have not [10]. Weaknesses in immediate verbal memory span are the most consistent finding (see Section 3.2), but it is unclear to what extent this is indicative of a specific cognitive deficit or of a broader primary attention disorder.

Behaviors commonly associated with ADHD including poor emotional regulation, low tolerance for frustration, aggression, oppositional/argumentative behavior, and mental rigidity/inflexibility can be significantly problematic and stressful for families with DMD. Given the physical limitations of boys with DMD, rating scales that assess ADHD behavior by measuring hyperactivity may result in false-negatives.

Obsessive-compulsive disorder (OCD) has not been examined in DMD; however, anecdotal accounts suggest that there may be an increased prevalence of OCD-related behaviors in this population. More specifically, parents of boys with DMD report that their sons demonstrate obsessive-like qualities including excessive concern with how things feel (such as sticky residues), need for symmetry/

exactness/evenness, fear of embarrassment, or other intrusive and distressing thoughts. Others report that their sons will have a tendency to get stuck on one idea or ask repetitive questions. Concerns related to compulsive-like behaviors including arranging or lining things up, checking, hand-washing, or repetitive behaviors have been also reported by parents. In addition, some report that their son has a hard time with transitions, or adjusting to disruption in routine or changes in wheelchair characteristics such as seating systems, control mechanisms, and adaptive equipment. While some of these behaviors may be present in conjunction with an autistic-spectrum disorder, they also appear on an independent basis. Dr. Poysky also noted that certain behaviors may not be related to OCD and may reflect difficulty with mental flexibility (adaptability), cognitive perseveration, and/or sensory hypersensitivities.

5. Medical treatment and behavior in duchenne muscular dystrophy

Brenda Wong (USA) concluded the second session by presenting on the impact that medical treatments can have on cognition and behavior, as well as medical management of behavioral disorders in DMD. Steroids (glucocorticoids) are the only pharmacological agents that have changed the natural history of DMD, prolonging independent ambulation, preserving cardiac and pulmonary functioning in the teen years, and preventing severe scoliosis. However, side effects may include mood swings and difficult behavior. While anecdotal accounts suggest that these negative reactions may improve over time, they continue to remain one of the primary reasons for discontinuation of therapy.

The impact of steroids on learning and memory is currently unclear. Endogenous glucocorticoids regulate hippocampal metabolism, physiologic functions, and memory, and have been found to be essential for maintaining prefrontal cortex cognitive functioning (working memory) [35]. Acute steroid treatment has been shown to result in reversible impairment of long-term memory functions [36] and retrieval of negative words [37], suggesting that emotional material is especially sensitive to the memory modulating effects of steroids. Some research indicates that glucocorticoid-associated memory effects may be dose-dependent [38].

The effect of multiple or prolonged corticosteroid exposure on cognition and behavior is unknown; however, recent research suggests that long-term prednisone therapy is associated with initial changes in mood, memory and hippocampal volume that appear to stabilize over time [39]. If confirmed, these results may be reassuring to families and caregivers of patients who use chronic glucocorticoid therapy to treat DMD. However, there may be as yet unidentified developmental effects of chronic steroid treatment. Testosterone is involved in learning and memory, and is reported to play an important role as a

neuroprotective agent in aging. Testosterone deprivation is associated with poor memory in men and replacement can enhance memory and spatial cognition [40]. Patients with DMD treated with chronic glucocorticoids develop growth failure and pubertal delays with testosterone insufficiency in their teen years. It is unclear if the testosterone insufficiency in these patients has any impact on cognitive functioning. Neuropsychological evaluations are recommended as a means to monitor the effects of glucocorticoids (in particular the dosing and duration) on memory and learning in boys who are receiving chronic steroid treatment.

Patients with DMD may have concomitant behavior problems that require pharmacotherapy. Although stimulants are the drugs of choice for treatment of ADD/ADHD, in rare cases they have been associated with sudden cardiac events (resulting in a US Food and Drug Administration “black box” warning), and are to be prescribed with caution for patients with DMD who have underlying cardiomyopathies. The use of stimulants should be used only after consultation with the patient’s cardiologist, who could closely monitor the patient’s pre and post-treatment cardiac status. Non-stimulant medications used by clinicians for ADD/ADHD also include atomoxetine, and “off-label” treatment with α -agonists (clonidine, guanfacine), bupropion and modafinil. Some of these non-stimulants (e.g., atomoxetine and α -agonists) may also have cardiac effects and need close cardiac monitoring as well. The possibility of using propranolol for treatment of intermittent explosive behaviors or episodic aggression in patients with DMD who demonstrate these problems was discussed. β -Blockers are used in the treatment of early cardiac dysfunction and have been previously studied with ACE-inhibitors for cardioprotection for Duchenne cardiomyopathy [41].

Finally, Dr. Wong described how psychopharmacotherapy may be associated with certain health risks for DMD patients with cardiomyopathy (prolonged QT interval with ziprasidone, cardiac autonomic dysfunction with anabolic steroids), and for patients on chronic steroid therapy (insulin resistance with risperidone and aripiprazole).

6. Conclusions and workshop outcomes

- (1) DMD is a multi-systemic disease requiring comprehensive evaluation and treatment. The behavioral health of patients and families is an important aspect of their care, and problems in this area can have a direct impact on quality of life and medical treatment. The inclusion of mental health professionals in the multi-disciplinary treatment team is therefore necessary.
- (2) Boys with DMD are at increased risk for behavior problems. Behavioral screening and comprehensive neuropsychological/developmental evaluation should be conducted for all boys with DMD as soon as possible following diagnosis. Although not an exhaustive list, guidelines for domains of particular importance and suggested measures are summarized in Table 1 (cognitive) and Table 2 (behavior). Because DMD is progressive, different issues may arise over time and ongoing evaluation and monitoring is recommended.
- (3) Multiple factors should be considered when determining the etiology of behavior problems in DMD; those that are the direct result of DMD (absence of dystrophin in the CNS resulting in cognitive dysfunction or neurodevelopmental disorders), as well as those that are “secondary” to the disorder (e.g., reactions to stress, family conflict, or physical limitations; medical treatment). Early identification of potential causative factors will allow targeted intervention before problems become exacerbated.
- (4) Behavioral interventions should be attempted to address problems encountered in the course of medical treatment, as an alternative to discontinuation of the treatment. In particular, strategies to address predictable side effects of steroids should be developed and implemented on a routine basis with families. Developing this plan prior to starting treatment may minimize the side effects, or reduce them to a level that the family does not need to consider discontinuing the steroids.

Table 1
Cognitive domains to be assessed and suggested measures

Domain	Measures
Intelligence	^a Wechsler Intelligence Scales (WPPSI-III, WISC-IV, WAIS-III), Raven’s Progressive Matrices
Verbal span	Digit Span, Token Test, Recalling Sentences, Non-sense Word Repetition
Academic – broad	Woodcock–Johnson Tests of Achievement, Wechsler Individual Achievement Test
Academic – phonological	Comprehensive Test of Phonological Processing
Academic – automatization	Reading Fluency, Math Fluency, Test of Word Reading Efficiency, Gray Oral Reading Test
Language	Peabody Picture Vocabulary Test, Clinical Evaluation of Language Fundamentals
Attention/executive	Symbol-Digit Modalities Test (Oral version), Verbal Fluency (FAS, animals, foods), Stroop Color-Word Test, ^a Delis-Kaplan Executive Function System

Please contact the corresponding author for references or publishing information related to these measures.

^a Performance on certain subtests may be spuriously lowered by deficits in verbal span or muscle/manual weakness.

Table 2
Behavioral domains to be assessed and suggested measures

Domain	Measures
General	Behavior Assessment System for Children, Child Behavior Checklist
Psychosocial	Personal Adjustment and Role Skills Scale, Parenting Stress Index, PedsQL Pediatric Quality of Life Inventory
Social	Social Skills Rating System
Autism	Social Communication Questionnaire, Autism Diagnostic Interview
AD/HD	Behavior Rating Inventory of Executive Function, Disruptive Behavior Rating Scale
OCD	Children's Yale-Brown Obsessive-Compulsive Scale
Sensory Processing	Sensory Profile

Please contact the corresponding author for references or publishing information related to these measures.

- (5) Informational material regarding the causes of and interventions for cognitive and behavior problems in DMD are needed for patients, families, school personnel, and other involved professionals. While initial versions have been developed, it was agreed that collaboration between the different organizations and experts involved to expand on these materials will be the most efficient and helpful approach in ensuring that they meet the ongoing needs of DMD families. The results of this workshop will be incorporated into these materials, with updated versions developed on an ongoing basis.
- (6) Given the very limited amount of research to date, additional studies examining the following areas are needed:
 - (a) The role of dystrophin and its isoforms in CNS development and functioning, including neuroimaging studies examining brain functioning in boys with DMD.
 - (b) The cognitive/neuropsychological deficits in DMD and their subsequent impact on patient behavior, social functioning, emotional adjustment, learning, and quality of life.
 - (c) The prevalence, nature, and course of neurodevelopmental disorders in DMD, in particular autistic-spectrum disorders, ADHD, OCD, specific learning disabilities, and sensory processing disorders.
 - (d) The interaction between parent and family-related factors (such as maternal depression) and patient behavior.
 - (e) Treatment/outcome studies addressing behavior and emotional health in DMD. Particular areas of interest include early prevention of specific learning disabilities (dyslexia), applied behavior analysis for autistic behaviors, social skills training for boys with social difficulties, the impact of behavioral interventions on treatment adherence, and cognitive/behavioral outcomes of new medical treatments currently in development.

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Appendix A. List of workshop participants

Doug Biggar, University of Toronto, Canada
 Kate Bushby, University of Newcastle upon Tyne, UK
 Laura Case, Duke University Medical Center, USA
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