DMD/BMD Carrier Symposium
PPMD Annual Conference
June 29, 2018

Multidisciplinary Evaluation of DMD Carriers
Cardiology, Psychology, Neuromuscular
Nationwide Children’s Hospital
Multi-Disciplinary Faculty*

Jerry Mendell, MD  Curran-Peters Chair Peds Research

Eric Camino, PhD  Study Coordinator Neuromuscular Center

Megan A Iammarino, PT, DPT  Neuromuscular Clinical Outcomes Specialist for NMD

May Ling Mah, MD, MS  Asst Prof Medicine & Peds, Pediatric Cardiology and Adult Congenital Heart Disease

Kan Hor, MD  Assoc Prof & Director Cardiac MRI

Jamie L Jackson, PhD  Asst Prof Pediatrics and Psychology

Linda H Cripe, MD  Prof Peds & Ped Cardiology

* Order of Speakers
RATIONAL/OBJECTIVES for Program

• Multiple previous studies raise questions about age of onset, frequency of symptoms, cardiac manifestations and long-term implications on life-expectancy using Echo/EKG

• Our study will better define cardiac outcomes by MRI and exercise stress testing and skeletal manifestations using quantified measures of strength & function

• An added dimension in our study explores health-related quality of life, emotional implications, and relationship of stress to physical performance

• Disease progression is assessed by longitudinal studies X 2 yrs
Program Topics: DMD/BMD Carrier Study

I. Jerry R Mendell, MD
   Introduction and Program Synopsis

II. Eric Camino, PhD
   Overview of Carrier Study – Patient Enrollment, Protocol Outline and Comparison of CK levels

III. Megan Iammarino, PT, DPT
   Evaluation of Muscle Strength (MVIC) & 6MWT

IV. May Ling Mah, MD, MS
   Cardiac Findings in Carriers by Exercise Stress Testing

V. Kan Hor, MD
   Cardiac Findings in Carriers by MRI

VI. Jamie Jackson, PhD
   Stress-induced Findings in Carriers: Psychosocial Findings in DMD Mothers

VII. Linda Cripe, MD
    Summary of Carrier Study
Study Overview: Characterization of clinical skeletal and cardiac impairment in carriers of DMD and BMD

Parent Project Muscular Dystrophy
Annual Conference 2018

Eric Camino, PhD
Carrier Study Overview - Enrollment

- July 8, 2016 – First enrolled patient visit
- Total women enrolled to-date – 103
  - 34 have completed 12-month visit
  - Begin final 24th month visits soon

- Study Cohorts
  - Cohort A – Women who are somatic carriers of DMD/BMD and have/had a child with DMD or BMD
  - Cohort B – Women who are not somatic carriers of DMD/BMD and have/had a child with DMD or BMD
  - Cohort C – Women who are not somatic carriers of DMD/BMD and do not have/had a child with DMD or BMD
  - Cohort D – Women who are somatic carriers of DMD/BMD and do not have/had a child with DMD or BMD
Carrier Study Overview - Enrollment

Cohort A – Somatic + affected child
  57 women confirmed carriers of DMD/BMD mutation
  52 have a child who has been diagnosed with DMD
  5 have a child who has been diagnosed with BMD

Cohort B – Non-somatic + affected child
  20 women who are not somatic carries of DMD/BMD mutation
  19 have a child who has been diagnosed with DMD

Cohort C – Non-somatic + no affected child
  26 age-matched women participated in study
  25 of the women are mothers

Cohort D – Somatic + no affected child
  Currently enrolling – Must be 18 years of age
Carrier Study Overview - Protocol

Longitudinal Observational Study – 3 visits to Nationwide Children’s Hospital
Baseline, 12 Month, 24 Month

- Cohort C only participates in the baseline visit

### Neuromuscular Assessments
- Manual Muscle Testing
- Quantitative Myometry
- 6 Minute Walk Test
- Time to Rise
- Active Seated

### Cardiology Assessments
- Cardiac MRI
  - Utilizing gadolinium contrast
- Treadmill Stress Test
  - Electrocardiogram

### Behavioral Assessments
- Qualitative Interview
  - At baseline for mothers with affected child
- Cognitive Evaluation
- Collection of Biomarkers for Stress
Carrier Study Overview – Serum CK Levels

Cohort A – Somatic + affected child
Cohort B – Non-somatic + affected child
Cohort C – Non-somatic + no affected child

<table>
<thead>
<tr>
<th>Comparison of CK Levels by Cohort</th>
<th>Elevated CK &gt;140 U/L</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cohort A (n=57)</td>
<td>33 (58%)</td>
</tr>
<tr>
<td>Cohort B (n=20)</td>
<td>4 (20%)</td>
</tr>
<tr>
<td>Cohort C (n=26)</td>
<td>0 (0%)</td>
</tr>
</tbody>
</table>

Elevated CK is a feature of carrier state, not a predictor.

Can elevated CK be used as a predictor of muscle weakness or cardiomyopathy in carriers?
Cardiac Findings in Carriers by Exercise Stress Testing

Parent Project Muscular Dystrophy
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Megan A Iammarino, PT, DPT
Functional Testing

• Physical therapists assessed overall physical functioning using the following standardized outcome measures:

  - 6 Minute Walk Test
  - Strength Testing
  - Time to Rise
  - ACTIVE-seated
6 Minute Walk Test

Sub-maximal test of aerobic capacity and endurance

Functionally meaningful difference in 6MWD ~30 meters, in diseased populations
Time to Rise

• The time it takes to move from lying on the floor to standing up

* For illustrative purposes only – No incentive was provided
ACTIVE-seated

- Video game that measures the amount of space accessible through reaching and leaning while seated
- Incorporates arm, shoulder, and trunk strength
Strength Testing

Maximum Voluntary Isometric Contraction (MVICT)

- Capture the greatest amount of force produced by a certain muscle
- Biceps, triceps, quadriceps, hamstrings, grip

No correlation found between carrier serum CK levels and strength of any tested muscle group
Total Muscle Strength
(Sum of the average of R and L knee and elbow flexion and extension and grip)
Performance on Functional Test from 6 Women with Below Expected Strength
Summary

• We have identified 6 women with sons with DMD that appear to have generalized weakness
• 3 of these women performed below average on functional testing
• Further evaluation will include longitudinal data to determine:
  • If the women with weakness decline over time
  • If additional women with sons with DMD fall below expected performance
  • If differences between groups develop
Cardiac Findings in Carriers by Exercise Stress Testing

Parent Project Muscular Dystrophy
National Meeting 2018
Scottsdale, Arizona

May Ling Mah, MD MS

No disclosures
Treadmill Exercise Testing

• Typical utility is to define functional capacity in patients and to exclude ischemic heart disease

• Ischemic disease = effect of coronary artery disease
  – Not suspected to be problematic early in Carrier Moms

• Carriers are highly functional, treadmill exercise testing will add value to traditional 6-minute walk test to help further define those “with” and “without” manifestation
Treadmill Exercise Testing
Results

• Maximal oxygen consumption (VO2 max)
  Recognized as an indication of a person’s fitness level
  • How much energy does your body give you to exercise?
  • Combination of heart, lungs, blood vessels and muscles working together

• No difference between somatic & non-somatic DMD moms
• Significant difference noted between DMD moms and controls
• Translation: being a DMD mom meant that you had lower general fitness level compared to age-matched control moms
Results

• VE/VCO2: was your heart the limiting factor?
  – NO DIFFERENCE in DMD moms vs. controls
  – The heart was not the specific limiting factor for any participant

• RER: measure of effort
  – Full efforts were given by 100% of participants and was not different
Results: Arrhythmia

- Premature Ventricular Contractions (PVCs) during exercise differed
- Known to be a marker of heart muscle “irritability” in non-DMD (dilated) cardiomyopathy studies
- Early beats are noted during exercise in 50% of somatic patients (25/49)

- Age matters
  - Ventricular ectopy with exercise
    - Mean 44.2 yrs vs. 39.5 yrs in those who did not (p=0.041)
Preliminary thoughts about results

- While our DMD moms did not appear as physically conditioned as our age-matched control moms
  - Deconditioning is multifactorial and was still at a respectable level (28 versus 35)
  - Exercise appears safe for DMD moms
    - No mom has had a cardiac evaluation (exercise or MRI finding) which would preclude exercise
    - Cardiac disease was NOT the limiting factor in any of the DMD moms
    - While arrhythmias were more common in Carrier moms, they were a very benign type of arrhythmia (PVCs) and none demonstrated sustained arrhythmia or more concerning pattern.
DMD/BMD Carrier Symposium
Cardiac Findings in Carriers by MRI

24th Annual Duchenne Connect Conference
Parent Project Muscular Dystrophy
Scottsdale, AZ
June 29, 2018

Kan N. Hor, MD
Director of Cardiac Magnetic Resonance Imaging Program
Nationwide Children’s Hospital
Columbus, Ohio, United States

#PPMDCConference
What is the impact of being a carrier?

What systems are affected?

The **Heart** is the most active muscle – how is it affected and how common is cardiomyopathy and heart failure related complications?

- **Cognitive / Stress and Impact on Cardiac Disease?**
- **Decreased Heart Function?**
- **Cardiomyopathy?**
- **Leads to Heart Failure?**
- **Loss of Muscle Mass?**
- **Weakness?**
- **Inflammation?**
- **Fibrosis?**
- **Exercise Limitation?**
- **Brittle and Weak?**
What is Known:
Basis for Expression of DMD in Carriers

- Some carriers have reduced production of dystrophin
- X-Chromosome Inactivation of the normal allele (chromosome) associated with clinical manifestation
- Bottom Line: There is a basis for the existence of the “disease” of carrier cardiomyopathy
What we think we know about DMD Carriers

- Often cardiac disease is the only manifestation
- Cardiomyopathy risk increases with age
  - Age < 16 years: no cardiac disease noted
  - Age 16-30 years: 6% with cardiac disease
  - Age 31-50 years: 9% with cardiac disease
  - Age > 50 years: 15% with dilated cardiomyopathy
- Definition of cardiac disease is unclear
- Diagnostic tool has been echocardiogram

What we think we know about DMD Carriers

- Newer studies suggest much higher incidence of cardiac and non-cardiac problems at a younger age than previously published.


Duchenne Muscular Dystrophy: a Survey of Perspectives on Carrier Testing and Communication Within the Family.
Hayes B1, Hassed S1, Chaloner JL2, Aston CE1, Guy C3.


Genetic and Early Clinical Manifestations of Females Heterozygous for Duchenne/Becker Muscular Dystrophy.
Papa R1, Madia F2, Bartolomeo D1, Trucco F1, Pedemonte M1, Traverso M2, Broda P1, Bruno C3, Zara F2, Minetti C4, Fiorillo C5.


Cardiac involvement in female Duchenne and Becker muscular dystrophy carriers in comparison to their first-degree male relatives: a comparative cardiovascular magnetic resonance study.
Florian A1, Rösch S2, Bietenbeck M1, Engelen M1, Stypmann J1, Waltenberger J1, Schtem U2, Yilmaz A3.


Myocardial Fibrosis and Left Ventricular Dysfunction in Duchenne Muscular Dystrophy Carriers Using Cardiac Magnetic Resonance Imaging.
Lanq SM1, Suhuy S2, Mazur W3, Sticha JU2, Rattan MS4, Jefferies JL2, Taylor MD2.
Defining Carrier Cardiomyopathy
Prevalence of EKG/Echo Abnormalities

- 129 definite carriers with DMD and BMD
- Echo abnormalities
  - 5.4% (n=7, all DMD) had “evidence of dilated cardiomyopathy”
    - 5 with signs or symptoms of CHF
  - 18% (n=23) had a dilated heart
  - 13% (n=17) “borderline” echo (i.e. wall motion abnormalities, unilateral atrial dilation)
- EKG abnormalities (not defined) in 47% (n=61)
- “Completely Healthy Heart” in 38%

Hoogerwaard et al. Clinical Chemistry 2001
Defining Carrier Cardiomyopathy
Prevalence of MRI Abnormalities

- Retrospective study
  - 7 out of 22 carriers had myocardial fibrosis by late gadolinium enhancement CMR.
  - Out of the 7 with fibrosis, 3 had LV dysfunction
  - At worst was mild (LVEF range 48-53%, normal is ≥ 55%)

Lang SM et al. Pediatr Cardio 2015
Defining Carrier Cardiomyopathy
Prevalence of MRI Abnormalities

- Retrospective study
  - 15 genetically confirmed DMD carriers
  - **ALL** had abnormalities by MRI
    - 80% had regional myocardial thinning > 1 segment
    - 13% apical non-compaction
    - 40% lateral non-compaction
    - 60% abnormal late gadolinium enhancement
    - Most had volumetric abnormalities

Prevalence of Carrier Cardiomyopathy

- It Depends . . .
- Lack of current definition of
  - “Manifesting”
  - “Non-manifesting”
Defining Carrier Cardiomyopathy

How is this study different?

- Large case-control study with genetic confirmation
  - DMD/BMD carriers moms (somatic)
  - DMD/BMD non-carrier moms (non-somatic)
  - DMD/BMD carrier non-moms
  - Healthy controls with normal CK

- Longitudinal Design

- Wholistic look at the patient

- Treadmill Testing
  - Has not been done in carriers

- Technical Improvements
  - Backbone of imaging is cardiac MRI
  - Novel techniques
Heart Function Assessment

How will the heart function be checked?

- Images of the heart will be obtained to evaluate structure and function
Heart Function: Cardiac MRI (CMR)

- **Advantages:**
  - Accurate measurements
    - *Traditional MRI Information*
      - *Function by ejection fraction*
      - *(LGE) Scar/Fibrosis assessment*
    - *Newer MRI Techniques*
      - *(T2) Edema/inflammation*
      - Myocardial strain for contractility
      - *(T1) Diffuse microscopic scar*
Cardiac MRI (CMR): The Heart in DMD

How the Heart Squeeze
Cardiac MRI (CMR): The Heart in DMD
How the Heart Squeeze

- Ejection fraction by cardiac MRI measures the global state on how well the heart squeezes.
Ejection Fraction

Patients (Blue = DMD Carrier, Red = Control)

- Average DMD Carrier EF ~ 60% (range 46-74%)
  - 11/74 DMD Carrier with LVEF < 55%
- Average control LVEF ~ 62% (range 50-74%)
  - 2/26 Control with LVEF < 55%

Hor et al, unpublished data
Cardiac MRI (CMR): The Heart in DMD Beyond Squeeze (fibrosis/scar imaging)

- Enhancement pattern unique to DMD (sub-epicardial region = Pink)
- Compared to Heart attack patients (sub-endocardial = Red)

DMD: white areas within pink (outer surface)

Heart Attack: white areas within red (inner surface)

Similar pattern as DMD boys

Hor et al, unpublished data
DMD Carrier CMR Results

Scar Assessment

- 25/54 (47%) of somatic DMD carrier has scar (youngest ~ 31 years old)
- 1/20 (5%) non-somatic DMD carrier has scar
- No control subjects have scar
- 16/24 (67%) of somatic DMD carrier with scar have normal heart function
- 8/11 (72%) of somatic DMD carrier with abnormal heart function have scar
- 2/29 (7%) of somatic DMD carrier without scar have heart abnormal heart function
- Carrier with scar are older (~ 45 years) compared to (~38 years) for those without scar

Hor et al, unpublished data
Psychosocial Findings in DMD Mothers

Jamie L. Jackson, Ph.D.
Assistant Professor of Pediatrics & Psychology
jamie.jackson2@nationwidechildrens.org
### Psychosocial Findings: How Did We Measure This?

<table>
<thead>
<tr>
<th>Health-Related Quality of Life (HRQoL)</th>
<th>Emotional Functioning</th>
<th>Social Support</th>
<th>Physical Symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Hospital Anxiety and Depression Scale (HADS)</strong></td>
<td></td>
<td></td>
<td><strong>Fatigue Severity Scale (FSS)</strong></td>
</tr>
<tr>
<td>• Physical Functioning</td>
<td>• Anxiety Symptoms</td>
<td>• Appraisal Support</td>
<td>• Symptoms of fatigue in the last week</td>
</tr>
<tr>
<td>• Bodily Pain</td>
<td>• Depression Symptoms</td>
<td>• Tangible Support</td>
<td></td>
</tr>
<tr>
<td>• Role Limitations due to Health Problems</td>
<td>• Perceived stress during last month</td>
<td>• Self-Esteem Support</td>
<td></td>
</tr>
<tr>
<td>• Role Limitations due to Emotional Symptoms</td>
<td><strong>Perceived Stress Scale (PSS)</strong></td>
<td>• Belonging Support</td>
<td></td>
</tr>
<tr>
<td>• General Mental Health</td>
<td>• Perceived stress during last month</td>
<td></td>
<td><strong>Pennebaker Inventory of Limbic Languidness (PILL)</strong></td>
</tr>
<tr>
<td>• Social Functioning</td>
<td><strong>Obsessive Compulsive Inventory-Revised (OCI-R)</strong></td>
<td></td>
<td>• Total physical symptoms reported</td>
</tr>
<tr>
<td>• Energy/Fatigue</td>
<td>• Total score for obsessive compulsive disorder symptoms</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Psychosocial Findings: DMD Mothers vs. Controls

**Health-Related Quality of Life (HRQoL)**
- Worse physical functioning
- More disruptions in daily roles
- More disruption to social life
- More pain
- Poorer general health ratings
- More recent negative health changes

**Emotional Functioning**
- More symptoms of depression and anxiety (40% clinically significant)
- More perceived stress
- NOT higher in obsessive compulsive symptoms

**Social Support**
- Poorer social support across all realms

**Physical Symptoms**
- Greater fatigue
- Greater frequency of physical symptoms
Psychosocial Findings: Somatic Mothers vs. Non-Somatic Mothers

<table>
<thead>
<tr>
<th>Health-Related Quality of Life (HRQoL)</th>
<th>Emotional Functioning</th>
<th>Social Support</th>
<th>Physical Symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Only difference identified: More pain interference</td>
<td>• No differences identified</td>
<td>• No differences identified</td>
<td>• No differences identified</td>
</tr>
</tbody>
</table>
## Psychosocial Findings: Somatic Mothers vs. Non-Somatic Mothers

<table>
<thead>
<tr>
<th>IQ Screening: WASI-II Subtests</th>
<th>Somatic n=45</th>
<th>Non-Somatic n=17</th>
</tr>
</thead>
<tbody>
<tr>
<td>VCI (Crystalized Abilities)</td>
<td>102.8</td>
<td>103.0</td>
</tr>
<tr>
<td>PRI (Non-Verbal Abilities &amp; Visuomotor/Coordination Skills)</td>
<td>99.9</td>
<td>104.9</td>
</tr>
<tr>
<td>FSQ-4 (Estimate of Cognitive Ability)</td>
<td>101.6</td>
<td>104.5</td>
</tr>
</tbody>
</table>

Scaled scores: 100 is “average” and 15 is one standard deviation

No differences identified
We have learned a lot......

- Being a carrier carries health risks
  - >50% of carriers have elevated CK
    - CK is less reliable than in boys with regards to predicting disease
  - Carriers demonstrate functional performance differences
    - 6 minute walk distance
    - Perform in the low-average range on ACTIVE videogame (reachable workspace volume)
We have learned a lot......

• Carriers are at risk of developing cardiomyopathy (identical to boys)
  • 50% of carriers have scar noted on CMR (as early as 30 years)
  • Scar noted before abnormal cardiac function develops
• Measures of global heart, lung, muscle conditioning were lower than controls for DMD moms
• Incidence of cardiac rhythm abnormalities were higher in DMD moms
We have learned a lot......

• It is stressful to be a mother of a child with DMD
  • DMD moms report significant stress, decreased emotional wellbeing, and poorer health as compared to women who are not caregivers
• Life experiences likely drive the diminished psychosocial wellbeing (not genetics)
Work still needs to be done......

- Is CK a marker to identify carriers at risk?
- How shall we follow the carrier heart?
  - How do CMR and exercise findings correlate?
    - Are individuals with greater scar burden at risk for cardiac rhythm problems?
  - How should we treat the carrier heart when abnormalities are noted?
  - What is the impact of a dedicated exercise program to a carrier’s health?
Work still needs to be done......

- What is the physical and emotional impact of stress on the carrier?
- How do changes in life circumstances (e.g., disease progression in sons) impact physical and emotional wellbeing?
- What are the targets for psychosocial intervention that integrate a mind-body approach
Longitudinal data is critical to defining carrier natural history......
We need you......

• Seeking women who are genetically confirmed carriers, but have not had the experience of being the primary caregiver to a child affected by DMD or BMD

  – Provide an opportunity for the investigators to separate contributions from being a caregiver to a child with chronic disease and the impact of genetics to overall health
Thank you PPMD

Parent Project
Muscular Dystrophy

JOIN THE FIGHT. END DUCHENNE.
THANK YOU from all of us at Nationwide Children’s