Abstract

Objective
We performed a prospective, cross-sectional analysis of neurodevelopmental concerns and psychosocial adjustment in relation to DMD mutations in young steroid-naive boys with dystrophinopathy.

Methods
We evaluated 196 steroid-naive boys with dystrophinopathy who were enrolled in the Finding the Optimal Regimen for Duchenne Muscular Dystrophy trial. The neurodevelopmental concerns and psychosocial adjustment challenges were analyzed in relation to DMD mutation. A parent or legal guardian reported neurodevelopmental concerns in 4 domains (speech, learning and attentional difficulties, and autism spectrum disorder [ASD]) and completed the Personal Adjustment and Role Skills Scale to assess psychosocial adjustment. We also assessed whether boys of DMD carrier mothers were more vulnerable to speech delay and learning difficulties.

Results
We found that 39% of boys were reported to have speech delay with a mean age of speaking at 28 months (range 7–66 months). Learning difficulties were reported in 28% of participants. Inattentive-overactive and oppositional-defiant behavior was reported in 8% and 5% of participants, respectively. Psychosocial adjustment challenges were reported in 4% of participants. An ASD diagnosis was reported in 3 participants. Speech delay and learning difficulties were more common in boys with mutations downstream of DMD exon 45. Neurodevelopmental concerns were not associated with DMD deletion, duplication, or point mutation subtype. Boys of DMD carrier mothers did not have longer speech delay or more learning difficulties.

Conclusion
Our data support evidence for a relationship between neurodevelopmental concerns and DMD mutation. A longitudinal assessment of developmental trajectory is necessary to evaluate how specific DMD mutations affect brain function.
Dystrophinopathies are allelic genetic disorders caused by mutations in the dystrophin gene located on the X chromosome. The full-length dystrophin protein and the various shorter dystrophin isoforms are expressed in a tissue-specific manner in skeletal muscle, cardiac tissue, and brain. There is increasing recognition that dystrophin plays a critical role in brain development and function. There is a higher prevalence of autism spectrum disorders (ASD), attention-deficit/hyperactivity disorder (ADHD), obsessive-compulsive disorder, and epilepsy in boys with dystrophinopathy. These clinical manifestations suggest the importance of dystrophin affecting crucial neurodevelopmental pathways during childhood.

Previous studies support a relationship between the cognitive phenotype and DMD genotype in dystrophinopathy with a differential vulnerability in those with mutations in the 3’ end of the dystrophin gene. Boys with mutations downstream of DMD exon 45, which specifically affects the brain-specific dystrophin isoform dp140, have structural brain abnormalities and deficits in performance-based psychometric measures. Boys with dystrophinopathy also have psychosocial adjustment difficulties as assessed by the Personal Adjustment and Role Skills Scale (PARS-III). The PARS-III is a parent-reported questionnaire that assesses psychosocial adjustment in children with chronic medical conditions. Whether boys with DMD mutations in the 3’ end of the dystrophin gene face more psychosocial adjustment challenges has not been evaluated previously. Further, additional contextual risk factors for neurodevelopmental concerns have not been evaluated in dystrophinopathy. We studied whether sons of DMD carrier mothers are more vulnerable to neurodevelopmental concerns.

We hypothesized that boys with mutations downstream of DMD exon 45 have more neurodevelopmental concerns and psychosocial adjustment challenges compared to boys with mutations upstream of DMD exon 45. The aims of this study were (1) to evaluate the relationships between 4 neurodevelopmental concerns (speech delay, learning disability, ASD, and attentional problems) and psychosocial adjustment and DMD mutation and (2) to explore the association between speech delay and DMD carrier status. We systematically evaluated these aims in a well-characterized cohort of young boys between ages 4 and 7 years with genetically confirmed dystrophinopathy who were enrolled in an international, prospective clinical trial comparing different regimens of steroids (Finding the Optimal Regimen for Duchenne Muscular Dystrophy [FOR-DMD]; NCT01603407).

Methods

Standard protocol approvals, registrations, and patient consents

The FOR-DMD clinical trial is registered under clinicaltrials.gov (NCT01603407). The study was approved by the local institutional review board/ethics committee at each participating institution. Written informed consent was obtained from all parents/legal guardians of the study participants. The study was conducted in accordance with the Declaration of Helsinki (2000) and the Principles of Good Clinical Practice according to the International Conference on Harmonization.

Study design and participants

The FOR-DMD trial is a multicenter, international, randomized, double-blind clinical trial evaluating the relative benefits and side effects of different steroid regimens in Duchenne muscular dystrophy (DMD). The trial enrolled boys with out-of-frame DMD mutations and who were steroid-naive at time of study entry. The trial excluded those boys who were unable to reliably complete study assessments. A detailed description regarding the trial eligibility criteria has been published. We evaluated neurodevelopmental concerns and psychosocial adjustment challenges at the first study visit in boys enrolled in the FOR-DMD trial.

Study measures

Parents or legal guardians completed study-related review of systems during the first study visit. Specifically, the participant’s medical history included age (in months) at which the subject began to speak in full sentences, speech delay (yes, no, unknown), and learning difficulties (yes, no, or unknown). If learning difficulties were known to be present, the parent or legal guardian was asked to rate the difficulty as mild, moderate, or severe. We also queried whether the study participant had a diagnosis of ASD and ADHD. There was also a free text area in which parents or legal guardians could report individual concerns that were not captured through study questions.

Study-related questionnaires

A parent or legal guardian completed the following questionnaires during the study participant’s screening visit: IOWA Conners scale for ADHD and PARS-III questionnaire for psychosocial adjustment. The IOWA Conners scale is a 10-item measure of inattentive-overactive (IO) and...
oppositional-defiant (OD) behavior in children. IO behavior was assessed by the sum of items 1–5 on the IOWA Conners scale, and a participant met clinical criteria for IO behavior if the score was greater than 10. OD behavior was assessed by the sum of items 6–10, and the participant met clinical criteria for OD behavior if the score was greater than 9. The PARS-III is a 28-item proxy instrument to assess 6 domains of psychosocial adjustment: peer relations, dependency, hostility, productivity, anxiety/depression, and withdrawal. A total score of less than 72 was considered clinically significant for a boy having psychosocial adjustment challenges.

**DMD mutation data**
All participants underwent DMD genetic testing. Dystrophin mutation data from study participants and dystrophin carrier status from biological mothers of enrolled children were collected at the first study visit. Dystrophin mutation data were available in 193 of 196 participants. The dystrophin carrier status of the biological mothers was available for 130 of 196 boys. Of the 130 mothers, 83 were carriers of the dystrophin mutation.

**Statistical analysis**
Participants with DMD mutations upstream vs downstream of DMD exon 45 were compared with respect to the prevalence of neurodevelopmental concerns (speech delay, learning and attentional difficulties, and ASD), IO behavior, OD behavior, and psychosocial adjustment challenges using Fisher exact tests. The 2 groups were compared with respect to IOWA Conners and PARS-III total and subscale scores using Wilcoxon rank sum tests. Similar secondary analyses were performed to compare boys based on DMD mutation type (deletion, duplication, point mutation). Boys with biological mothers who were carriers of the dystrophin mutation were compared to those with biological mothers who were not carriers regarding the prevalence of speech delay and learning difficulties using Fisher exact tests. A 2-tailed significance level of 5% was used for hypothesis testing; for comparisons among the 3 groups defined by mutation type, a Bonferroni-adjusted significance level of 0.017 was used. All statistical analyses were performed using SAS version 9.3 (SAS Institute, Cary, NC).

**Data availability**
De-identified individual participant data and other study-related documents will be made available following conclusion of the double-blind trial. The study protocol has been published previously. The data will be deposited in a publicly available repository 1 year after the primary clinical trial report has been submitted for publication, and will be available indefinitely.

**Results**

**Demographic data and clinical characteristics**
We enrolled 196 boys in the trial. The mean age at study entry was 5.8 years (range 4.1–8.0 years, SD 1.0). Participants were recruited from 5 countries: Canada (n = 13), Germany (n = 20), Italy (n = 22), United Kingdom (n = 59), and United States (n = 82). Race was identified as white (n = 166), Asian (n = 9), mixed (n = 5), black (n = 3), others (n = 7), and unknown (n = 6). Of the 188 participants in whom ethnicity was known, 31 identified themselves as Hispanic.

IOWA Conners total and subscale scores were available in 183 and 185 participants, respectively. The mean IOWA Conners total score was 8.5 (range 0–25, SD 5.9) (n = 183). The mean IOWA subscale score was 4.9 (range 0–15, SD 3.8) (n = 185), and the mean OD subscale score was 3.6 (range 0–15, SD 3.1) (n = 185). The mean PARS-III total score was 86.2 (range 61–107, SD 9.3) (n = 171); the mean subscale scores were as follows: peer relations 10.7 (range 5–16, SD 3.0) (n = 182); dependency 11.8 (range 4–16, SD 2.3) (n = 185); hostility 18.0 (range 7–24, SD 3.6) (n = 182); productivity 10.0 (range 4–16, SD 2.2) (n = 184); anxiety/depression 20.3 (range 14–24, SD 2.3) (n = 187); and withdrawal 14.7 (range 7–16, SD 1.5) (n = 191).

**DMD mutation data**
The location of the DMD mutation was available in 193 of the 196 participants; the remaining 3 participants enrolled in the study via a protocol waiver had a positive family history of dystrophinopathy or absent dystrophin on muscle biopsy. Eighty-eight boys (46%) had mutations upstream of DMD exon 45 and 105 boys (54%) had mutations downstream of DMD exon 45. Of the 193 boys, 137 had deletions, 34 had point mutations, and 22 had duplications.

**Associations between DMD mutations and neurodevelopmental concerns**
Speech delay was reported for 74 of 192 participants (39%); data were missing in 4 participants. Speech delay was more common in boys with mutations downstream of DMD exon 45 (48%) than in those with mutations upstream of DMD exon 45 (27%) (p = 0.005, table 1). The mean age of talking in this cohort was 29 months (range 7–66 months, SD 10.7) (n = 165), and older in boys with mutations downstream of DMD exon 45 (30.3 months) compared to boys with mutations upstream of DMD exon 45 (26.7 months) (p = 0.03, table 1). The distributions of the age at speech acquisition between the boys with mutations upstream and downstream of DMD exon 45 are shown in the figure.

Learning difficulties were reported for 49 of 178 boys (28%), including 20% of those with mutations upstream and 34% of those with mutations downstream of DMD exon 45 (p = 0.03, table 1). Among the 48 participants for whom the severity of learning difficulties was reported, the severity was mild in 69% (33/48), moderate in 29% (14/48), and severe in 2% (1/48). A formal diagnosis of ASD was reported in 3 participants, all of whom had DMD mutations downstream of DMD exon 45 (table 1).
Complete IOWA Conners scale data were available in 183 participants. Fourteen of the 183 participants (8%) met criteria for IO behavior, including 10% of those with mutations downstream of DMD exon 45 and 5% of those with mutations upstream of DMD exon 45 (p = 0.27, table 1). The DMD mutations among these 14 participants included 10 deletions, 2 point mutations, and 2 duplications. Nine of the 183 participants (5%) met criteria for OD behavior, including 8% of those with mutations downstream of DMD exon 45 and only 1% of those with mutations upstream of DMD exon 45 (p = 0.04, table 1). All 9 of these participants had deletions. ADHD frequency was higher in boys with DMD mutations downstream of DMD exon 45 (5%) than in boys with DMD mutations downstream of DMD exon 45 (0%), though this difference did not reach statistical significance (p = 0.06, table 1).

**Table 1 Neurodevelopmental concerns by DMD mutation location**

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Upstream of DMD exon 45 (n = 88)</th>
<th>Downstream of DMD exon 45 (n = 105)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Speech delay</td>
<td>27</td>
<td>48</td>
<td>0.005</td>
</tr>
<tr>
<td>Age began speaking, mo</td>
<td>26.7 (10.3)</td>
<td>30.3 (10.8)</td>
<td>0.03</td>
</tr>
<tr>
<td>Learning difficulties</td>
<td>20</td>
<td>34</td>
<td>0.03</td>
</tr>
<tr>
<td>ADHD diagnosis</td>
<td>0</td>
<td>5</td>
<td>0.06</td>
</tr>
<tr>
<td>ASD diagnosis</td>
<td>0</td>
<td>2</td>
<td>0.50</td>
</tr>
<tr>
<td>IOWA Conners</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IO subscale</td>
<td>4.7 (3.2)</td>
<td>5.2 (4.4)</td>
<td>0.44</td>
</tr>
<tr>
<td>OD subscale</td>
<td>3.1 (2.7)</td>
<td>4.1 (3.5)</td>
<td>0.13</td>
</tr>
<tr>
<td>Total</td>
<td>7.9 (5.2)</td>
<td>9.2 (6.6)</td>
<td>0.25</td>
</tr>
<tr>
<td>IO subscale &gt;10</td>
<td>5</td>
<td>10</td>
<td>0.27</td>
</tr>
<tr>
<td>OD subscale &gt;9</td>
<td>1</td>
<td>8</td>
<td>0.04</td>
</tr>
<tr>
<td>PARS-III</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Peer relations</td>
<td>10.6 (2.9)</td>
<td>10.9 (3.0)</td>
<td>0.43</td>
</tr>
<tr>
<td>Dependency</td>
<td>11.8 (2.5)</td>
<td>11.9 (2.2)</td>
<td>0.69</td>
</tr>
<tr>
<td>Hostility</td>
<td>18.2 (3.6)</td>
<td>17.8 (3.7)</td>
<td>0.59</td>
</tr>
<tr>
<td>Productivity</td>
<td>10.2 (2.2)</td>
<td>10.0 (2.3)</td>
<td>0.72</td>
</tr>
<tr>
<td>Anxiety/depression</td>
<td>20.4 (2.2)</td>
<td>20.2 (2.4)</td>
<td>0.72</td>
</tr>
<tr>
<td>Withdrawal</td>
<td>14.5 (1.8)</td>
<td>14.8 (1.8)</td>
<td>0.41</td>
</tr>
<tr>
<td>Total</td>
<td>86.2 (9.9)</td>
<td>86.2 (8.8)</td>
<td>0.97</td>
</tr>
<tr>
<td>PARS-III total &lt;72</td>
<td>4</td>
<td>4</td>
<td>1.00</td>
</tr>
</tbody>
</table>

Abbreviations: ADHD = attention-deficit/hyperactivity disorder; ASD = autism spectrum disorder; IO = inattentive-overactive; OD = oppositional-defiant; PARS-III = Personal Adjustment and Role Skills Scale.
Values are mean (SD) or %.

**Associations between DMD mutation subtypes and neurodevelopmental concerns**

The prevalence of speech delay was comparable among those boys with DMD deletion, DMD duplication, and DMD point mutation. There were no statistically significant differences in the mean age at speaking (in months) among the DMD mutation subtypes. Likewise, the prevalence of learning difficulties was comparable among the DMD mutation subtypes. These results as well as comparisons among the 3 DMD mutation subtypes with respect to IOWA Conners scores are summarized in table 2.

**Associations between DMD mutation, DMD mutation subtypes, and psychosocial adjustment**

Of the 193 participants, 7 boys (4%) scored lower than the clinical cutoff score of 72 on the PARS-III, reflecting higher risk for psychosocial adjustment difficulties. Of the seven participants who had deletions, all 7 had deletions. The PARS-III total and subscores were comparable between boys with mutations upstream and downstream of DMD exon 45 (table 1). Similarly, there were no statistically significant differences in PARS-III total and subscale scores among the DMD mutation subtypes (table 2).
biological mothers who were boys. Recently it has been found that dystrophin plays of biological mothers who were not carriers of the dystrophin mutation (43% vs 34%, p = 0.35). Learning difficulties in boys were reported by 32% of biological mothers who were DMD carriers, but this difference was not statistically significant (p = 0.14).

**Associations between DMD carrier status and speech delay and learning disability**

The percentage of boys with speech delay was not significantly different between biological mothers who were and were not carriers of the dystrophin mutation (43% vs 34%, p = 0.35). Learning difficulties in boys were reported by 32% of biological mothers who were DMD carriers and by only 18% of biological mothers who were not DMD carriers, but this difference was not statistically significant (p = 0.14).

**Discussion**

The original description of DMD noted speech difficulties in boys. Recently it has been found that dystrophin plays a critical role in brain development. Full-length dystrophin and shorter dystrophin isoforms may have distinct roles during brain development, such as synaptogenesis and axon guidance. A better understanding of the neurobiological mechanisms by which dystrophin and its isoforms influence brain development and function could lead to personalizing interventions to improve neurodevelopmental outcomes.

In this study, we systematically evaluated the associations between parent-reported speech delay, learning and attention difficulties, and psychosocial adjustment challenges and DMD mutation location in 196 young boys with dystrophinopathy enrolled in the FOR-DMD trial. The prevalence of speech delay in our cohort was 39%. A novel finding of our study is that boys with mutations downstream of DMD exon 45 had higher frequency and more speech delay compared to boys with mutations upstream of DMD exon 45. Speech delay as a contextual risk factor in boys with dystrophinopathy has been well-documented. Lundy et al. found that the occurrence of speech delay was 10-fold greater in dystrophinopathy than in the general population. In this Welsh cohort, the authors found that 71% of boys with dystrophinopathy failed to attain either single words at greater than 13.7 months or meaningful sentences at greater than 29 months, measures that are indicators of speech and language developmental milestones, respectively. Speech delay was reported as one of the most common developmental concerns in the largest DMD natural history study (NCT00468832). Our data, and those from previously published studies, support the evaluation of creatine kinase in a young boy presenting with speech delay. Another inclusive strategy is to form engaged partnerships between pediatricians and neuromuscular physicians, facilitated through patient advocacy groups, to reduce the delay in establishing the diagnosis of dystrophinopathy in a young boy presenting with speech delay.

Our data support the high prevalence of speech delay in dystrophinopathy, and also highlight a differential vulnerability based on DMD mutation. This could be due in part to the role of dystrophin in both neuronal and glial function.

Studies from human brain gene expression and preclinical studies support diverse but synergistic neurobiological functions for dystrophin. Doorenweerd et al. reported that dystrophin protein dp140, which uses DMD exon 45 as a unique first promoter, is highly expressed in human cerebral cortex and cerebellum, regions that are critical for language and executive function. Coexpression analysis showed that genes associated with ASD and intellectual disability—such as those that regulate neuron development, neuron morphology differentiation, and axon guidance—are significantly coexpressed with dystrophin dp140. Also, dystrophin dp140 was recently shown to be expressed by oligodendrocytes, and abnormal myelin development is seen in the mdx mouse model of DMD. Diffuse microstructural white matter abnormalities are detected on brain imaging in boys with DMD. Myelin integrity is critical for cognition, as shown in several neurologic disorders, probably because one of the roles of myelin is in synchronization of action potential across distant brain regions.

While lateralization of language networks in the brain occurs in infancy, the pathophysiology of speech problems in dystrophinopathy remains unclear and specifically, how the absence of dystrophin affects speech is unclear. Our findings would posit that specific dystrophin isoforms in the brain may play different functional roles during development. Further,

**Figure** Box and whisker plot of the distribution of age at speech acquisition in boys with mutations upstream and downstream of DMD exon 45.
how speech delay affects developmental trajectories in dystrophinopathy is not known. Following children with receptive-expressive language delay, Hampton et al. found that language delay persisted when these children were followed for up to 12 months. Soim et al., in a population-based study in dystrophinopathy, showed that boys receiving speech therapy were more likely to repeat a grade and to use resources at school. These studies highlight that speech delay increases resource utilization, and may be associated with comorbid learning difficulties and less-optimal developmental trajectory. While many of the boys receive accommodations in school, longitudinal follow-up of how speech delay affects educational and vocational outcomes is needed. In addition, targeted screening and intervention strategies for those with speech delay may optimize developmental trajectory.

In this study, we did not find any association between the prevalence of psychosocial adjustment concerns and DMD mutation location. The PARS-III total and subscale scores in our cohort were comparable to those published by Hendriksen et al. These authors noted that these boys reported poorer peer relations as they grew older. Our cohort is much younger than those previously published, and may explain the lack of association between psychosocial adjustment concerns and DMD mutation location. A previous study showed that cumulative loss of multiple dystrophin isoforms may increase neurodevelopmental burden, and the longitudinal nature of the FOR-DMD trial will permit assessment of psychosocial adjustments through early childhood.

We used one of the most commonly used proxy measures to evaluate attentional problems in children: the IOWA Conners scale. In our cohort of young, steroid-naive boys (n = 196) between ages 4 and 7 years, a small number of participants fulfilled criteria for a higher risk of attentional problems (n = 14), as a formal clinical diagnosis of ADHD cannot be

<table>
<thead>
<tr>
<th>Table 2 Neurodevelopmental concerns by DMD mutation type</th>
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</thead>
<tbody>
<tr>
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</tr>
<tr>
<td>Speech delay</td>
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<tr>
<td>Anxiety/ depression</td>
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<tr>
<td>Withdrawal</td>
</tr>
<tr>
<td>Total</td>
</tr>
<tr>
<td>PARS-III total &lt;72</td>
</tr>
</tbody>
</table>

Abbreviations: ADHD = attention-deficit/hyperactivity disorder; ASD = autism spectrum disorder; IO = inattentive-overactive; OD = oppositional-defiant; PARS-III = Personal Adjustment and Role Skills Scale. Values are mean (SD) or %.
established before age 6. We observed that boys with mutations downstream of DMD exon 45 scored higher in OD symptoms compared to those with mutations upstream of DMD exon 4S, though these results did not reach statistical significance. Pane et al.11 evaluated 103 boys with dystrophinopathy and showed that up to 36% met DSM-IV criteria for ADHD. Compared to this earlier study, the prevalence of ADHD in our cohort is much lower. One possible reason for this is that our cohort is much younger; the mean age of participants in our study is 5.8 years, compared to the mean age of 12 years in the cohort described by Pane et al. It is likely that the entire spectrum of ADHD symptoms have not become manifest at the time of study enrollment in FOR-DMD. Also, Pane et al. used DSM-IV criteria, whereas we used the IOWA Conners scale. Population-based prevalence of ADHD in dystrophinopathy is approximately 23%.12

Subclinical cognitive deficits have been reported in carriers of other X-linked disorders such as fragile X disease42 and urea cycle disorder.43 To evaluate whether such familial, intergenerational risk occurs in dystrophinopathy, we explored whether participants whose mothers are dystrophin mutation carriers are more vulnerable to having speech delay and learning difficulties. We did not find an association between dystrophin carrier status and neurodevelopmental concerns.

Our study has some limitations. The FOR-DMD trial had only limited evaluation of neurodevelopmental concerns and did not corroborate parent-reported neurodevelopmental concerns with objective psychometric testing. Second, the present study is a cross-sectional evaluation of the neurodevelopmental concerns in clinical trial participants, and may not be fully representative of the general DMD population. Finally, the age at study entry may have had an effect on parent-reported concerns. For example, the age at which screening for speech delay is performed also has an effect on sensitivity45 as older children may have caught up in language skills.46 While there are several confounding factors that are inherent to an international study of this nature with varying differences in culture, access to medical care, social support, insurance, and health resources, what is clear is that based on epidemiologic evidence, speech delay is associated with increased utilization of school-based resources in dystrophinopathy.41

Despite these limitations, the strength of our study includes the large number of participants studied (n = 196), the international cohort, the young age (4–7 years), and steroid-naïve boys. The clinical outcomes in dystrophinopathy have improved remarkably in the last decades.57,48 Several drugs are being developed to improve skeletal muscle health in dystrophinopathy, including personalized gene-based therapies.49,50 Yet there are very few longitudinal studies with a large sample that have carefully evaluated the neurodevelopmental and cognitive needs of this population. With consideration to include dystrophinopathy in newborn screening, addressing neurodevelopmental concerns allows for opportunities to improve long-term outcomes in this medically vulnerable population.

**Author contributions**

M. Thangarajh, J. Hendriksen, M. McDermott, B. Martens, K. Hart, R. Griggs: study concept and design. M. Thangarajh, J. Hendriksen, M. McDermott, B. Martens, R. Griggs: data analysis including statistical evaluation and data interpretation. M. Thangarajh prepared the first draft of the manuscript. M. Thangarajh, J. Hendriksen, M. McDermott, and R. Griggs revised the manuscript.

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**Disclosure**

The authors report no disclosures relevant to the manuscript. Go to Neurology.org/N for full disclosures.

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