HHS Public Access

Author manuscript

J Dev Behav Pediatr. Author manuscript; available in PMC 2016 July 01.

Published in final edited form as:

J Dev Behav Pediatr. 2015 ; 36(6): 455–463. doi:10.1097/DBP.0000000000000177.

Neurobehavioral Concerns among Males with Dystrophinopathy Using Population-Based Surveillance Data from the Muscular Dystrophy Surveillance, Tracking, and Research Network

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Abstract

Objective—To describe the occurrence of selected neurobehavioral concerns among males with a dystrophinopathy and explore associations with corticosteroid or supportive device use.

Method—Medical record abstraction of neurobehavioral concerns was conducted for 857 affected males from 765 families, born since 1982 and followed through 2011, and enrolled in the population-based Muscular Dystrophy Surveillance, Tracking, and Research Network. Cumulative probabilities for attention deficit/hyperactivity disorder (ADHD), behavior problems, and depressed mood were calculated from Kaplan-Meier estimates for the subsample of oldest affected males (n=765). Hazard ratios (HRs) and 95% confidence intervals (95%CIs) for corticosteroid and supportive device use were estimated from Cox regression models with time-dependent covariates.

Results—Of the 857 affected males, 375 (44%) had at least one of the three selected neurobehavioral concerns; a similar percentage (45%) was found among the 765 oldest affected males. The estimated cumulative probabilities among these oldest affected males were 23% for ADHD, 43% for behavior problems, and 51% for depressed mood. Corticosteroid (HR=2.35, 95%CI=1.75,3.16) and mobility device (HR=1.53, 95%CI=1.06,2.21) use were associated with behavior problems. Use of a mobility device (HR=3.53, 95%CI=2.13,5.85), but not

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Conflicts of Interest: The other authors have indicated they have no potential conflicts of interest relevant to this article to disclose.

corticosteroids, was associated with depressed mood. ADHD was not significantly associated with corticosteroid or mobility device use. Respiratory assist device use was not examined due to low numbers of users prior to onset of neurobehavioral concerns.

Conclusion—Selected neurobehavioral concerns were common among males with a dystrophinopathy. Reported associations highlight the importance of increased monitoring of neurobehavioral concerns as interventions are implemented and disease progresses.

Keywords

Dystrophinopathy; Neurobehavioral; ADHD; Neuromuscular Disorder

OBJECTIVE

Duchenne and Becker muscular dystrophies, together referred to as dystrophinopathies, are caused by mutations in the dystrophin gene (*DMD*) on the X-chromosome and result in progressive muscle weakness.[1,2] Duchenne muscular dystrophy (DMD) is the form most commonly diagnosed in early childhood and affects approximately 1:3500 males.[2] Males with DMD generally require a wheelchair full-time by age 12 years and have shortened life expectancies, most often due to cardiac or respiratory failure. Becker muscular dystrophy (BMD) has a prevalence estimated at one-fifth of that reported for DMD.[1] BMD has a less stereotyped course than DMD, and typically has later onset and more slowly progressive weakness, along with variable life expectancy.[1,2] Recent treatments, including use of corticosteroids and respiratory support devices, have extended the survival of those with dystrophinopathies by delaying respiratory and cardiac complications.[3]

In addition to skeletal muscle involvement, learning disorders or cognitive impairment are often part of the dystrophinopathy phenotype.[4–7] Among the neurobehavioral concerns studied, higher frequencies of ADHD,[6,8,9] autism spectrum disorder,[8,10–13] and obsessive-compulsive disorder (OCD)[8] have been reported for those affected with a dystrophinopathy compared to the general population.[8,11] Other studies have reported high levels of clinically significant externalizing and internalizing behaviors[11,13–15] and difficulties with social functioning[11,14–16] among affected individuals. These neurobehavioral and psychosocial concerns have been attributed, in part, to underlying neurocognitive deficits[17] and physical limitations that may arise with greater disease severity.[11,15,18,19] Statistically significant associations between neurobehavioral concerns and indicators of disease progression or treatment have not been consistently reported.[6,8,11,13,15] Most, but not all, of these studies were limited to males with DMD, although specific diagnostic criteria were not consistently defined.

Although frequent occurrences of neurobehavioral concerns are suggested, existing studies have methodological limitations. Many relied on convenience samples identified from clinics[6,9,10,12–15,20] or recruited from patient support or advocacy groups,[8,15] which may not be representative of the overall patient population. These studies were also cross-sectional, sampled a broad age range of patients, and many relied on behavioral checklists for self- or parent-report of neurobehavioral concerns.[8,9,11,13,15,16,20] These methodological limitations make it difficult to fully evaluate frequencies of neurobehavioral concerns among those with

a dystrophinopathy and preclude the use of appropriate analytic methods that could provide more accurate frequency estimates and evaluate time-ordered associations with disease progression and treatments.

To complement these previous studies and address some of their limitations, we used surveillance data collected through the Muscular Dystrophy Surveillance, Tracking, and Research Network (MD STAR*net*)[21,22] to describe frequencies of selected neurobehavioral concerns and associations with medical interventions among males with childhood-onset dystrophinopathy. MD STAR*net* data were collected through annual medical record abstraction in defined geographic areas, providing a population-based sample of those affected with dystrophinopathies. The findings from our study will provide clinicians and families with information about the risk of neurobehavioral concerns, thereby promoting optimal monitoring and timely management of such concerns.

METHOD

Study Population and Sample

The methods of Muscular Dystrophy Surveillance, Tracking, and Research Network (MD STAR*net*) have been described elsewhere.[22] Briefly, starting in 2004, the MD STAR*net* retrospectively identified dystrophinopathy cases who were born since January 1, 1982, diagnosed by age 21 years, and resided in an MD STAR*net* site [Arizona (AZ), Colorado (CO), Iowa (IA), and the western part of New York State (wNY)]; Georgia (GA) and Hawaii (HI) joined the MD STAR*net* in 2005 and 2008, respectively. For each case identified, trained medical abstractors reviewed medical records and entered data into an electronic surveillance instrument. Abstracted data included sociodemographic data, clinical signs and symptoms, diagnostic/clinical tests, family history of dystrophinopathy, medical treatments received, and medical complications. Data on schooling, rehabilitation, mobility, and neurobehavioral concerns were also collected. Since the initiation of surveillance, all retrospectively identified and newly diagnosed cases were prospectively followed through annual medical record abstraction through December 31, 2011 (for cases ascertained before 2011), December 31, 2012 (for cases ascertained in 2011), or until death or migration out of an MD STAR*net* site. Surveillance data collection was approved either through changes to existing public health surveillance regulations (CO, GA, IA, wNY) or institutional review board approvals (AZ, HI).

Selected clinical data abstracted were reviewed by a clinical review committee composed of health care providers experienced in treating individuals with dystrophinopathies and assigned a case status: possible, probable, definite, asymptomatic, or female.[21] All possible cases had recorded clinical symptoms related to a dystrophinopathy and elevated creatine kinase. Probable cases also had an X-linked pedigree consistent with a dystrophinopathy. Definite cases had a confirmed *DMD* mutation, a muscle biopsy showing absent dystrophin, or an X-linked pedigree and an affected family member with a *DMD* mutation or diagnostic muscle biopsy. Cases who met criteria for definite, but did not show any clinical symptoms, were defined as asymptomatic. Females who were diagnosed with a dystrophinopathy before age 21 years and had a *DMD* mutation or diagnostic muscle biopsy were also ascertained. Each site performed quality control checks, and data with possible errors were

sent back to abstractors for further review.[22] Data from each MD STAR*net* site were de-identified and pooled into a combined database that included cases classified as definite, probable, and affected females from each site.

We analyzed the pooled MD STAR*net* surveillance dataset, version 7 (release date June, 2012), which included 795 definite male cases, 80 probable male cases, and 9 affected females for a total of 884 cases. We excluded cases from Hawaii (n=18), due to restricted ascertainment and a limited follow-up period, and affected females (n=9), due to unique clinical and genetic features of females with a dystrophinopathy. The final analytic sample comprised 857 affected males with definite or probable dystrophinopathy from 765 families.

Neurobehavioral Concerns and Intervention

Neurobehavioral concerns documented in the medical records were entered into the abstraction instrument according to predefined categories of depression, behavior problems, ADHD, anger management, or other concerns. A text field was available to provide additional details about concerns listed as other. After review, the concerns listed in the other text field were recoded into the following selected subtypes: ADHD, behavior problems, or depressed mood. The final categories combined the predefined categories and those recoded from the other text field into the following subtypes: ADHD, behavior problems (conduct problems, externalizing behaviors, aggression, anger management issues), or depressed mood (depression, bipolar disorder). For each subtype, we also calculated the age at first documentation of each neurobehavioral concern.

At each annual follow-up abstraction, all medications and recommendations for and participation in counseling documented in the medical record were entered into the abstraction tool. Medications were reviewed and coded into the following classes: antidepressants, anticonvulsants, anxiolytics, antipsychotics, and psychostimulants. We coded counseling as received if documented as received at any point in time for a specific neurobehavioral concern. For cases where counseling was not coded as received, counseling was coded as none, unknown, or recommended but not started.

Sociodemographic and Disease-Related Characteristics

We included the following selected characteristics to describe cases: MD STAR*net* site, case race/ethnicity (non-Hispanic white, Hispanic, or other), and age at last health encounter. Data available for analysis of treatments and supportive devices included first use of: corticosteroids, a mobility device (wheelchair or scooter, at least part-time), and a respiratory support device (continuous positive airway pressure, biphasic positive airway pressure, tracheostomy). Data recorded for corticosteroids included date or age when first used, dates or ages when dosage was changed or discontinued, and reason for discontinuation. Data recorded for use of a mobility device or respiratory support device included date when first used and frequency of use.

Statistical Analysis

We conducted the analyses using Statistical Analysis Software (SAS) version 9.3 (SAS Institute, Cary, NC). We estimated the observed frequencies of each neurobehavioral

concern for the total sample of all affected males (n=857) and two subsamples selected to evaluate comparability of the oldest affected male sample to all dystrophinopathy cases in MD STAR*net* and other studies: 1) only the oldest affected male from each family (n=765) and 2) only oldest affected males who were at least 17 years of age at last follow-up (n=309). Descriptive statistics calculated included counts for categorical variables (i.e., MD STAR*net* site, race/ethnicity), as well as means (*M*), medians (*Mdn*), standard deviations (*SD*), and minimum and maximum (*min*, *max*) values for continuous variables (i.e., age at last health encounter; onset ages for each neurobehavioral concern; and onset ages for use of corticosteroids, a mobility device, and a respiratory support device). For reporting mental health interventions, males who had a single documented neurobehavioral concern (i.e., ADHD only, behavior problems only, or depressed mood only) or a combination of 2 or more concerns (e.g., ADHD plus behavior problems) were identified to allow examination of concern-specific interventions. Frequencies of counseling received and medication classes prescribed, or the combination of these interventions, were then calculated for each selected neurobehavioral concern.

For selected neurobehavioral concerns, we used the Kaplan-Meier method to estimate cumulative probabilities for each concern through age 29 for the sample of oldest affected males. Due to high censoring rates, mean and median survival times are not reported. To evaluate associations between each neurobehavioral concern and corticosteroid treatment or use of a supportive device, crude and adjusted hazard ratios (HR)s were estimated from Cox regression with time-dependent covariates. MD STAR*net* site was included as a fixed covariate in the adjusted analyses. Corticosteroid use was coded into annual variables with any use coded as ‘yes’ if corticosteroids were used at least one day during that year and as ‘no use’ if there was not a single day of use documented for that year. This threshold was chosen because onset of behavior problems was an outcome of interest but may also be an indication for discontinuing steroid therapy. Time-dependent coding for use of a mobility device or respiratory support device were coded as ‘no use’ for each year up until the age at first use and as ‘yes’ for the year of first use and each year thereafter. Because the time-dependent covariates were coded annually, specific dates were reviewed to ensure accurate temporal ordering was captured (e.g., onset of part-time wheelchair use did not occur after onset of depressed mood within the same year).

Comparative Analyses

For comparative purposes, we constructed two additional sets of analytic samples that more closely represented the published maximum age of risk for a specific neurobehavioral concern[23] or the maximum age included in national studies of childhood-onset neurobehavioral concerns.[24] For the first sample, an age of risk approach was used, whereby the maximum follow-up age was defined as the published maximum age of risk for a given neurobehavioral concern or at least 95% of the observed age distribution (i.e., up to and including the 14th birthday for ADHD and behavior problems, and the 19th birthday for depressed mood). For the second sample, a population-based approach was used to create a sample consistent with ages based on samples recruited for national studies of neurobehavioral concerns.[24] The maximum age for this approach was up to and including the 17th birthday for each neurobehavioral concern examined. For each approach, the age at

final follow-up was recoded to the defined maximum age. Using onset of behavioral problems as an example, the age of risk approach coded all final follow-up ages that occurred after the 14th birthday as 14 years, whereas the population-based approach coded all final follow-up ages that occurred after the 17th birthday as 17 years.

RESULTS

The sample distribution by Muscular Dystrophy Surveillance, Tracking, and Research Network (MD STAR*net*) site showed a higher number of dystrophinopathy cases from AZ (22%), CO (22%), and GA (27%), with lower but approximately equal numbers from IA (14%) and wNY (13%) (data not shown). Cases were also predominantly non-Hispanic white (66%), followed by Hispanic (21%) and other race/ethnicity (13%), and their average age at last follow-up abstraction averaged 15 years 6 months (*min, max* = 1 – 29 years) (data not shown). For the total sample of all affected males (n=857), nearly one-half had at least one documented neurobehavioral concern (Table 1). Behavior problems (26%) were most frequently documented, followed by ADHD (18%) and depressed mood (17%). The oldest affected male subsample showed similar distributions as those for the total sample of males. Finally, analysis of the subsample of oldest males in the family who were at least 17 years of age at the time of last follow-up abstraction showed a higher frequency for depressed mood (31%) but lower frequencies for behavior problems (21%) and ADHD (18%).

Due to the similarity of frequency estimates across the total and oldest affected male samples, the remainder of findings are from analyses restricted to the latter subsample to avoid shared non-genetic factors (e.g., increased monitoring by caregivers or treating physicians of younger affected siblings due to clinical presentation and treatments received by older affected sibling) that may contribute to neurobehavioral concerns or treatments received. In this subsample of 765 males, 29% (n=225) had one recorded neurobehavioral concern, 13% (n=97) had two, and 3% (n=24) had all three (data not shown). On average, first concerns about ADHD and behavior problems occurred around age 8 years (*SD*=3 and 4, respectively; *min, max*=3, 18 and 2, 27, respectively), and first concerns about depressed mood occurred around age 13 years (*SD*=4; *min, max*=4, 27) (data not shown). Among all oldest affected males, 414 (54%) used corticosteroids, 564 (74%) used a mobility device at least part-time, and 208 (27%) had used a respiratory support device (data not shown). On average, corticosteroids were initiated at approximately 7 years of age (*SD*=3; *min, max*=2, 25); use of mobility and respiratory support devices was initiated at approximately 9 (*SD*=3; *min, max*=3, 24) and 16 years of age (*SD*=4; *min, max*=6, 26), respectively (data not shown).

Of the 346 cases with at least one recorded neurobehavioral concern, 238 (69%) received some form of mental health intervention (Table 2). Of those, 88 (25%) received neuropsychiatric medication only, 58 (17%) participated in counseling only, and 92 (27%) received both counseling and medication. Use of mental health interventions varied by type of neurobehavioral concern (Table 2); a low proportion (29%) of males with behavior problems only were prescribed neuropsychiatric medication. Conversely, higher proportions of males with ADHD only (52%) or depressed mood only (63%) were prescribed medication; stimulants were the most commonly prescribed for ADHD and antidepressants were most commonly prescribed for depressed mood. Counseling was least likely to be

recommended for those with ADHD only (57%). Counseling was recommended but not started for 12 males with ADHD only (6 were also prescribed medication), 25 with behavior problems only (5 were also prescribed medication), 20 with depressed mood only (14 were also prescribed medication), and 23 with a combination of two or more concerns (15 were also prescribed medication) (data not shown). The reasons why counseling was not initiated by the families were not indicated. Finally, the group with the lowest frequency of any mental health intervention was behavior problems only, for whom 56% had no documented intervention. Most cases (>80%) with depressed mood only or combinations of neurobehavioral concerns had the highest frequency of any mental health intervention.

Kaplan-Meier survival curves, estimated through age 29 years, showed cumulative probabilities of 23% for ADHD, 43% for behavior problems, and 51% for depressed mood (Table 3, and see Supplemental Digital Content, Figure 1, which shows estimates from Kaplan-Meier results for each neurobehavioral concern). The cumulative probabilities estimated from the Kaplan-Meier method were slightly higher than the observed frequencies for ADHD (23% vs 19%, respectively), but substantively higher than those for behavior problems (43% vs 26%, respectively) and depressed mood (51% vs 19%, respectively).

Cox regression analyses showed the hazard of ADHD was increased for corticosteroid users compared to non-users, but the crude HR was not statistically significantly different from 1.0; conversely, a non-significant reduced hazard of ADHD was found for use of a mobility device (Table 4). The crude HRs were significantly larger than 1.0 for risk of behavior problems, with hazards 2.4 times higher during years in which corticosteroids were used and 53% higher during years in which a mobility device was used (Table 4). The crude HR for the association between depressed mood and corticosteroids was found to be different from 1.0, but not statistically significant; however, the hazard of depressed mood was 3.5 times more likely during years in which a mobility device was used. Adjusting for MD STAR*net* site as a fixed factor in the cox regression analyses did not substantively change the HRs and their statistical conclusion (data not shown).

Comparative Analyses

The cumulative probability estimates from the comparative analyses for the age of risk sample, which recoded maximum follow-up ages to disorder-specific ages, were similar to the estimates from the original sample for ADHD (22% vs 23%), but lower for behavior problems (28% vs 43%) and depressed mood (30% vs 51%) (Table 1 Supplemental Digital Content, and Figure 2 Supplemental Digital Content, which show Kaplan-Meier results for analysis of the age recoded samples). The results for the population-based recoded samples, which recoded maximum follow-up ages to 17 years for all outcomes, were similar to the age of risk recoded samples with a slight increase in the cumulative probability for behavior problems (30% vs. 28%) and a slight decrease for depressed mood (25% vs. 30%).

The conclusions from the Cox Regression analyses of the age-recoded analytic samples were similar to those from the original sample of oldest affected males. The HRs for ADHD remained statistically non-significant for use of corticosteroids (see Supplemental Digital Content, Figure 3, which shows crude hazard ratios for associations between corticosteroids and neurobehavioral concerns for age recoded analytic samples) or a mobility device (see

Supplemental Digital Content, Figure 4, which shows crude hazard ratios for associations between mobility device use and neurobehavioral concerns for age-recoded analytic samples). HRs for behavior problems calculated from each analytic sample did not change in magnitude from those of the previous sample and remained statistically significant. Finally, the magnitude of the HR for the associations between depressed mood and corticosteroid use in the population-based sample increased in magnitude and reached statistical significance, and the HR for use of a mobility aid increased in magnitude and retained significance.

DISCUSSION

Our study reports on the frequencies of ADHD, behavior problems, and depressed mood documented in the medical records of males with childhood-onset dystrophinopathies identified by the population-based Muscular Dystrophy Surveillance, Tracking, and Research Network (MD STAR*net*).[22,25] Nearly one-half of the total sample had at least one of these three neurobehavioral concerns. Behavior problems were most frequently recorded, followed by ADHD and depressed mood. Compared to population estimates among males age 9–16 years, our observed frequency of behavior problems (26%) was similar to published estimates (30%).[26] In contrast, our observed frequencies for ADHD (19% vs ~8%)[27–30] and depressed mood (19% vs 7%-13%)[26,27] were nearly three times higher than population estimates.

Of those studies that reported on neurobehavioral concerns among individuals with a dystrophinopathy, our observed frequency of ADHD was higher compared to a study that used parent-reported physician diagnoses (12%, ages 5–18 years)[8] but lower than studies that conducted formal ADHD evaluations (32%, ages 4–16 years)[6,31] or relied on parent report of symptoms (50–62%, ages 8–15).[9,13] Study differences were also found for the frequency of behavior problems from those that relied on parent reports on behavior checklists (e.g, Child Behavior Checklist, Strengths and Difficulties Questionnaire) with higher frequencies of behavior problems (>40%) than our observed estimate of 26%.[11,13] These checklists may include a broad range of behaviors that may not have been identified through medical record review, thereby resulting in higher reported frequencies. Similarly, comparisons with studies of the frequency of depressed mood showed variability by methods with reported frequencies ranging from no evidence of depression from parent-report[13,15] or self-report,[9,20] to a frequency of 52% (ages 2–17) from a study that observed mood.[14]

Our examination of mental health interventions showed variability in treatment approaches by type of neurobehavioral concern. As expected, ADHD only was most often treated with psychostimulants, whereas depressed mood only was treated with antidepressants. The frequency of medications prescribed for the treatment of ADHD and depressed mood is consistent with that reported by Banihani et al.[31] Behavior problems only had the lowest frequencies for both intervention modes. Concomitant treatment with medication and counseling was most common among those with more than one neurobehavioral concern and least frequent among those with ADHD or behavior problems only. As with care recommendations for the management of the physical morbidities of dystrophinopathy,

further development and evaluation of evidence-based treatments of neurobehavioral concerns among individuals with childhood-onset dystrophinopathies is needed.

Our use of longitudinal data allowed analysis of time-ordered associations between neurobehavioral concerns and use of corticosteroids or a mobility device. We showed a statistically significant higher risk of behavior problems among corticosteroid users, which is consistent with clinical observations, but inconsistent with previous studies that showed no association.[11,15,19] Our findings that corticosteroid use did not significantly increase the risk for ADHD is consistent with previous cross-sectional studies that also failed to show significant associations between steroid use and ADHD.[6,11,13,15] The absence of a significant association suggests that ADHD may be part of the dystrophinopathy phenotype and, regardless of corticosteroid use, may reflect how deficient dystrophin production in the brain contributes to attentional deficits in this population.[4–6,16,32] We also observed that use of a wheelchair or scooter at least part-time was associated with increased risk of behavior problems and depressed mood, but not ADHD. Mixed findings have been reported for associations between declines in mobility, as documented by mobility device use in this study, and neurobehavioral concerns. A small study of males with DMD failed to find significant associations between parent-reported behavior problems and indicators of clinical severity (e.g., muscle wasting, absence of independent ambulation)[13]. In contrast, other studies have reported a role of declining mobility on behavioral and emotional adaptation[11,15,18,19]. These findings suggest monitoring of specific neurobehavioral concerns may differ by treatments implemented and stage of disease progression.

We used multiple analytical approaches to evaluate frequencies of neurobehavioral concerns among males with a dystrophinopathy. These approaches included use of time-to-event analyses (i.e., Kaplan-Meier method) and comparative analyses that employed multiple sample definitions to account for age of risk for each outcome and, where possible, allowed comparison with samples from general population studies. We found relatively stable observed and cumulative probabilities across all samples and analytic methods for ADHD (18–23%), which was not surprising because DSM-IV diagnostic criteria require symptom onset prior to age 7 years and the majority (91%) of cases were past this age at last follow-up. The behavior problems we examined (e.g., anger, conduct disorder, aggressive behavior) are also generally characterized as childhood-adolescent disorders but showed greater variability across samples and analytic methods, with observed frequencies ranging from 21–26%, and cumulative probabilities ranging from 28–43%. Our highest probability observed for occurrence of behavior problems was from Kaplan-Meier estimates for oldest affected males (43%), and the lowest were from our samples that restricted follow-up to mid- to late-adolescence (28–30%). This variability in estimates suggests that the occurrence of behavior problems in childhood-onset dystrophinopathy may extend beyond the expected upper age limit generally reported for disruptive behaviors in general population studies.[23,29] The extended age of onset could also be attributed, in part, to the role of corticosteroids and response to disease progression (e.g., frustration with decreasing mobility or increasing social isolation), as supported by the significant associations between these factors and onset of behavior problems. Finally, frequencies associated with depressed mood also varied by our sample types and analytic methods. The observed frequency for depressed mood was higher among cases who were at least age 17 years (31%) compared to

our sample of oldest affected males only (17%); conversely, our age recoded samples showed lower cumulative probabilities when we restricted the sample to early or late adolescence (30% and 25%, respectively). These findings are consistent with a late-onset disorder, such as depression, and highlight the potential underestimation of risk for depressed mood in dystrophinopathies if the sample does not include older patients.

Our study has many methodological and analytical advantages compared to previous cross-sectional studies of patients with dystrophinopathy. The MD STAR*net* provides the largest population-based sample of individuals with childhood-onset dystrophinopathies in the United States. The sample size permitted use of complex analytic methods to evaluate the lifetime risk of neurobehavioral concerns, specifically, the use of time-to-event analytic methods (i.e., Kaplan Meier method). Our use of longitudinal surveillance of both neurobehavioral concerns and medical treatments and supportive devices also permitted evaluation of time-ordered associations that might not be possible with a cross-sectional study design. Furthermore, our reliance on medical record review may have minimized the impact of recall bias on frequency estimates generated from cross-sectional studies[33] and permitted examination of prescribed mental health interventions used to treat neurobehavioral concerns in this population.

Despite the methodological and analytical advantages, our findings need to be interpreted with caution. The MD STAR*net* identifies and tracks cases with childhood-onset dystrophinopathies within a defined geographical areas, potentially limiting generalization to the entire United States population.[22] Our analyses did not distinguish between DMD and BMD but rather focused on the inclusive dystrophinopathy diagnosis. We recognize that ignoring this distinction may affect extrapolation of expected frequencies of specific neurobehavioral concerns within each dystrophinopathy subtype due to variability in dystrophin deficiency.[34] However, there should be little influence on the association analyses between our indicators of disease severity and neurobehavioral concerns studied. Clinical data were predominantly abstracted from neuromuscular medical records, which may have led to an underestimation of the frequency of concerns not listed in the reviewed records and the absence of results from formal neuropsychiatric evaluation and diagnosis. Furthermore, additional neurobehavioral concerns reported in previous studies of dystrophinopathy (e.g., autism spectrum disorder, cognitive functioning) were not analyzed due to inconsistent documentation in the medical records and lack of access to requisite diagnostic test results (e.g., cognitive function evaluations). Our data collection also did not allow determination of whether neuropsychiatric medications were prescribed for a neurobehavioral concern or for an alternative co-morbid condition. However, the patterns of prescribed medications within the neurobehavioral categories provide us with limited external validity to the categories of concerns we defined from review of medical records. Another limitation is the quality of the event dates recorded. Although we conducted careful review of these dates, they may not accurately reflect the actual onset of a neurobehavioral concern, as time will lapse between the initial observation by the caregiver and reports to a healthcare provider; thus, there may be some misclassification in the time ordering of events. In addition, the neurobehavioral concerns studied were treated analytically as independent events, when the true nature of analyzed, and unanalyzed (e.g., autism spectrum

disorder), neurobehavioral concerns may represent a continuum of behaviors (e.g., ADHD and behavior problems fall within the DSM-IV attentive and disruptive behaviors axis) or may be temporally related (e.g., behavior problems increases likelihood of experienced depressed mood). Lastly, detection and documentation of neurobehavioral concerns may not be standard across clinics or treating healthcare providers and may reflect caregiver report rather than formal diagnoses; thus, the data recorded in the medical record could reflect differences in health care provision or reporting of these concerns by caregivers or patients.

In conclusion, our findings identified neurobehavioral concerns as common co-morbidities of childhood-onset dystrophinopathies. Our findings suggest that use of corticosteroids is associated with an increased risk of behavior problems, ADHD might be a part of the dystrophinopathy neurocognitive phenotype, and the risk of depressed mood increases with disease severity. Considering these findings, and consistent with the recommendations of the 2010 DMD Care Considerations,[18] the use of brief screening tools in the neuromuscular office, referrals for standardized evaluation and monitoring of neurobehavioral concerns, and where appropriate, provision of pharmacological interventions and improved access to psychosocial counseling should be encouraged in this patient population. Future studies should continue to explore biological etiologies in order to promote early identification and determine appropriate interventions.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

ACKNOWLEDGEMENT

This work was funded by cooperative agreements (U01 DD000189 and U01 DD001119) from the Centers for Disease Control and Prevention. The authors thank members of the MD STAR*net* data sharing committee for their manuscript review and input. We also acknowledge the efforts of all the study coordinators, abstractors, and data managers in data collection and cleaning. All the authors contributed to the conception, design, analysis, interpretation of data, and final approval of the manuscript.

Source of Funding: Dr. Mathews has received institutional support for clinical trials from Serepta Therapeutics, Prosensa, Eli Lilly, Viropharma, and PTC.

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Table 1

Frequencies and percentages of neurobehavioral concerns among males with dystrophinopathies from the Muscular Dystrophy Surveillance, Tracking, and Research Network (MD STAR*net)*, 1982–2011

	Total sample[2]		Oldest affected male only sample		Oldest affected male only restricted sample – age 17[3]	
Neurobehavioral concern[1]	***n***	**%**	***n***	**%**	***n***	**%**
Sample sizes	857	-	765	-	309	-
None	482	56	419	55	152	49
ADHD	156	18	146	19	56	18
Behavior problems	223	26	202	26	66	21
Depressed mood	150	17	143	19	97	31

ADHD=attention deficit/hyperactivity disorder.

[1] Males may have more than one documented neurobehavioral concern, thus, the categories are not mutually exclusive, and the total % may exceed 100%.

[2] Included all affected males (older and younger siblings) from a family. Average age of younger affected siblings (n=92; *Mean*=13.47, *Standard Deviation*=5.87; minimum, maximum=1, 26).

[3] All males who were at least 17 years of age at last follow-up clinic visit.

Table 2

Types of mental health interventions by type of neurobehavioral concern[1] among oldest affected males with dystrophinopathies from the Muscular Dystrophy Surveillance, Tracking, and Research Network (MD STAR*net*), 1982–2011 (n=346)

	ADHD only	Behavior problems only	Depressed mood only	Multiple concerns (>=2)
Interventions	**n (%)**	**n (%)**	**n (%)**	**n (%)**
Totals	63	95	67	121
Neuropsychiatric Medications[2]				
Any medication	33 (52)	28 (29)	42 (63)	77 (64)
Antidepressants	7 (11)	11 (12)	37 (55)	51 (42)
Anticonvulsants	3 (5)	10 (11)	10 (15)	19 (16)
Anxiolytics	7 (11)	6 (6)	11 (16)	23 (19)
Antipsychotics	2 (3)	7 (7)	1 (1)	10 (8)
Stimulants	29 (46)	8 (8)	0 (0)	42 (35)
Counseling				
Not recommended	36 (57)	41 (43)	18 (27)	21 (17)
Recommended not received	12 (19)	25 (26)	20 (30)	23 (19)
Received	15 (24)	29 (31)	29 (43)	77 (64)
Neuropsychiatric Medication or Counseling Received				
None	24 (38)	53 (56)	12 (18)	19 (16)
Medication only	24 (38)	13 (14)	26 (39)	25 (21)
Counseling only	6 (10)	14 (15)	13 (19)	25 (21)
Both medication and counseling	9 (14)	15 (16)	16 (24)	52 (43)

ADHD=attention deficit/hyperactivity disorder.

[1]The calculation of ‘ADHD only’, ‘Behavior problems only’, ‘Depressed mood only’, and ‘Multiple concerns’ used all three subtypes of neurobehavioral concerns to classify.

[2]Males may have been prescribed more than one neuropsychiatric medication.

Table 3

Kaplan-Meier results for neurobehavioral concerns among oldest affected males with dystrophinopathies from the Muscular Dystrophy Surveillance, Tracking, and Research Network (MD STAR*net*), 1982–2011 (n=765)

Models	Count with concerns	Censored n (%)[1]	% without concerns	% with concerns
ADHD	146	619 (81)	77	23
Behavior problems	202	563 (74)	57	43
Depressed mood	143	622 (81)	49	51

ADHD=attention deficit/hyperactivity disorder.

[1] No documentation of neurobehavioral concern at last health encounter

Table 4

Crude hazard ratios (cHR)s and 95% confidence intervals (CI) from Cox regression with time dependent covariates predicting neurobehavioral concerns among oldest affected males with dystrophinopathies from the Muscular Dystrophy Surveillance, Tracking, and Research Network (MD STAR*net*), 1982–2011 (n=765)

Models	cHR	95% CI
ADHD		
Corticosteroids[1]	1.31	0.92–1.88
Mobility assistive device	0.85	0.55–1.30
Behavior problems		
Corticosteroids[1]	2.35	1.75–3.16
Mobility assistive device	1.53	1.06–2.21
Depressed mood		
Corticosteroids[1]	1.33	0.94–1.88
Mobility assistive device	3.53	2.13–5.85

ADHD=attention deficit/hyperactivity disorder.

[1] Corticosteroid use defined as at least one day of use within a year.