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Sleep Disorders in Boys with Duchenne Muscular Dystrophy

THESE

préparée sous la direction du Docteur Christopher NEWMAN, PD et MER
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par

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Sleep Disorders in Boys with Duchenne Muscular Dystrophy

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RAPPORT DE SYNTHESE

Introduction La dystrophie musculaire de Duchenne (DMD) est une myopathie progressive liée au chromosome X qui atteint environ un garçon sur 3500. Des troubles du sommeil (TDS) sont fréquemment rapportés par ces patients Les études effectuées à ce jour se sont essentiellement concentrées sur les troubles respiratoires liés au sommeil. Les TDS débutent toutefois fréquemment avant l'installation d'un trouble ventilatoire nocturne et de nombreux autres facteurs peuvent en être la cause.

Objectif L'objectif de cette étude est d'évaluer la fréquence des TDS chez les garçons avec une DMD et d'en identifier les facteurs de risque.

Méthode Il s'agit d'une étude transversale effectuée par questionnaire postal adressé aux parents de tout garçon âgé de 4-18 ans avec une DMD, suivi dans deux centres tertiaires de réhabilitation pédiatrique (Lausanne et Dublin). Les TDS sont évalués à l'aide de la 'Sleep Disturbance Scale for Children' (SDSC), validée sur 1157 enfants sains. Elle permet d'obtenir un score total et des scores pour six facteurs représentant les TDS les plus fréquents (troubles de l'endormissement et du maintien du sommeil (TEMS), éveil nocturne-cauchemars, transition veille-sommeil, somnolence diurne excessive, troubles respiratoires associés au sommeil (TRS), hyperhidrose du sommeil). Un T-score supérieur à 70 (>2DS) est considéré comme pathologique. Les associations potentielles entre des scores pathologiques et des facteurs individuels (âge, mobilité diurne et nocturne, douleur), thérapeutiques (orthèses nocturnes, ventilation non-invasive, médication) et environnementaux (facteurs socio-familiaux) sont évaluées à l'aide d'analyses univariées ($\chi 2$) et de régressions logistiques ascendantes.

Résultats Seize garçons sur 63, soit 25.4%, présentent un score total pathologique en comparaison au 3% attendus dans la population générale. Les TEMS (29.7%), les TRS (15.6%) et l'hyperhidrose du sommeil (14.3%) sont les TDS les plus prévalent.

Le besoin d'être mobilisé la nuit par un tiers (OR=9.4; 95%CI: 2.2-40.7; *p=0.003*) et être l'enfant d'une famille monoparentale (OR=7.2; 95%CI: 1.5-35.1; *p=0.015*) sont des facteurs de risque indépendants pour un score total pathologique. Le besoin d'être mobilisé la nuit par un tiers (OR=18.0; 95%CI: 2.9-110.6; *p=0.002*), le traitement par corticostéroïdes (OR=7.7; 95%CI: 1.4-44.0; *p=0.021*) et être l'enfant d'une famille monoparentale (OR=7.0; 95%CI: 1.3-38.4; *p=0.025*) sont des facteurs de risque indépendants pour un TEMS.

Discussion Cette étude montre une prévalence élevée des TDS chez les garçons avec une DMD (25% contre 3% attendus dans la population générale). Le besoin d'être mobilisé la nuit par un tiers est identifié comme un facteur de risque important pour un score total pathologique et un TEMS. Il reflète vraisemblablement un degré d'atteinte motrice tel qu'il limite les mouvements spontanés et les adaptations posturales du sommeil, ayant pour conséquence une diminution importante de la qualité du sommeil. Les enfants vivant dans un foyer monoparental présentent plus fréquemment un score total pathologique et des TEMS, possiblement en lien avec un stress psychologique plus important dans ces familles. Le traitement par corticostéroïdes est identifié comme facteur de risque pour un TEMS. Une adaptation du schéma ou du dosage permet généralement de limiter cet effet secondaire. Si nécessaire, un traitement par Mélatonine peut être instauré.

Aucune association n'a pu être mise en évidence entre les facteurs analysés et les TRS, possiblement en raison du petit nombre de garçons ayant rapporté de tels symptômes et du fait que certains symptômes d'hypoventilation nocturne ne sont pas évalués par la SDSC. Par ailleurs, la valeur prédictive de l'anamnèse, comme celle des fonctions pulmonaires diurnes, est connue pour être limitée, raison pour laquelle une oxy-capnométrie est effectuée de routine en dessous d'une capacité vitale forcée de 50%. Elle permet, si nécessaire, l'instauration précoce d'une ventilation non-invasive, limitant ainsi vraisemblablement l'impact de l'hypoventilation nocturne sur la qualité du sommeil dans notre population.

Plusieurs limitations sont à évoquer. Le petit nombre de patients ne permet pas d'exclure d'autres associations potentielles. La nature transversale de l'étude augmente le risque de causalité inverse. Cette étude n'inclut pas de mesure quantitative du sommeil. Les questionnaires adressés aux parents ont toutefois pu être démontrés comme fiables hormis pour les TRS. Un biais de non-réponse ne peut pas être totalement exclu, bien que le taux de réponse soit élevé (86,5%) et qu'il n'y ait pas de différence significative entre les populations de répondeurs et non-répondeurs.

Conclusion La prévalence des TDS est élevée chez les garçons avec une DMD et leurs causes sont multiples. Les facteurs de risques sont physiques (immobilité nocturne), pharmacologiques (corticothérapie) et environnementaux (famille monoparentale). Compte tenu de son impact sur la qualité de vie, l'évaluation du sommeil doit être systématique en consultation et ne pas se limiter aux seuls troubles ventilatoires nocturnes.

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REGULAR ARTICLE

Sleep disorders in boys with Duchenne muscular dystrophy

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ABSTRACT

Aim: Determine the frequency and predictors of sleep disorders in boys with Duchenne Muscular Dystrophy (DMD).

Method: Cross-sectional study by postal questionnaire. Sleep disturbances were assessed using the Sleep Disturbance Scale for Children (validated on 1157 healthy children). A total sleep score and six sleep disturbance factors representing the most common sleep disorders were computed. Potential associations between pathological scores and personal, medical and environmental factors were assessed.

Results: Sixteen of 63 boys (25.4%) had a pathological total sleep score compared with 3% in the general population. The most prevalent sleep disorders were disorders of initiating and maintaining sleep (DIMS) 29.7%, sleep-related breathing disorders 15.6% and sleep hyperhydrosis 14.3%.

On multivariate analysis, pathological total sleep scores were associated with the need to be moved by a carer (OR = 9.4; 95%CI: 2.2–40.7; p = 0.003) and being the child of a single-parent family (OR = 7.2; 95%CI: 1.5–35.1; p = 0.015) and DIMS with the need to be moved by a carer (OR = 18.0; 95%CI: 2.9–110.6; p = 0.002), steroid treatment (OR = 7.7; 95%CI: 1.4–44.0; p = *0.021*) and being the child of a single-parent family (OR = 7.0; 95%CI: 1.3–38.4; p = 0.025).

Conclusion: Sleep disturbances are frequent in boys with DMD and are strongly associated with immobility. Sleep should be systematically assessed in DMD to implement appropriate interventions.

INTRODUCTION

Duchenne Muscular Dystrophy (DMD) is a progressive myopathy affecting one in 3,300-6000 live male births (1,2). Mutations in the X-linked dystrophin gene result in a loss of functional dystrophin, an essential element for the structural integrity of muscle cells (3–5), which makes them prone to plasma membrane leakage and finally muscle fibre degeneration. The disease often manifests with mildly delayed motor milestones or gait disturbances. The progressive muscle weakness leads to loss of ambulation at 10–12 years and finally to cardiac and respiratory insufficiency in the late teens. Few persons with DMD survive beyond their thirties (2), even with clinical interventions such as non-invasive ventilation or steroid therapy. Despite widespread efforts, no curative treatment is currently available and steroids are still the only treatment proven to slow the natural course of the disease (6,7).

Our clinical experience suggests that DMD is associated with disturbed sleep of various origins, of which the most studied are sleep-related breathing disorders. These have been widely described in the literature (8–10), due to their increasing frequency with age and their therapeutic consequences (non-invasive or invasive ventilation) (11,12). However, several other sparsely studied factors that are frequently encountered in this population seem to alter these children's sleep. Musculo-skeletal pain, which is frequent in subjects with DMD (13), decreased bed mobility,

Abbreviations
DIMS, Disorders of Initiating and Maintaining Sleep; DMD, Duchenne Muscular Dystrophy; DOA, Disorders of Arousal; DOES, Disorders of Excessive Somnolence; NIV, Non-Invasive Ventilation; SDSC, Sleep Disturbance Scale for Children; SHY, Sleep Hyperhydrosis; SRBD, Sleep-related Breathing Disorders; SWTD, Sleep–wake Transition Disorders

Key notes
- Children with DMD are highly prone to sleep disturbances.
- The need to be turned by a carer associated with immobility seems to be a major burden on the quality of sleep.
- Sleep-related breathing disorders are not the main sleep disorder in DMD.

medication (e.g. oral steroids) or the use of positioning devices are all potential contributors to sleep difficulties. Moreover, primary or secondary behavioural and psychological problems, as well as familial and social difficulties, may adversely affect sleep.

Until now, sleep disorders in DMD have been mainly studied in relation to sleep-related breathing disorders, which affect non-ambulant patients from their teenage years.

The aim of our study was to determine the prevalence of sleep disorders in boys and teenagers with DMD and to identify associated factors by analysing parents' responses to a validated sleep disturbance scale.

METHOD

Design

Cross-sectional study conducted by postal questionnaire (14).

Participants

The target population consisted of all children aged 4–18 years with a diagnosis of DMD and who were regularly followed in two tertiary paediatric neurorehabilitation outpatient clinics (Paediatric Neurology and Neurorehabilitation Unit, Lausanne University Hospital, Lausanne, Switzerland; Central Remedial Clinic, Dublin, Ireland). Diagnosis was ascertained by a positive mutation analysis in the dystrophin gene (84%) or by substantially reduced levels of dystrophin on biopsy, associated with typical clinical features (16%). Seventy-four children were eligible, 54 in Dublin and 20 in Lausanne. A cover letter describing the study and the validated sleep disturbance scale was sent to the parents. Non-responders received a phone reminder from the local investigator. Sixty-four questionnaires were returned (overall response rate 86.5%), 19 in Lausanne (95%) and 42 in Dublin (77.8%). Sixty-three questionnaires were fully completed. Signed consent for data use was obtained for every patient, and the study was approved by the Ethics Committee of the University of Lausanne and the Central Remedial Clinic's institutional review board.

Data collection

The Sleep Disturbance Scale for Children (SDSC) was selected because of its thorough validation, its good level of internal consistency and test–retest reliability, the availability of normal data and the overlap of the normative age group (6 years 6 months–15 years 4 months) with that assessed in the present study. Furthermore, age and sex showed no significant effect on total sleep scores in the normal population.

The SDSC was originally validated on a randomly selected sample of 1157 healthy children from the general population. It assesses the sleep behaviour and occurrence of sleep disturbances during the previous 6 months (15). The scale contains 26 items rated on a Likert-type scale, for example, 'How many hours sleep does your child get on most nights?' (1 indicates 9–11 h, 2 indicate 8–9 h, 3 indicate 7–8 h, 4 indicate 5–7 h and 5 indicate <5 h) and 'The child startles or jerks parts of the body while falling asleep' (1 indicates never; 2 indicate occasionally [once or twice or less/month]; 3 indicate sometimes [once to twice/week]; 4 indicate often [three to five times/week]; 5 indicate always [daily]). A total sleep score is obtained by summing the item scores. The original factor analysis yielded six sleep disturbance factors representing the most common areas of sleep disorders in childhood and adolescence: (i) Disorders of sleep-related breathing (SRBD); (ii) Disorders of initiating and maintaining sleep (DIMS); (iii) Disorders of arousal (DOA); (iv) Disorders of sleep–wake transition (SWTD); (v) excessive somnolence (DOES); and (vi) sleep hyperhydrosis (SHY).

For the present study, the original scale was completed with items regarding the socio-familial situation (parents' marital status and current parental employment), the current medication, the use of night postural equipment (positioning devices), the use of non-invasive ventilation and/or tube-feeding, the need to be turned by a carer during the night and the presence of bed-sharing with parent(s). While answering the questionnaire, the parents were asked to consider the previous 6 months. Information about motor impairment was obtained from the participants' medical files.

Statistical analysis

General characteristics of the study population were analysed by frequencies. A total sleep score and scores for the different sleep disturbance factors were computed and converted into a binary variable based on normative data (T-score of more than 70, i.e. >2SD, was regarded as pathological (15)). Total sleep disturbance and individual sleep disturbance factors were represented by frequencies. Potential associations between a pathological sleep score (total and individual sleep disturbance factors), age, socio-familial situation (parents' marital status, parental unemployment, bed-sharing), motor impairment (ambulatory status, moved by carer), medical interventions (steroids, use of postural equipment, e.g. night-time ankle foot orthotics at least 3 nights/week, NIV, tube-feeding) and pain were assessed by bivariate analyses (χ^2), and crude odds ratios (OR) with their 95% confidence intervals (CI) were computed. Forward stepwise logistic regression was then conducted to identify independent risk factors for pathological total sleep score and for each sleep disorder factor. Dummy variables were created for categorical parameters. Variables that showed no contribution to any of the sleep factors ($p > 0.20$) were excluded from these models.

Overall model evaluation was performed with omnibus tests of model coefficients. Each model was assessed for goodness-of-fit with the Hosmer and Lemeshow x^2 statistic ($p < 0.10$ indicating a lack of fit). Analyses were performed with SPSS (version 12.0; SPSS Inc., Chicago, IL, USA), and $p < 0.05$ was considered significant.

RESULTS

General characteristics

The study population consisted of 64 boys with a mean age of 10.5 years (SD 4.3; range: 4 years 6 months–18 years

8 months). For subsequent analysis, they were subdivided into three age categories: 4–8 years, 28 children (43.8%); 9–13 years, 16 children (25%); and 14–18 years, 20 children (31.3%). Physical impairment was assessed by ambulatory status and by the need to be turned during the night. Thirty-four children were non-ambulant (53.1%). Fifteen (23.4%) boys had to be turned during the night, of whom 5 (7.8%) were turned three to five nights per week and ten (15.6%) every night. Thirty-five patients were reported to be treated with steroids (54.7%). One patient was treated with melatonin. Seven patients (10.9%) were part-time ventilated (NIV) and one patient needed tube-feeding. Night-time postural equipment (exclusively ankle foot orthotics) was used by 31 children (49.2%): every night by 17 children (27%), three to five nights per week by eight children (12.7%) and two nights or less per week by six children (9.5%).

Eleven children lived in a single-parent family (17.2%). Unemployment was reported in five families (7.8%). Bed-sharing was reported at least once a week in 13 families (20.3%): it took place every night in four families (6.3%), three to five nights per week in one family (1.6%) and one to two nights per week in eight families (12.5%).

Table 1 Bivariate and multivariate analyses of variables associated with a pathological total sleep score

		Total sleep disorder	
Variable	n	Crude OR (95%CI)	Corrected OR (95%CI)
Age in year			
4–8	28	Baseline	
9–13	16	3.6 (0.9–14.3)	
14–18	19	1.2 (0.3–5.3)	
Parental status			
Single	11	**5.0 (1.3–19.9)**	**7.2 (1.5–35.1)**
Unemployed	5	5.2 (0.8–34.5)	
Motor function			
Non-ambulant	33	1.7 (0.5–5.6)	
Moved by carer at night	14	**6.8 (1.9–25.1)**	**9.4 (2.2–40.7)**
Steroids	35	1.0 (0.3–3.3)	
Non-invasive ventilation	7	1.2 (0.2–6.9)	
Night splints	25	2.0 (0.6–6.5)	
Pain	3	6.4 (0.5–76.3)	

OR, odds ratio; CI, confidence interval.
Significant results ($p < 0.05$) are indicated in bold type.

Table 2 Bivariate and multivariate analyses of variables associated with a disorder of initiating and maintaining sleep (DIMS)

		DIMS	
Variable	n	Crude OR (95%CI)	Corrected OR (95%CI)
Age in year			
4–8	28	Baseline	
9–13	16	2.3 (0.6–8.6)	
14–18	20	1.0 (0.3–3.8)	
Parental status			
Single	11	3.7 (1.0–14.1)	**7.0 (1.3–38.4)**
Unemployed	5	1.6 (0.3–10.7)	
Motor function			
Non-ambulant	34	1.3 (0.4–3.9)	
Moved by carer	15	**5.9 (1.7–20.3)**	**18.0 (2.9–110.6)**
Steroids	35	2.3 (0.7–7.0)	**7.7 (1.4–44)**
NIV	7	0.9 (0.2–5.3)	
Night splints	25	1.3 (0.4–4.0)	
Pain	3	5.1 (0.4–59.5)	

OR, odds ratio; CI, confidence interval.
Significant results ($p < 0.05$) are indicated in bold type.

Sleep disturbance scale for children results

The total sleep score could be computed for 63 of 64 children, of whom 16 (25.4%) had a pathological score: five children in the age category 4–8 years (17.9% of this age category), 7 in the age category 9–13 years (43.8%), and 4 in the age category 14–18 years (21.1%).

Disorders in initiating and maintaining sleep (DIMS) were observed in 19 children (29.7%), sleep-related breathing disorders (SRBD) in 10 (15.6%), disorders of arousal (DOA) in 5 (7.8%), sleep–wake transition disorders (SWTD) in 6 (9.4%), excessive somnolence (DOES) in 7 (10.9%) and sleep hyperhydrosis (SHY) in 9 (14.3%).

Thirty-seven children had none of these sleep disorders (58.7%), 12 experienced one sleep disorder (19%), five presented two sleep disorders (7.9%), three and four sleep disorders where each experienced by four children (6.3% each), and one child had all six sleep disorders (1.6%). For one child, the total sleep score could not be computed as one question (SHY) remained unanswered.

The overall model evaluations suggested that for SRBD, DOA, SWTD, DOES and SHY none of the variables were significantly associated to the outcome (data not shown).

On multivariate analysis, a pathological total sleep score was significantly associated with the need to be moved by a carer (OR = 9.4; 95%CI: 2.2–40.7; p = 0.003) and being the child of a single-parent family (OR = 7.2; 95%CI: 1.5–35.1; p = 0.015) (Table 1). The multivariate analysis of variables associated with a pathological DIMS score (Table 2) showed significant associations with the need to be moved by a carer (OR = 18.0; 95%CI: 2.9–110.6; p = 0.002), being treated with steroids (OR = 7.7; 95%CI: 1.4–44; p = 0.021) and being the child of a single-parent family (OR = 7.0; 95%CI: 1.3–38.4; p = 0.025).

Both of these models achieved satisfactory goodness-of-fit with the Hosmer–Lemeshow x^2 statistic (total sleep score: degrees of freedom = 2, $x^2 = 0.33$, p = 0.85; disorders of initiation and maintenance of sleep: degrees of freedom = 4, $x^2 = 2.1$, p = 0.72).

DISCUSSION

Our study indicates a high prevalence of sleep disturbance in patients with DMD. By setting a threshold T-score of 70 (above 2 standard deviations, i.e. above centile 97) for the sleep disturbance scale for children, a pathological total sleep score would affect approximately 3% of children in the normal population (15). This threshold was selected to

identify children who have a clinically significant sleep disorder, exceeding common sleep disturbance in childhood. In our study population, 25% of the children had a pathological total sleep score and 42% experienced at least one clinically significant sleep disorder. Furthermore, the prevalence was clearly elevated (above 10%, i.e. more than triple the normal population) for the following four sleep factors: difficulty in initiating and maintaining sleep (29.7%), sleep-related breathing disorders (15.6%), sleep hyperhydrosis (14.3%) and excessive somnolence (10.9%).

The only factors that were associated with a total sleep disturbance in the present study were the need to be turned and being the child of a single-parent family. This need to be moved by a carer most likely indicates a degree of motor impairment that does not permit the usual spontaneous movements and postural adaptations that occur during sleep and seems to be a major burden on the quality of sleep. Furthermore, it was also strongly associated with disorders of initiating and maintaining sleep.

While it has been well described that healthy young adults change position 20–40 times per night, and children even more (16), the exact role of spontaneous movements during sleep remains largely unknown. It has been suggested that the sleep position is related to sleep quality and some sleep disorders (including breathing disorders). Some authors hypothesized that spontaneous movement during sleep aim to relieve pain secondary to prolonged immobilization (the 'discomfort' theory) (17).

We failed to demonstrate an association of sleep-related breathing disorders with any of the analysed factors. Possible explanations are the small number of patients in whom these disorders were reported, the fact that an adequate respiratory follow-up enables early identification and intervention on such disturbances, and also that certain of the common symptoms of night-time hypoventilation such as headaches on wakening are not assessed in the SDSC, while other symptoms are included in other disorder groups (disorders of excessive somnolence, sleep hyperhidrosis). Symptoms of SRBD are often subtle and unspecific in an early stage and can therefore easily be missed by carers. Both symptoms and lung functions have limited predictive value in boys with DMD (8), therefore the diagnosis of SRBD in this population relies either on nocturnal polysomnography or more frequently on nocturnal pulse oxymetry and capnography. These are routinely performed once to twice per year after loss of ambulation and/or decrease of forced vital capacity below 50% of the predicted value (12), and allow for the prompt institution of NIV when required.

Disorders of initiating and maintaining sleep were significantly more frequent in children treated by steroids. Steroids are known to influence sleep behaviour in children (18). Even if in our experience, such disturbances have never led to an interruption of the treatment, parents should be questioned about the subject. Adaptation of the dosage or therapeutic plan, or a pharmacological treatment could be proposed and improve the symptoms and therefore possibly the compliance. Medication with a central nervous system depressant effect should of course be avoided due to potential further respiratory compromise, but melatonin, in particular the slow-release form, may be considered in case of disorders of initiation and maintaining of sleep (19). Children living in single-parent families were also significantly more likely to present disorders of initiating and maintaining sleep. Psychosocial stressors have been reported to affect the quality of sleep in normal children (20), and these are possibly higher in single-parent families.

The use of night positioning devices showed no significant association with any sleep disorder. The main reason for this is that they are probably abandoned when they affect the child's sleep.

The main limitation of our study was the limited sample size. As for other studies on rare diseases, selection of an adequate number of subjects was a major challenge and potential associations could have been missed. The data collection was a cross-sectional survey; however, some of the subject's characteristics (diagnosis, treatment, motor impairment) were obtained through the medical files and had therefore been recorded before the questionnaire was sent to the families (at most 6 months prior). Even if our study did not include quantitative sleep measurements, parental reports have been demonstrated to be reliable in detecting sleep disturbance in children compared to objective measurements (21,22), with the exception of SRBD, which would have required a systematic polysomnography be performed in all of our study population, including the ambulant children. A certain degree of non-response bias cannot be excluded even with a high overall response rate (86.5%). However, there was no significant difference between responders and non-responders when looking for known parameters such as age, treatment, motor function and environmental factors. The two centres were reference clinics for neuromuscular disorders covering the vast majority of patients in their respective regions (French speaking Switzerland and Republic of Ireland), and therefore, our sample was representative of the DMD population. Finally, ascertainment of intellectual impairment was not performed due to the difficulties to do this by a posted questionnaire. Moreover, the medical file of most patients did not contain any objective evaluation. Intellectual impairment is, however, well known to be associated with sleep disturbance (23,24) and frequent among boys with DMD, with estimates ranging from 20% to as much as 50% in some studies (25,26).

CONCLUSION

Our study suggests that boys affected by DMD are highly prone to sleep disturbances and that these are far from being due only to sleep-related breathing disorders. We demonstrated that physical (need to be turned by a carer), medical (treatment with steroids) and environmental factors (single-parent household) may affect these patients sleep. Due to their important impact on quality of life, we believe that sleep disturbance should not only be assessed to detect nocturnal hypoventilation, but also to evaluate

other risk factors that could be treated by environmental, behavioural or pharmacological interventions.

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DECLARATION OF INTEREST SECTION

The authors report no conflicts of interest.

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