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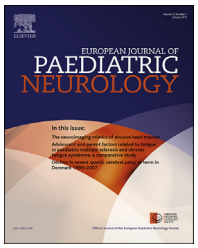

Original article

Methylphenidate use in males with Duchenne muscular dystrophy and a comorbid attention-deficit hyperactivity disorder

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ABSTRACT

Attention-deficit hyperactivity disorder (ADHD) is a common comorbidity in Duchenne muscular dystrophy (DMD). Until now, treatment with methylphenidate (MPH) has never been systematically assessed and described in this population. Our aim was to evaluate the effectiveness and safety of short acting MPH for learning problems in males with DMD and ADHD. Neuropsychological (cognition and behavior) and medical data of a sample of ten males (mean age = 8.1 years, range 6.3–9.8) with DMD and an ADHD diagnosis was retrospectively analyzed at baseline (T0; without MPH), short-term follow-up (T1; with MPH; mean interval T0-T1 = 8.3 months, range 4.3–15.6), and long-term follow-up (T2; mean interval T1-T2 = 23.1 months, range 2.6–77.7). An initial MPH dose of 5 mg/day was given on school mornings, with an increase of 2.5–5 mg/week depending on individual tolerance and treatment response, until a sufficiently effective dose was reached (range 0.2–0.6 mg/kg/day). At T1, results demonstrated an improvement in attention (i.e. concentration, impulsivity, and distractibility) in four patients. Suboptimal effects were reported in four patients, and no effects in two patients. At T2, seven patients showed considerable improvement in attention. No major side effects were reported. Overall, our data show that short acting MPH can be clinically effective for learning problems in males with DMD and ADHD, with regular cardiac follow-up, and close monitoring of side effects and neuropsychological effects. Furthermore, this underscores the importance of the use of validated

Abbreviations: ADHD, Attention-deficit hyperactivity disorder; BP, blood pressure; DMD, Duchenne muscular dystrophy; HR, heart rate; MPH, methylphenidate.

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cognitive and behavioral measurement tools with adequate sensitivity to objectively evaluate the effect of MPH.

1. Introduction

Duchenne muscular dystrophy (DMD) is an X-linked neuromuscular disorder with a prevalence of approximately 1 in 5000 live male births.[1] It is caused by mutations in the *DMD* gene (*Xp21*) that encodes for the dystrophin protein, resulting in the absence of this protein. Absence of dystrophin generally results in characteristic progressive muscle weakness, which eventually leads to fatal cardiac and respiratory complications.[2] In addition to the progressive muscle weakness, learning, neurocognitive, and behavioral disorders are common in DMD.[3–6] Particularly, high prevalence rates of attention-deficit hyperactivity disorder (ADHD; 32% versus 5.3% in the general population) have been described in DMD,[5–7] and the milder variant Becker muscular dystrophy,[8] which often results in learning problems. Consequently, appropriate mental health screening (i.e. Strength and Difficulties Questionnaire, and Personal Adjustment and Role Skills Scale-III), neuropsychological assessment (cognition and behavior), and pharmacological treatment with stimulants or α-adrenoceptor agonists has been recommended for the diagnosis and treatment of ADHD comorbidity in DMD, as part of the recently updated international standards of care guidelines.[9] However, the optimum ADHD treatment in DMD is not well characterized, and the effectiveness of stimulants has not been systematically assessed and described in this population. Methylphenidate (MPH) has been shown to reduce ADHD symptoms (i.e. hyperactivity, impulsivity, and inattentive behavior), and improve associated behavior, academics, and social functioning in children, adolescents and adults without DMD.[10] In DMD, MPH prescription has been limited because of the presence of comorbidities, such as a cardiomyopathy[2] or epilepsy.[11] With regard to these comorbidities, sympathomimetic agents (i.e. MPH) could potentially provoke complications in these patients. Other potential side effects, such as motor tics, sleep or mood disorders have also been previously reported in neurological disorders.[12] Therefore, the evaluation of MPH is of great importance especially in this population. The present study reports for the first time a systematic medical and neuropsychological evaluation of MPH treatment in ten patients with DMD and ADHD. Our aim was to evaluate the effectiveness and safety of short acting MPH for learning problems in males with DMD and a comorbid ADHD diagnosis.

2. Materials and methods

2.1. Participants

Reported subjects were males with DMD and a comorbid ADHD diagnosis attending the outpatient clinic of the Kempenhaeghe Centre for Neurological Learning Disabilities, Heeze, The Netherlands. Subjects were included if they met the following inclusion criteria: (1) were males, (2) had a proven mutation of the dystrophin gene, (3) had a diagnosis of ADHD according to the Diagnostic and Statistical Manual of Mental Disorders-IV (DSM-IV) criteria[13] (4) had medical and neuropsychological data of baseline and short-term follow-up, (5) received no other psychological interventions, except for psychoeducation, on baseline and follow-up, (6) did not use any psychostimulants on T0, and only MPH on T1, and (7) had an adequate proficiency in Dutch. Exclusion criteria were (1) an age younger than three or older than sixteen years at time of inclusion, and (2) physical immobility of upper extremities (hand and arm function), which may affect the neuropsychological test scores. Ethical approval was granted by Kempenhaeghe Ethics Committee and informed parental consent was obtained. The study was conducted in accordance with the 18th World Medical Assembly, Helsinki 194.

2.2. Study design

The diagnosis of ADHD was established by an experienced neuropsychologist (JH) and child neurologist (JV or SK) based on (1) the DSM-IV criteria for ADHD,[13] (2) teacher and parents observations, and (3) an extensive neuropsychological assessment.[14] All subjects received an extensive medical (performed by treating cardiologist and child neurologist JV or SK) and neuropsychological work-up (performed by JH) as part of regular care at baseline (T0). Medical work-up consisted of standard prescribing practices and guidelines with additional care considerations focusing on the general medical condition of each individual subject (i.e. disease status, cardiac status, medication interactions) based on the international standards of care guidelines for DMD.[9] Cardiac status was evaluated based on standard cardiovascular tract (hetero)anamnesis, blood pressure (BP), heart rate (HR), electrocardiogram and non-invasive imaging (e.g. cardiovascular MRI), which were used to establish cardiac function, rhythm abnormalities, and to screen for underlying anatomical abnormalities that could affect cardiovascular health.[15] Neuropsychological work-up consisted of objective neurocognitive and behavioral assessment, and subjective behavioral observations. Treatment started after parents informed consent, and approval of the treating child cardiologist. All subjects were treated with short acting MPH on the indication of attention problems which were most prominent during school resulting in learning problems. An initial dose of 5 mg/day was given in the morning before school, with an increase of 2.5–5 mg/week depending on individual tolerance and treatment response,

until a sufficiently effective dose was reached (range 0.2–0.6 mg/kg/day).[16] A second dose for the afternoon school program was given around 12.00 h in addition to the morning dose if needed based on good clinical practice. None of the subjects used MPH at home, on weekends or holidays. Since behavioral problems were not the main problem in this population, we did not prescribe the extended release MPH over time. Treatment effects and potential adverse effects were evaluated at short-term follow-up (T1) and long-term follow-up (T2) as part of regular care.

2.3. Assessments

For this study, behavioral assessment consisted of subjective behavioral observations from patients, parents, teachers and the clinical team, and objective assessment using the Child Behavior Checklist-Attention Problems subscale (CBCL-AP). In line with the CBCL manual, t-scores greater than or equal to 63 were deemed to be in the clinical range.[17] A change in clinical range is defined as a clinically relevant effect. Neurocognitive assessment consisted of the Symbol Search subtest of the Wechsler Intelligence Scale for Children-III (WISC-III), to measure processing speed. Raw scores were converted to standardized age-related scores (SS; with a range of 1–19, mean 10 and standard deviation (SD) of 3 in healthy controls).[18] In line with the Wechsler manual, a change in SS of 3 is defined as a clinically relevant effect. Full intelligence quotient (FIQ) was also assessed by the WISC-III.[18] Neuropsychological assessment was focussed on each individual request for help based on good clinical practice, and at least consisted of abovementioned assessment tools.

2.4. Statistical analysis

Descriptive statistics displayed frequencies and means (SD) of demographic and disease-related characteristics. Wilcoxon rank sum tests were used to assess differences between baseline and short-term follow-up of CBCL-AP and processing speed. Underlying assumptions were checked before carrying out actual analyses. Normality distributions of residuals were checked by visual inspection of histograms. All statistical analyses were carried out using SPSS version 24 for MAC OS X. Results were considered statistically significant if $p < 0.05$.

3. Results

3.1. Participants

Reported subjects were males with DMD and a comorbid ADHD diagnosis (mean age = 8.1, SD = 1.3, range 6.3–9.8 years). Intelligence quotient (IQ) as assessed by the WISC-III[18] ranged between 66 and 118 (mean IQ = 91.8, SD = 17.6). Subject characteristics are summarized in Table 1. Within our clinical sample, subject 7 was previously diagnosed with absence epilepsy; he was seizure free with sodium valproate. Subject 9 had an oppositional defiant disorder, which was treated with dipiperon. Dyslexia was diagnosed in subject 10. Subjects 7–9 had problems with sleeping throughout the night at T0.

3.2. MPH effect at short-term follow-up

Mean time between T0 and T1 was 8.3 months (SD = 3.4, range 4.3–15.6).

3.2.1. Medical effects

Medical monitoring data concerning BP, HR, height and weight (Body Mass Index) remained within the normal range for the evaluated age category. Regular cardiac follow-up showed no cardiovascular side effects. Additionally, no seizures were noted. Reported side effects consisted of loss of appetite in subject 10, and delayed sleep onset (subjects 1–2, subject 6, subject 9), whereupon melatonin was prescribed in subject 1 with success. Of the four patients who reported delayed sleep onset, one patient (subject 1) used a relatively high MPH dosage (0.5 mg/kg/day; maximum daily dose of 15 mg in two doses with latest administration time at 12.00 h).[19] One patient (subject 8) with problems sleeping throughout the night at baseline developed delayed sleep onset when using MPH. Two patients discontinued treatment due to a lack of effect (subjects 9–10).

3.2.2. Neuropsychological effects

At T1, patients, parents, teachers and the clinical team observed an improvement in attention (i.e. concentration, impulsivity, and distractibility) in four patients (subject 1, subjects 3–5). Suboptimal effects - which were defined as starting, yet insufficient effects on attention - were observed in four patients (subject 2, subjects 6–8). No effects were noted in subjects 9 and 10. Behavioral assessments ($n = 5$) showed a trend towards significance (Mdn T0 = 63, Mdn T1 = 57), $z = -1.841$, $p = 0.066$, and a clinically relevant effect (cut off value < 63) in two patients. Neurocognitive assessment ($n = 8$) showed no statistically significant effect (Mdn T0 = 11, Mdn T1 = 12), $z = -0.736$, $p = 0.462$ and in one patient a clinically relevant effect (SS > 3) was found.

3.3. MPH effect at long-term follow-up

Mean time between T1 and T2 was 23.1 months (SD = 26.7, range 2.6–77.7). At T2, Medical monitoring data (i.e. BP and Body Mass Index) were within the normal range and no cardiovascular side effects were described. One patient discontinued treatment due to mood problems (subject 2). Behavioral observations of patients, parents, teachers and the clinical team showed an improvement in attention in seven patients (subject 1, subjects 3–8). In subjects 6–8 with suboptimal effects at T1 an improvement in attention was observed at T2.

4. Discussion

This is the first study reporting on the clinical effectiveness and safety of short acting MPH treatment for learning problems in ten males with DMD and a comorbid ADHD diagnosis using an extensive medical and neuropsychological work-up at baseline, and short-term follow-up. Results demonstrate that MPH treatment considerably improves attention in seven subjects according to the subjective reports of patients,

Table 1 – Subject characteristics and MPH effects (N = 10).

Subject	Age (years)	DNA mutation	MPH dose T1 (mg/kg/day)	MPH adverse effect	T0-T1 MPH effect	T1-T2 MPH effect
1	7	Deletion exon 8-13	0,5	Delayed sleep onset	+	+
2	9	Deletion exon 51-54	0,2	Delayed sleep onset	+/–	–
3	9	Deletion exon 49-50	0,3	NAE	+	+
4	9	Deletion exon 51	0,3	NAE	+	+
5	9	Deletion exon 52	0,3	NAE	+	+
6	6	Deletion exon 45 - 50	0,2	Delayed sleep onset	+/–	+
7	8	Out of frame exon 45-52	0,2	NAE	+/–	+
8	7	Deletion exon 58	0,2	NAE	+/–	+
9	7	Deletion exon 46-52	0,4	Delayed sleep onset	–	–
10	6	Deletion exon 48-54	0,3	Loss of appetite	–	–

NOTE: mg = milligram, MPH = methylphenidate, NAE = no adverse effects, T0 = baseline, T1 = short-term follow-up, T2 = long-term follow-up, + = subjective reported positive effect of MPH, +/– = subjective reported suboptimal effect of MPH, – = subjective reported no effect of MPH.

parents, teachers and the clinical team at long-term follow-up. No major side effects were reported.

4.1. *Neuropsychological outcomes*

Literature on neuropsychological evaluation of MPH is scarce in neurological disorders. A recent study evaluated the effect of MPH in Neurofibromatosis type 1, a neurogenic disorder in which ADHD comorbidity is common as well. Full-scale IQ scores improved significantly in Neurofibromatosis type 1 patients with ADHD who received MPH.[20] These improvements in full-scale IQ scores were also correlated with an improvement in reaction time variability based on the Test of Variables of Attention.[20] Furthermore, MPH use has been shown to significantly reduce behavioral and social dysfunction, causing lower CBCL scores in Neurofibromatosis type 1 patients with ADHD.[21] Both the CBCL-AP and the Conners Rating Scale Revised are the most commonly used measurements to support the diagnosis of ADHD in children and adolescents, and previous research on the diagnostic accuracy of these scales yielded moderate sensitivity and specificity in supporting the diagnosis of ADHD.22 Unfortunately, in our study only five patients completed the CBCL-AP at baseline and short-term follow-up, thus our results are rather explorative.

4.2. *Side effects*

Reported side effects in our subjects were having difficulty falling asleep, which is in line with previous finings in patients with ADHD without comorbidity.[12] Stimulants may exacerbate delayed sleep-onset, but may also be related to a rebound effect - increase over baseline values in ADHD symptoms when MPH wears off - rather than to the medication itself.[23] Notably, difficulty falling asleep often occurs during titration, and may improve over time.[24] Management of sleep problems in our subjects consisted of sleep problems and health education, and melatonin prescription with positive results, which is in line with previous research.[25,26] Neurological side effects, such as motor tics or seizures, were not reported in our subjects, even though one patient had epilepsy. MPH also has a potential impact on cardiac functioning which may have clinical consequences, especially in DMD patients. It is a sympathomimetic agent that increases noradrenergic and dopaminergic transmission, which affects HR and BP.[27] A recent systematic review on cardiovascular effects of MPH in children and adolescents with ADHD found a significant effect on systolic BP. Since this is considered a risk factor for cardiovascular morbidity and mortality during adult life, it was recommended that BP and HR should be monitored closely and regularly.[28] As cardiac management is already part of regular care of DMD patients, all subjects were regularly seen and monitored by their child cardiologist, and BP and HR remained stable from baseline to follow-up.

4.3. *Limitations*

Due to our small sample, there might be a lack of power to observe effects on the objective neuropsychological outcome variables. Additionally, the time between the baseline and short-term follow-up was not equal for each subject, and may have been too short to measure clinical effects on cognition. The ten subjects which are described in this study, were all seen for regular outpatient clinical care. Information of certain cognitive variables (working memory and attention measures) and behavioral variables (CBCL-AP) were limited or not available. Thereby, the change between baseline and short-term follow-up on these measures could not be analyzed accurately.

4.4. *Future perspectives*

Further prospective research should include a follow-up time of at least six months and one year, and needs to include an age-matched control group of DMD males with a comorbid ADHD without MPH or receiving other treatment to determine whether the effects are caused by MPH treatment. To further evaluate the different dose effects of MPH in this population, a second long-term follow-up neuropsychological work-up should be included. This neuropsychological work-up should be performed using a standard protocol of validated ADHD specific tools, such as the CBCL-AP or Conners Parent Rating Scale[22]/IOWA Conners Rating Scale,[29] as well as the Strenght and Difficulties Questionnaire and Personal Adjustment and Role Skills Scale-III as recommended in the international standards of care guidelines for DMD.[9] Importantly, since these measurement tools are developed for the general

population, certain items involving physical mobility may not be applicable for patients with impaired motor function, and should be interpreted with caution. Whether these ADHD specific tools are sensitive for ADHD comorbidity in DMD patients should be further investigated. Eventually, the effect of MPH should be evaluated in a larger sample preferably using a randomized control trial design.

5. Conclusions

Current data shows clinically effective use of short acting MPH for learning problems in males with DMD and a comorbid ADHD diagnosis, with regular cardiac follow-up, and close monitoring of side effects and neuropsychological effects. Overall, our results underscore the importance of the use of validated behavioral – psychosocial measurement tools, and use of psychopharmacological interventions in DMD as recommended in the international standards of care guidelines for DMD.

Declarations of interest

The authors have stated that they had no interests which might be perceived as posing a conflict or bias. Dr Hendriksen received personal grants from Spieren voor Spieren Foundation (grant number SvS15-) and Duchenne Parent Project Netherlands (grant 2016 on non-motor problems in Duchenne), which do not inappropriately influence this work.

Contributors' statement

Drs Lionarons and Drs Hellebrekers equally contributed to writing the manuscript, entering, checking, analysis and interpreting the clinical data. Dr Klinkenberg was responsible for medical work-up, and assisted in drafting the manuscript. Prof Faber assisted in drafting the manuscript. Prof Vles was responsible for medical work-up, and contributed to study design, study coordination, interpretation of data, and writing the manuscript. Dr Hendriksen was responsible for neuropsychological work-up, study design, study coordination, interpretation of data, and writing the manuscript. All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejpn.2018.09.005.

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