

# Brain-related comorbidities in boys and men with Duchenne Muscular Dystrophy:

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## Original article

# Brain-related comorbidities in boys and men with Duchenne Muscular Dystrophy: A descriptive study



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## ABSTRACT

**Aim:** Duchenne Muscular Dystrophy (DMD) is more than a muscle disease since there is a higher prevalence of neuropsychological comorbidities. Similarly, the prevalence of epilepsy is increased. Given the nowadays-increasing interest in brain-related comorbidities in DMD, this study aimed to evaluate the relationship between DMD, epilepsy, and associated neurodevelopmental disorders in an international sample of DMD patients.

**Method:** Using a questionnaire-based study we investigated the occurrence of self/by-proxy reported brain-related comorbidities in a group of 228 DMD patients. We evaluated the presence of epilepsy and other brain-related comorbidities, but also the specific mutation in the dystrophin gene. With respect to epilepsy, all individually reported epilepsy cases as based on the questionnaire results including information provided on epilepsy treatment, EEG abnormalities, and a description of how a typical seizure would look like, were independently and blindly re-assessed by two external paediatric neurologists (Cohen's kappa of 0.85).

**Results:** Based on the latter, 18 (7.9%) DMD patients were considered to have epilepsy. In patients with both DMD and epilepsy, certain other brain-related comorbidities (i.e.

**Abbreviations:** AD(H)D, Attention Deficit (Hyperactivity) Disorder; AEDs, Anti-epileptic drugs; ASD, Autism Spectrum Disorder; BMD, Becker Muscular Dystrophy; CNS, Central Nervous system; DMD, Duchenne Muscular Dystrophy; EEG, Electro-encephalogram; GABA, Gamma-aminobutyric acid; ILAE, International League Against Epilepsy; IQ, Intelligence Quotient; OCD, Obsessive Compulsive Disorder; TLE, Temporal Lobe Epilepsy.

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attention deficit hyperactivity disorder, obsessive compulsive disorder, anxiety disorders and sleep disorders) were significantly more prevalent.

**Conclusion:** This study is supportive of a high occurrence of epilepsy and other brain-related comorbidities in DMD. Furthermore this study shows for the first time that the frequency of some of these disorders appear to be further increased when epilepsy is present next to DMD. As this study is limited by the self/by proxy setup and the lack of response rates, future studies should elucidate the true incidence of the (triangular) cooccurrence between epilepsy, neurodevelopmental deficits, and DMD.

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## 1. Introduction

Duchenne Muscular Dystrophy (DMD) is an X-linked recessive hereditary disorder caused by a mutation in one of the largest genes of the human genome<sup>1</sup> – the dystrophin gene – and is mainly known by its severe and progressive physical course. The absence of the dystrophin protein in muscle tissue makes muscles prone to degradation, ultimately resulting in cardiac and respiratory impairment in later stages of the disease,<sup>2,3</sup> thereby causing premature death.<sup>4</sup>

The role of the dystrophin protein in DMD is not only limited to muscle function. It has become increasingly clear that DMD is more often associated with lower average intellectual abilities – i.e. an IQ of one standard deviation below the mean<sup>5</sup>-, learning disabilities like dyslexia,<sup>6</sup> and (neuro) behavioural disorders such as an increased prevalence of attention deficit (hyperactivity) disorder (ADHD),<sup>7</sup> and autism spectrum disorder (ASD).<sup>8–11</sup> Recently, Ricotti and colleagues therefore introduced the term “*dystrophin associated neurodevelopmental syndrome*”.<sup>12</sup>

Although both researchers and clinicians have become somewhat more aware of these potential brain-related comorbidities, a straightforward genotype–phenotype correlation has so far not emerged.<sup>7,13,14</sup> The hypothesis that distal mutations encompassing the shorter Dp140 and Dp71 isoforms result in more profound cognitive impairment<sup>15–18</sup> has been (re-) proposed.<sup>12,14,19–22</sup> However, a mutation in the full-length dystrophin protein (Dp427) of *mdx* mice (the animal model for DMD) was also correlated with some extent of cognitive impairment.<sup>13</sup> Therefore, it seems rather likely that the cumulative number of individual gene products affected by a mutation would be directly correlated with the incidence and severity of cognitive impairment in DMD.<sup>12,14,18</sup>

In addition, a relationship between (the lack of) dystrophin and hyperexcitation seems to exist.<sup>23</sup> Three, independent studies demonstrated an increased prevalence of epilepsy in muscular dystrophy populations, ranging from 3.1% to 12.3%.<sup>24–26</sup> These studies are, however, limited by modest samples sizes and by the fact that in one study both DMD and Becker Muscular Dystrophy (BMD) patients were included.<sup>24</sup> Thus, further international studies are needed to investigate the increased prevalence of epilepsy in DMD. Similarly to DMD, neurodevelopmental comorbidities are more prevalent among epilepsy patients. Therefore, DMD and epilepsy may share common denominators.

The primary aim of this observational surveillance study was to (i) specifically examine the occurrence of epilepsy in an international population of patients with DMD by means of an online self/by-proxy report questionnaire. Furthermore, we aimed to (ii) evaluate whether other brain-related comorbidities were more frequently reported among DMD patients with epilepsy compared to those without. Finally (iii), in order to shed more light on the relatively novel association between epilepsy and DMD – including the genetic mutation-, epilepsy characteristics were comprehensively described.

## 2. Material & methods

### 2.1. Patients

Men and parents of boys from 15 countries (13 Europe, USA, Australia; see Table 1 for some of the countries and the respective response rates) were invited through the assistance of major national DMD charities within each country to participate in the study. The distribution of information on the study was carried out by the Dutch Parent Project, a non-profit organization focused entirely on Duchenne and Becker muscular dystrophy, and from there sent to the aforementioned different (Duchenne) muscular dystrophy parent associations across the world. The different associations, in turn, distributed the information letter to the patients and their parents. The ways of information distribution varied among countries: in most countries (e.g. Italy, Netherlands) the survey appeared on the community website and in the regular newsletter (e.g. the UK), whereas other countries (e.g. Australia, Belgium) put it on their Facebook webpage in order to draw attention. Participants were invited to complete a web-based online questionnaire. In order to reduce selection-bias, it was explicitly stressed that every boy or parent was supposed to complete the questionnaire, also if an epilepsy diagnosis had never been suspected or made.

### 2.2. Questionnaire

The questionnaire was developed by two paediatric neurologists; one with specific expertise in DMD, the other with particular expertise in epilepsy. Both the information letter and the website with the online survey itself contained information on how to complete the questionnaire. In order to

**Table 1 – Characteristics of participating countries in this questionnaire study.**

Country	Association	Distribution via	Addressed (N)	Responded (n)	Response rate
Netherlands	DPP-NL	- Newsletter - Website/Facebook	N = 279	n = 55	19.7%
USA	UPPMD	- Community website - FACES Coordinators	N/A	n = 42	N/A
Australia	Foundation Duchenne	- Facebook page	N/A	n = 16	N/A
Belgium	DPP-B	- Facebook page	N = 222	n = 20	9.0%
UK	Action Duchenne	- Newsletters	N/A	n = 15	N/A
Italy	Parent Project Onlus	- Newsletter - Community website	N = 594	n = 60	10.6%
Ireland		- Newsletter	N/A	n = 5	N/A

Abbreviations: DPP = Duchenne Parent Project, B = Belgium/NL = Netherlands, FACES = Families Advocating, Connecting, Educating, and Supporting (part of Parent Project Muscular Dystrophy), UPPMD = United Parent Projects Muscular Dystrophy.

include an international population, native speakers translated the questionnaire into English and Italian. Boys with DMD older than 16 years were instructed to complete the questionnaires with assistance from their parents. For boys younger than 16, parents were instructed to complete the surveys.

The online questionnaire consisted of 19 multiple choice and open questions (the original questionnaire has been included in the [appendix](#)). The first part consisted of general questions such as date of birth, nationality, age of DMD diagnosis, medication use, but also the presence of sleep disorders or other brain-related comorbidities such as lower intellectual abilities and ADHD (see [Table 2](#)). The second part focussed entirely on whether there has been made an epilepsy diagnosis and on the epilepsy characteristics. During the design of the questionnaires the authors classified and defined epilepsy according to the most recent International League Against Epilepsy (ILAE) classification<sup>27</sup> and implemented it as such in the survey.

To assist in confirmation and classification of epilepsy the following was asked: a description of a typical seizure, age of onset of seizures, seizure types, seizure frequency, EEG characteristics, anti-epileptic drugs (AEDs), and response to AEDs. Two external (i.e. not part of the research group) child neurologists from Maastricht University Medical Centre with expertise on epilepsy independently inspected the blinded questionnaire data of all patients reported to have epilepsy to confirm whether they indeed had epilepsy. Concordance between the two observers was calculated by means of Cohen's Kappa. Any cases for which there was a lack of agreement, were reviewed by a third paediatric neurologist, blinded to the responses of the other two neurologists. This third and last assessment was decisive for the final allocation of the three remaining patients.

Ethical approval was obtained from the local ethics committee of Kempenhaeghe epilepsy centre, Heeze, as part of Maastricht University, the Netherlands.

### 2.3. Data analysis

General descriptive sample characteristics such as the mean and median age at study entry, and mean of DMD diagnosis, were calculated. The results of the questions regarding intelligence, presence of brain-related comorbidities, and/or

learning disorders were transformed in frequencies and subsequently expressed as percentages. This was done, first, for the collective DMD population ([Table 2](#)), and then for the epilepsy and the non-epilepsy sub-groups separately ([Table 4](#)). Difference in proportions between the epilepsy and the non-epilepsy group were investigated by means of a Fisher's exact test.<sup>28</sup> For all statistical analyses SPSS (version 16) was used.

**Table 2 – Overview of the reported (brain-related) comorbidities in the collective DMD sample studied (N = 228), and in comparison to the normal population as based on the literature.**

Comorbidity	n	DMD (%)	Normal population (%)
<b>Cognitive level</b>			
Serious impairment (IQ < 70)	11	4.8	2
Moderate impairment (70 < IQ < 85)	29	12.7	13.5
Normal (85 < IQ < 115)	98	43.0	68
Higher level (IQ > 115)	37	16.2	15.5
Unknown IQ level	53	23.2	–
Total	228	100	–
<b>Learning disability</b>			
No learning disability	141	61.8	–
Reading disability	17	7.5	3–10 <sup>6</sup>
Arithmetic disability	21	9.2	5 <sup>29</sup>
Reading and arithmetic disability	6	2.6	–
Other learning disability	30	13.2	–
Unknown	13	5.7	–
Total	228	100	–
<b>Neuropsychiatric diagnosis</b>			
ADHD	19	8.8	7 <sup>9</sup>
Autism spectrum disorder (ASD)	22	9.6	<0.1 <sup>9</sup>
Obsessive compulsive disorder (OCD)	11	4.8	2.3 <sup>9</sup>
Anxiety disorder	15	6.6	4.7 <sup>a,30</sup>
Depressive disorder	8	3.5	3.0 <sup>b,31</sup>
<b>Neurological disorders</b>			
Epilepsy	18	7.9	0.5–1 <sup>32</sup>
Sleep disorders	17	7.5	3 <sup>33</sup>

<sup>a</sup> For men only, 7.3% for all anxiety disorders among men and women.

<sup>b</sup> This number reflects the prevalence of a current major depressive disorder; 12 month prevalence was 5.28, life time prevalence 13.2%.

**Table 3 – Collective seizure type- and AED frequencies in a sample of DMD patients with epilepsy.**

Seizure type	Subtype	n	%
Generalised	Absence seizures	7	36.8
	Tonic seizures	0	0.0
	Tonic-clonic seizures	6	31.6
	Myoclonic seizures	0	0.0
Focal	Focal seizures	6	31.6
	<b>Total</b>	<b>19</b>	<b>100</b>
AED	Carbamazepine	1	4.5
	Ethosuccimide	1	4.5
	Lamotrigine	4	18.2
	Levetiracetam	4	18.2
	None	4	18.2
	Oxcarbazepine	1	4.5
	Phenobarbital	1	4.5
	Topiramate	1	4.5
	Valproate	4	18.2
	Zonisamide	1	4.5
	<b>Total<sup>a</sup></b>	<b>22</b>	<b>100</b>

Note: also AED's for patients who are seizure-free now, yet were used in the past are listed in this table. For individual (i.e. per patient) characteristics, see Table 5.

<sup>a</sup> The fact that more AED's are reported, compared to patients, can be clarified by the fact that four patients used two AEDs. Similarly, some patients had multiple seizure types (again, see Table 5).

### 3. Results

269 questionnaires were submitted. Of these, 41 were excluded (36 because of missing information and 5 because these participants had BMD), resulting in questionnaires on 228 DMD patients being available for analyses.

The mean age of this total group at completion of the questionnaire was 13.25 years (SD = 7.58), with a minimum of 0 and a maximum of 32.5 years. The diagnosis DMD was made at a mean age of 3.61 years (SD = 2.05 years) with a range from 0 to 13 years. Of the patients with DMD, 159 (70.4%) used steroids, either currently (93.7%), or in the past (6.3%), yet stopped for multiple reasons, particularly because of reported side effects. Deflazocort and prednisone were used almost equally often (48.4% and 47.8% respectively). Six patients (3.8%) did not know which steroid they were taking, amongst other because they participated in trials.

The IQ level was not known in 53 patients (23.2%). Forty patients (17.5%) turned out to have impaired intellectual abilities (IQ < 85). Patients and/or parents reported other learning- and cognitive disorders, including dysgraphia, concentration difficulties, language and speech (processing) difficulties, memory difficulties, general developmental delay, and problems with information processing. Additional characteristics on self/by-proxy reported brain-related comorbidities (e.g. ASD and learning disorders) in this DMD cohort are described in Table 2. As patients and parents participated anonymously in this survey, additional data on the sample characteristics and the characteristics of the non-responders were not available.

Thirty-two subjects with possible epilepsy were initially identified. However, reasons for exclusion from the eventual epilepsy group were insufficient information provided and/or not meeting the criteria for epilepsy (n = 10) and the presence

**Table 4 – Reported brain-related comorbidities in DMD patients with and without epilepsy. Patients with DMD and besides epilepsy report on generally lower intellectual capabilities (however, a significant difference could not be detected) and significantly more behavioural co-morbidities such as ADHD and OCD. Next, they report more frequently on anxiety disorders. Learning, specifically with regards to reading and mathematics, appeared not to result statistically more often in problems when a concomitant epilepsy diagnosis was present. Finally, a significant association between the two neurological disorders studied in relation to DMD in this study (i.e. epilepsy and sleep disorders) was observed.**

Epilepsy (n = 18)		Non-Epilepsy (n = 210)		P-value
<i>Intelligence</i>		<i>Intelligence</i>		
Impairment (IQ < 85)	35.3%	Impairment (IQ < 85)	21.5%	0.226
Normal intelligence (IQ: 85–115)	47.1%	Normal intelligence (IQ: 85–115)	56.9%	0.453
Higher functioning (IQ > 115)	17.6%	Higher functioning (IQ > 115)	21.5%	1.000
<i>Neuropsychiatry</i>		<i>Neuropsychiatry</i>		
ADHD	38.9%	ADHD	6.2%	0.000
ASD	11.1%	ASD	9.5%	0.687
OCD	16.7%	OCD	3.8%	0.046
Anxiety	22.2%	Anxiety	5.2%	0.022
Depression	11.1%	Depression	2.9%	0.124
<i>Learning disorders</i>		<i>Learning disorders</i>		
Dyslexia	22.2%	Dyslexia	9.6%	0.110
Dyscalculia	22.2%	Dyscalculia	11.7%	0.254
<i>Other disorders</i>		<i>Other disorders</i>		
Sleep disorder	33.3%	Sleep disorder	5.2%	0.001

\* P-values were considered significant at an alpha < 0.05.

of (solely) febrile seizures (n = 4). Thus, there were 18 subjects with physician confirmed epilepsy (Cohen's Kappa, 0.850, SE = 0.102), and as such epilepsy was present in 7.9% (95% CI 4.9–12.4%) of the patients that participated in this study. Eleven boys or men were currently having epilepsy (61.1%), whereas 7 boys suffered from it in the past (38.9%). All epilepsy patients, including additional epilepsy-related characteristics, are shown in Table 5. The age of onset ranged from 0 to 16 years (mean 9.24 years, SD = 4.76 years). EEG's were made in 17 patients (94.4%) and revealed abnormalities in 13 DMD patients (76.5%). Seizure frequency varied from less than one per year (42.3%) to almost daily (14.2%); the remaining patients (43.5%) had seizures varying from less than once a week to more than once per year. AEDs, however, had been able to control most of the reported seizures as 8 boys (53.8%) reported to be seizure free now, 5 patients (38.5%) reported a 50% reduction, whereas in one patient no change was noted. AED effectiveness was unknown in 4 patients (27.8%). One patient without epilepsy used sodium valproate (Depakine) for the control of migraine. Information on seizure types and AEDs has been displayed in Table 3. Three patients with epilepsy were not on AEDs – of whom two not yet – which was in one case related to the (very) recent seizure-onset and in one case due to the very young age. Corticosteroids, as part of DMD treatment, were used in 11 of the DMD patients with epilepsy (61.2%).

**Table 5 – Characteristics for all DMD patients with epilepsy, both in present and past, including reported cognitive abilities and concomitant diagnosis with neurodevelopmental disorders.**

#	Age	Cou-ntry	Isoform	Age of onset	Seizure type	Seizure frequency	EEG	Treatment	Seizure Control	Family history	IQ	NPD/sleep	LD
1	12 yr.	AUS	–	–	–	Used to <1×/month	Abn	Used to take sodium valproate ( <i>Epilim</i> )	Seizure-free	N	<85	N	N
2	31 yr.	USA	Dp427	14 yr.	Focal (TLE)	<1×/year	Abn	Lamotrigine	Seizure-free	N	>115	N	N
3	17 yr.	USA	Dp427, Dp140	16 yr.	Focal (TLE)	<1×/month	Abn	Oxcarbazepine, Levetiracetam	50% reduced	N	AVG	N	N
4	7 yr.	SA	Dp427	6 yr.	Tonic-clonic	<1×/year	Nor	Sodiumvalproate ( <i>Epilim</i> )	Seizure-free	N	<85	ADH/ASD	N
5	24 yr.	USA	–	10 yr.	Absence Tonic-clonic	<1×/month	Abn	Levetiracetam, VNS	50% reduced	P	AVG	N	N
6	29 yr.	USA	–	13 yr.	Focal	–	Abn	Used to take Carbamazepine	Seizure-free	P	AVG	ADH/	Y
7	14 yr.	USA	Dp427, Dp140*	9 yr.	Absence	Almost daily	Abn	Lamotrigine, ethosuccimide	50% – reduced	N	AVG	Sleep	Y
8	13 yr.	ITA	Dp427, Dp140*	6 yr.	Absence Tonic-clonic	<1×/month	Abn	Lamotrigine, Sodium valproate ( <i>Depakine</i> )	Seizure-free	N	<85	ADH/	Y
9	1 yr.	ITA	Dp427, Dp140*	1 yr.	Absence	<1×/year	Abn	None	–	N	AVG	N	N
10	17 yr.	USA	Dp427	16 yr.	Tonic-clonic	<1×/year	Abn	None (still awaiting treatment initiation)	–	N	<70	ADH/ASD, OCD, depr	Y
11	13 yr.	USA	Dp427, Dp140	7 yr.	Focal, Tonic-clonic	–	Abn	Lamotrigine, Zonisamide	50% – reduced	P	<85	ADH/ANX	Y
12	25 yr.	AUS	Dp427	11 yr.	Focal	–	Nor	Used to take sodium valproate ( <i>Epilim</i> )	Seizure-free	N	–	N	N
13	15 yr.	USA	Dp427, Dp140*	15 yr.	Absence	<1×/month	Abn	Levetiracetam	50% – reduced	N	>115	ADH/OCD sleep	N
14	13 yr.	NZE	Dp427, Dp140*	9 yr.	Absence	Used to be almost daily	Abn	Used to take Topiramate	Seizure-free	N	AVG	sleep	N
15	22 yr.	NL	Dp427, Dp140*	5 yr.	Absence	Used to be <1×/year	N	None	–	N	AVG	N	N
16	–	–	Dp427	9 yr.	Focal, Tonic-clonic	<1×/month	Nor	None	–	N	>115	ADH/OCD ANX sleep	N
17	14 yr.	USA	Dp427	0 yr.	–	<1×/year	Abn	Used to take Phenobarbital	Seizure-free	N	<85	N	Y
18	20 yr.	USA	Dp427, Dp140	10 yr.	idiopathic pro-voked	–	Nor	Used to take Levetiracetam	No change	N	AVG	ANX depr sleep	N

Abbreviations: Abn. = abnormal, Anx = Anxiety disorder, ADH/ = Attention Deficit Hyperactivity Disorder, ASD = Autism Spectrum Disorder, AUS = Australia, AVG = Average (85 < IQ < 115), Depr = Depressive disorder, ITA = Italy, IQ = Intelligence Quotient, LD = learning disorder, N = No/Negative, NL = Netherlands, Nor. = normal, NPD = Neuropsychiatric disorder, NZE = New-Zealand, P = positive, SA = South- Africa, sleep = sleep disorder, TLE = Temporal Lobe Epilepsy, USA = United States of America, VNS = vagal nerve stimulation, Y = yes (here: presence of learning disorder), yr. = years, – = missing, \* = not with certainty known whether Dp140 is affected due to the unpredictable effect of mutations between intron 44 and exon 51 on Dp140 expression (see discussion).

Six boys/men (35.3%) with epilepsy were cognitively impaired (5 patients with moderate impairment, i.e. an IQ below 85, and 1 with serious impairment, i.e. an IQ of below 70), eight patients (47.1%) had an average IQ - i.e. between 85 and 115 -, and three patients (17.6%) had an IQ higher than 115 (for one patient the IQ-score was not known). This did not differ significantly from the DMD group without epilepsy (N = 210; the IQ was unknown for 52 patients in this subgroup): 21.5% with intellectual impairment (24 patients with moderate impairment and 10 with serious impairment), 56.9% with a normal IQ, and 21.5% with an IQ > 115 (depicted in Table 5, together with the respective p-values). From Table 4 it can furthermore be concluded that all neuropsychiatric comorbidities and learning disorders (here: dyscalculia and dyslexia) were reported in both groups. The comorbidities ADHD, OCD, anxiety-, and sleep disorders were significantly more prevalent in the epilepsy subgroup.

Although mutations were reported in a relatively small proportion of patients, the following was reported on the type and location of the mutation in the dystrophin gene within the epilepsy cohort: in 3 patients (16.7%) the mutation was not known, 6 patients (33.3%) had a mutation upstream of exon 45, whereas in 3 patients (16.7%) the mutation was located, at least partly, between exon 51 and exon 62. In the 6 remaining patients (33.3%), the mutation was located between intron 44 and 51 (as indicated by Dp140\* in Table 5). None of the patients with epilepsy had a mutation downstream of exon 63; consequently in none of the epilepsy patients Dp71 was affected, nor were all three isoforms involved in any patient. The consequences of the abovementioned on the expression of the different dystrophin isoforms have been summarized in Table 5 (per patient).

## 4. Discussion

This study supports an increased occurrence of brain related comorbidities in DMD, particularly with regards to epilepsy. Furthermore, and more importantly, this study is the first to show that some of these disorders (i.e. ADHD, OCD, anxiety, and sleep disorders) are significantly more often present in DMD patients additionally having epilepsy. This is a new finding, which may have important clinical implications.

### 4.1. Epilepsy is more often reported in DMD populations

The population studied here is the largest group of DMD patients so far evaluated in relation to epilepsy. Almost 8% of the DMD patients and parents reported to have a diagnosis of epilepsy. This is substantially higher than in the general paediatric population (0.5–1%),<sup>32</sup> and comparable to the prevalence found by a recent Italian study with a different set-up.<sup>26</sup> Ten other patients who reported to suffer from epilepsy were, based on the strict criteria used, excluded from the epilepsy group since their answers were lacking important clinical data in order to confirm the presence of epilepsy. Therefore, the occurrence of epilepsy might even be higher in this group of boys with DMD, even though the ascertained number of 7.9% is in keeping with the published literature. Furthermore, absence seizures were the most frequently reported seizure type

among this cohort. Consequently, the concomitant diagnosis of epilepsy in DMD patients, which is not well known in clinical practice, might be easily overlooked or confused with neuropsychiatric disorders such as AD(H)D. This diagnostic overshadowing is an important (new) aspect in DMD.

Apart from that, we identified 6 DMD patients with provoked seizures; i.e. two patients in whom the seizures were precipitated by video/computer screens (these were included in the epilepsy group as they were considered to have epilepsy by both child neurologists as based on the clinical information provided) and the four patients with febrile seizures (who were excluded from the epilepsy group). Furthermore one of the excluded five BMD patients was considered to have Rolandic epilepsy without EEG abnormalities and treated with Depakine, which resulted in seizure remission. Finally, one mother (a carrier of the mutation in the DMD gene) reported to have generalized epilepsy, whereas her son did not have seizures.

### 4.2. Additional brain related comorbidities in DMD in relation to epilepsy

Our study supports the increased prevalence of neurodevelopmental comorbidities in DMD (Table 2) as compared to the general paediatric population.<sup>5–7,9,11,34–36</sup> Especially ASD and OCD were again, more frequently reported compared to the general population.<sup>9</sup> This is interesting, since epilepsy is also frequently associated with neurodevelopmental impairment.<sup>37,38</sup> Indeed, epilepsy diagnosed in addition to DMD was associated with an increased occurrence of neurobehavioral comorbidities such as ADHD and OCD as Table 4 illustrates. Remarkably, DMD patients diagnosed with epilepsy also reported significantly more often on an anxiety disorder. This is in line with previous studies demonstrating that epileptic seizures are associated with anxiety disorders that furthermore affect mortality, seizure status, and quality of life.<sup>39</sup> Unsurprisingly, in boys and men with both DMD and epilepsy, a third of the patients reported to have sleep problems, compared to only 5.2 percent in the non-epilepsy DMD group. It has been suggested that the abovementioned disruption of the neuronal GABA architecture due to the lack of Dp427 in the brain may partly explain the sleep disorders seen in DMD.<sup>13</sup> Whether this may possibly be exacerbated by (poor)seizure control, number or effectiveness of AEDs, or perhaps due to indirect, potential consequences of seizures is unclear and deserves attention in future research. This association is however important given the fact that sleep problems influence quality of life – but also behaviour, cognition, and even seizure control – negatively.<sup>40</sup>

### 4.3. Mutations and isoforms in relation to epilepsy in DMD

Within this cohort, in all patients with epilepsy and with the known mutation (n = 15), the mutation was located upstream of exon 62, thereby either affecting both Dp427 and Dp140 or Dp427 alone. This is similar to the recent findings by Pane and colleagues.<sup>26</sup> The full-length isoform, Dp427, was thus affected in all patients. This could be attributed to the fact that the region between exon 2 and 20 and exon 45–53 are two common deletion hotspots<sup>41</sup> causing the absence of Dp427m (muscle). This also results in the absence of brain Dp427c

(cerebrum), which is known to anchor GABA<sub>A</sub> (gamma-aminobutyric acid) receptors post-synaptically.<sup>42</sup> We recently demonstrated a Dp427 up-regulation in temporal lobe epilepsy patients, possibly revealing a dystrophin-mediated counteracting mechanism towards hyperexcitable brain networks by means of exerting more inhibitory GABA input.<sup>43</sup> Conversely, since such mechanisms are defective in the brains of DMD patients, this may clarify seizure threshold alterations, hence making boys with DMD theoretically more prone to develop epilepsy.

Six patients reported to have a mutation between exon 45 and 51. Since these exons constitute the 5' untranslated region of Dp140, it is unpredictable whether Dp140 is expressed in these patients.<sup>18</sup> Dp140 has so far not been linked to hyperexcitation from a theoretical nor practical perspective, not least since it seems to be rather developmentally regulated<sup>44,45</sup> – notwithstanding its possible relationship with cognitive deficits.<sup>19</sup>

None of the epilepsy patients reported to have a distal mutation that would furthermore affect Dp71, and hence all three isoforms. The lack of a distal mutation in the dystrophin gene is possibly the consequence of the fact that these mutations are generally rare,<sup>12</sup> as also reflected by the fact that in only four of the patients within the total cohort studied here and with known mutation ( $n = 168$ ), Dp71 was expected to be missing as based on mutation analyses. Thus, in contrast to the cognitive problems, where it has been proposed that the distal mutations – particularly including Dp71<sup>14,20,21</sup> – would have a more profound effect on cognitive deficits, this may not necessarily be the case for epilepsy. This is intriguing given the fact that a deficiency in Dp71, albeit theoretically, may have a profound effect on epileptogenesis by different mechanisms involving water-channels, potassium channels, and the blood–brain barrier.<sup>23</sup> Therefore once again, the rarity of this mutation should be considered and stressed, which – in combination with the small sub-group of patients with both DMD and epilepsy – also impeded a meaningful analysis.

#### 4.4. Study limitations and future perspectives

We chose the self-report questionnaire in order to acquire a large and global group of DMD patients by making use of relatively novel means such as social media aiming to reach more people within the target audience. A limitation of the latter is the lack of insight in response rates, which were only known for the Italian, Belgian, and Dutch population, yet were difficult to estimate. Furthermore, these known response rates were low, as can be seen in Table 1. Therefore, the true numbers reported for epilepsy may have been overestimated given the risk of (selection-) bias. We tried to reduce this bias by stressing that every DMD patient (and/or their parents) should complete the questionnaire.

Although the percentage of patients with ASD and OCD in our study was similar compared to previous studies, ADHD was less frequently reported (i.e. reports in literature demonstrated rates of 11.7% in one study<sup>9</sup> and 20–30% in multiple other studies<sup>7,22,46</sup>). Concerning the data on IQ scores it remains true that differences between the epilepsy and the non-epilepsy group are to some extent difficult to compare because of missing data (approximately 25% in the non-epilepsy group).

These missing data may also partly clarify why our population is not per se representative with regards to the occurrence of learning or intellectual disabilities as only five percent had intellectual impairment (i.e. IQ scores <70), whilst this was found to be 34.8% in the largest meta-analysis hitherto performed.<sup>5</sup> This suggests there might be a population bias in the cohort studied here. Similarly, internalizing problems (anxiety and depression) might be under-represented in this study population as Ricotti et al. identified 24% to have such problems.<sup>12</sup> Banihani and colleagues found anxiety in 27%,<sup>22</sup> whereas one other study identified 51% of the patients to have a depressed mood.<sup>46</sup> These differences could additionally be partly attributed to the self/by-proxy nature of this study.

As mentioned, the accuracy of using a self/parent report for collecting information on brain-related comorbidities or mutations – of which the data was furthermore only known for a small proportion of patients and should thus be interpreted with caution – can be questioned. However with regards to the primary outcome of this study, i.e. epilepsy, subsequent assessment by two external neurologists as based on additional objective information provided was performed in order to enhance the accuracy of the numbers presented here.

Since it was not feasible to translate the survey into all the languages of the countries to which an invitation to participate was sent, the three languages expected to be most relevant to our sample were chosen. However, possible language problems among people in other countries, might have also contributed to selection bias. As patients filled out the questionnaire anonymously, we were not able to contact patients, or their clinicians, for additional information.

More preclinical research is required in order to understand the pathophysiological relationship between (a lack of) dystrophin and epilepsy. In addition, cross sectional population based studies should confirm the existence of a possible triangular relationship between DMD, epilepsy, and neurodevelopmental disorders. Furthermore, long-term longitudinal studies should evaluate the consequences of epilepsy and AED usage (including polytherapy) for boys and men with both DMD and epilepsy. More research on this association between DMD and epilepsy, its cause and consequences for clinical care, will increase awareness among clinicians, ultimately diminishing the possible effects of diagnostic overshadowing.

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## 5. Conclusion

The results from this survey reveal that patients with DMD and their parents more frequently report on epilepsy and other brain related-comorbidities, which is supportive on an increased prevalence of epilepsy in DMD. As clinicians may not be aware of this, a possible diagnosis of epilepsy may be easily overshadowed by DMD and/or its spectrum of neurodevelopmental features. This is particularly true, as sleep disorders, AD(H)D, OCD, and anxiety disorders appear to occur more frequent among boys with both DMD and epilepsy. Moreover, since such comorbidities are also more often observed in epilepsy, a common underlying pathological mechanism (e.g. the absence of dystrophin) may be considered. More research is needed to examine the existence of a potential *syndrome* or triad including DMD, epilepsy, and

neurodevelopmental disorders, in other words whether epilepsy could possibly be added to the recently proposed “dys-trophin associated neurodevelopmental syndrome”.

### Conflict of interest

The authors whose names are listed immediately below certify that they have NO affiliations with or involvement in any organization or entity with any financial interest (such as honoraria; educational grants; participation in speakers' bureaus; membership, employment, consultancies, stock ownership, or other equity interest; and expert testimony or patent-licensing arrangements), or non-financial interest (such as personal or professional relationships, affiliations, knowledge or beliefs) in the subject matter or materials discussed in this manuscript.

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### Appendix

Questionnaire (English version for parents), part I.

## Epilepsy in Duchenne Muscular Dystrophy: questionnaire-study

### Answerform

1. Date of birth of your son: month  year

2. Country of origin   
State

3. What is your son's specific diagnosis?  Duchenne  Becker  
- at what age was the diagnosis made?  years (fill in age in years)  
- What is the proven mutation of your son?

4. Is your son on steroid therapy?  Yes  No  
- If yes, at what age did he start steroids?  years  
- What steroids does he use?  Prednisone  Deflazacort  Other  
Please specify other

5. What other medication does your son use?

6. What is the cognitive level of your boy?

7. Is your son visiting regular school?

8. Does your boy have a learning disability?   
Please specify other

9. Has one of the following diagnosis been formally made for your son (more answers possible)?  
Check All That Apply  Attention Deficit Hyperactivity  
 Autism Spectrum Disorder  
 Obsessive Compulsive Disorder  
 Anxiety Disorder  
 Depressive Disorder  
 Sleep disorder  
 Other  
Please specify other

## Questionnaire (English version for parents), part II.

**10. Is your son suffering from epilepsy?**  Yes  No  in the past, not currently

**11. What was the age of onset of seizures?**  years (fill in age in years)

**12. What type of seizures has your son?**  
Check All That Apply

Febril seizures  
 Tonic clonic seizures  
 Tonic seizures  
 Absence seizures  
 Myoclonic Seizures  
 Simple partial seizures  
 Complex partial seizures  
 Other

Please specify other

**13. How frequent do the seizures occur?**

**14. Please write down a short description of a typical seizure of your son:**

**15. Was an EEG made?**  Yes  No

- if yes, were there abnormalities on EEG?  Yes  No

**16. Does he use anti-epileptic medication?**  Yes  No

- If yes, which medications does he use?

**17. Are these medications effective?**

**18. Does he experience limitations in daily functioning due to the epilepsy?**  Yes  No

**19. Is there epilepsy in your family?**  Yes  No

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