Journal of Neurology (2022) 269:3461–3469
https://doi.org/10.1007/s00415-022-11040-y

REVIEW

Epileptic disorders in Becker and Duchenne muscular dystrophies: a systematic review and meta-analysis

Carlos Pascual-Morena[1] · Vicente Martínez-Vizcaíno[1,2] · Alicia Saz-Lara[1] · José Francisco López-Gil[1] · Jaime Fernández-Bravo-Rodrigo[1,3] · Iván Cavero-Redondo[1]

Received: 3 February 2022 / Revised: 16 February 2022 / Accepted: 17 February 2022 / Published online: 1 March 2022

Abstract

Dystrophin alterations in the brain have been associated with an increased risk of epilepsy in Becker and Duchenne muscular dystrophies (BMD and DMD). Moreover, an association between the mutation site and the risk of epilepsy is not ruled out. The aim of this systematic review and meta-analysis was to estimate the prevalence of epilepsy in BMD and DMD populations and to establish a possible association between the site of mutation in the dystrophin gene and the risk of epilepsy. Systematic searches of Medline, Scopus, Web of Science, and Cochrane Library were conducted to identify relevant studies published from inception to January 2022. Observational studies of participants with BMD/DMD estimating the prevalence of epilepsy were included. The main outcome was the prevalence of epilepsy, and the secondary outcome was the prevalence ratio considering genotype. A random effects meta-analysis was performed for the prevalence of epilepsy. Eight studies were included in the systematic review and meta-analysis. The prevalence of epilepsy was 7% (95% CI 3–11%) in BMD, 5% (95% CI 2–8%) in DMD, and 5% (95% CI 3–7%) in the overall estimate. No association was observed between mutation site and the prevalence of epilepsy. BMD/DMD is strongly associated with the prevalence of epilepsy, with a higher prevalence in BMD/DMD populations than in the general population, probably owing to alterations in Dp427. The current evidence does not support the hypothesis that Dp140 or Dp71 affect epilepsy risk.

Keywords Epidemiology · Epilepsy · Duchenne muscular dystrophy · Becker muscular dystrophy · Systematic review · Meta-analysis

Introduction

Becker and Duchenne muscular dystrophies (BMD and DMD) are two neuromuscular diseases caused by several mutations, including point mutations, deletions, or duplications, in the *dystrophin* gene [1, 2], affecting one in 18,000–30,000 male births [3] and one in 3500–9000 male births [4], respectively. In BMD, these mutations do not affect the reading frame, allowing for partially altered but functional dystrophin expression. However, in DMD, the reading frame is affected, with an absolute or almost absolute absence of dystrophin. Alterations of dystrophin lead to sarcolemmal instability, muscle degeneration, and replacement by fibrotic tissue, with progressive muscle weakness and reduced ambulation ability. BMD progression is usually slow, with ambulatory ability in adulthood and a normal life expectancy [2, 5]. Conversely, and despite treatment optimization, the emergence of new treatments, and phenotype variability, DMD continues to

✉ Alicia Saz-Lara
alicia.delsaz@uclm.es

Carlos Pascual-Morena
carlos.pascual@uclm.es

Vicente Martínez-Vizcaíno
vicente.martinez@uclm.es

José Francisco López-Gil
josefrancisco.lopez@uclm.es

Jaime Fernández-Bravo-Rodrigo
jaime.fernandezbravo@alu.uclm.es

Iván Cavero-Redondo
ivan.cavero@uclm.es

[1] Health and Social Research Center, Universidad de Castilla—La Mancha, 16071 Cuenca, Spain

[2] Facultad de Ciencias de La Salud, Universidad Autónoma de Chile, 3460000 Talca, Chile

[3] Pharmacy Service, Hospital Virgen de La Luz, 16002 Cuenca, Spain

have a poor prognosis, with loss of ambulation in adolescence and life expectancy into the third or fourth decade of life [5–9].

In addition to muscle, dystrophin is also expressed in the brain as full-length isoforms (Dp427c and Dp427p) as well as short isoforms (Dp140 and Dp71). These isoforms are expressed in the hippocampus, the Purkinje cells of the cerebellum, and the amygdala, with important roles in GABAergic transmission (Dp427), fetal development (Dp140), glutaminergic transmission and blood–brain barrier formation (Dp71). Depending on the mutation site, one or more isoforms will be affected. Thus, an association of BMD and DMD has been observed with several neuropsychiatric and neurological disorders, including epilepsy [10–14]. In the case of epilepsy, some mechanisms have been proposed that could explain the increased risk associated with BMD/DMD. The absence of Dp427 produces an aberrant clustering of $GABA_A$ receptors, with an increase in extrasynaptic $GABA_A$ receptors. All this leads to a dysfunctional GABA inhibitory pathway, increasing the spread of seizures. Moreover, Dp427 has been shown to be upregulated in temporal lobe epilepsy in people without dystrophy, indicating a possible compensatory mechanism. In BMD/DMD, this mechanism could be lost, lowering the seizure threshold and increasing the risk of epilepsy. The absence of Dp71 could also contribute to neuronal hyperexcitability through altered potassium and water homeostasis due to alterations in Kir4.1 and aquaporin-4 clustering in astrocytic/astroglial terminal feet, leading to increased potassium levels. Finally, the absence of Dp71 causes important alterations in the integrity of the blood–brain barrier, exposing the brain to substances that cause hyperexcitability (e.g., albumin) [15, 16].

Although epilepsy is known to be common in dystrophinopathies, the overall prevalence in populations with BMD/DMD is unknown. It is also possible that the genotype in BMD/DMD (i.e., which isoforms are affected) influences the prevalence of epilepsy, as occurs in other neuropsychiatric and neurodevelopmental disorders in these patients [14]. Therefore, this systematic review and meta-analysis aims to estimate the prevalence of epilepsy in populations with BMD or DMD and to determine whether there is a genotype–prevalence association considering the mutation site.

Methods

We conducted this systematic review and meta-analysis according to the Meta-analyses of Observational Studies in Epidemiology (MOOSE) guidelines [17] and the Cochrane Collaboration Handbook [18]. Moreover, the study was registered in PROSPERO (Registration Number: CRD42021284753).

Search strategy

The Medline, Scopus, Web of Science, and Cochrane Library databases were systematically searched for relevant studies published from inception to January 2022. Grey literature, including the Theseo, OpenGrey, Google Scholar, and Networked Digital Library of Theses and Dissertations databases, was searched. The references of the included studies were also reviewed. Search terms included *prevalence, incidence, survey, questionnaire, frequency, epidemiology, ratio, rate, dystroph*, "duchenne muscular dystrophy", "becker muscular dystrophy", duchenne, dmd, bmd, neurological disorder*, neurological disease*, epilepsy, seizure*, with appropriate Boolean operators. Study authors were contacted if necessary. The complete search strategy is included in Supplementary Appendix S1. The literature search was conducted independently by two reviewers (CP-M and IC-R), and disagreements were resolved by consensus or by a third reviewer (VM-V).

Inclusion/exclusion criteria

The inclusion criteria were as follows: (1) participants: study populations with BMD or DMD (no age restrictions); (2) design: observational studies, including cross-sectional, retrospective, prospective, or case series studies; and (3) outcomes: (i) prevalence of epilepsy (main outcome), and (ii) genotype–prevalence association (secondary outcome). Mutations downstream of exon 45 were considered Dp140−, while mutations downstream of exon 63 were considered Dp71−. There were no language restrictions.

Exclusion criteria were as follows: (1) participants: studies including participants with other dystrophies, studies unable to determine the prevalence of epilepsy in patients with BMD or DMD; (2) design: studies with an insufficient sample to obtain a proportion (e.g., single case studies); (3) outcome: cohorts of only patients with epilepsy, studies reporting only febrile seizures.

Data extraction

An ad hoc table was performed with the data extracted from the included studies. It included (1) reference (authors and year of publication); (2) country; (3) design (cross-sectional, prospective, retrospective, case series); (4) population (disease, sample, age); (5) outcome (prevalence of epilepsy, genotype–epilepsy association).

Risk of bias assessment

We assessed the risks of bias of the included studies with the Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies of the United States National Institutes of Health National Heart, Lung, and Blood Institute [19]. This tool consists of 14 domains evaluating different aspects of study design and statistical methods and studies are scored as good, fair or poor. Considering the number of domains with risks of bias, the overall bias was good, fair, or poor.

Risk of bias assessment was conducted independently by two reviewers (CP-M and IC-R), and disagreements were resolved by consensus or with a third reviewer (VM-V).

Data synthesis

A narrative synthesis and ad hoc table of each study was performed for the main outcome (i.e., prevalence of epilepsy) and for the secondary outcome (genotype–prevalence association). The prevalence and its 95% confidence interval are shown, with 0.00 indicating 0% prevalence and 1.00 indicating 100% prevalence. The genotype–prevalence association was expressed, when possible, as a prevalence ratio and 95% confidence interval. When not possible, the percentage of patients with Dp140 or Dp71 present or absent in the population of participants with epilepsy was described. Occasionally, the site of the mutation was also considered.

A random effects meta-analysis [20, 21] was performed to determine the prevalence of epilepsy according to population subgroup (i.e., BMD, DMD, BMD + DMD). The overall prevalence of epilepsy in all participants with these dystrophinopathies was also estimated. Heterogeneity (I^2) was evaluated, and it was considered not important if it was < 30%, moderate if it was 30–50%, substantial if it was 50–75%, and considerable if it was > 75% [18, 22]. The p value of the heterogeneity was also considered. Finally, publication bias was assessed visually using the funnel plot [23]. A sensitivity analysis with study-by-study exclusion was conducted to determine the possible influence of studies with estimates that distort the real estimate.

All statistical analyses were performed with the statistical program STATA SE, version 15 (StataCorp, College Station, TX, US). Moreover, the statistical package *metaprop*, available for STATA, was used to estimate prevalence.

Results

Of the 4154 studies identified, eight met the inclusion/exclusion criteria (Fig. 1) [24–31] and were included in the systematic review (Table 1) and meta-analysis, including three studies on BMD, five on DMD, and two on BMD + DMD. Twelve studies were excluded with reasons (Supplementary Table S1).

There were two studies of participants from Italy [29, 29], two from Japan [26, 31], two from the United Kingdom [24, 28], two from the United States [25, 28], and one each from Australia [28], Belgium [28], China [30], Ireland [28], Iran [27], and the Netherlands [28]. The systematic review and meta-analysis included 1536 participants, of whom 157 had BMD, 872 had DMD, and 507 had either BMD or DMD. The sample size of the studies ranged from 28 to 307 participants. However, only two studies reported the mean age of the participants, which was lower in DMD participants than in BMD participants. Eight studies determined the prevalence of epilepsy, four reported the genotype of patients with epilepsy, and of these, only two reported the genotype of participants with and without epilepsy (a necessary condition for calculating the prevalence ratio). Finally, in three studies data were extracted from medical records, and in five studies from interviews or questionnaires. In half of the studies the type of epilepsy of the patients and whether or not they were well controlled were available. The method of data collection and the type of epilepsy diagnosed in each study are included in Supplementary Table S2.

Systematic review

Table 2 shows the findings of the prevalence of epilepsy in this population, and Table 3 and Fig. 2 show the genotype–prevalence association.

In BMD participants, the prevalence of epilepsy ranged from 0.07 to 0.08, while in DMD participants, it ranged from 0.02 to 0.13. In the two studies that did not separate BMD and DMD participants, the prevalence ranged from 0.02 to 0.06. There was no statistically significant difference in prevalence between BMD, DMD, and BMD + DMD groups. Regarding the genotype–prevalence association, in BMD, a PR = 0.48 (0.03, 8.71) and PR = 0.46 (0.03, 7.44) were observed for Dp140+ vs. Dp140− and for Dp71+ vs. Dp71−, respectively [26]. Conversely, in DMD, a PR = 0.50 (0.11, 2.15) and a PR = 1.07 (0.07, 16.46) were observed for upstream mutations exon 31 vs. 31–62 and for Dp71+ vs. Dp71− [29]. Finally, in a study with a relatively large sample of participants with epilepsy with a known genotype [28], there were more participants with Dp140− than with Dp140+, although the prevalence ratio could not be estimated.

Risk of bias assessment

According to the Quality Assessment Tool for Observational Cohorts and Cross-Sectional Studies from Study Quality Assessment Tools, the overall bias was scored as good in all studies. By domain, a risk of bias was only detected in 1

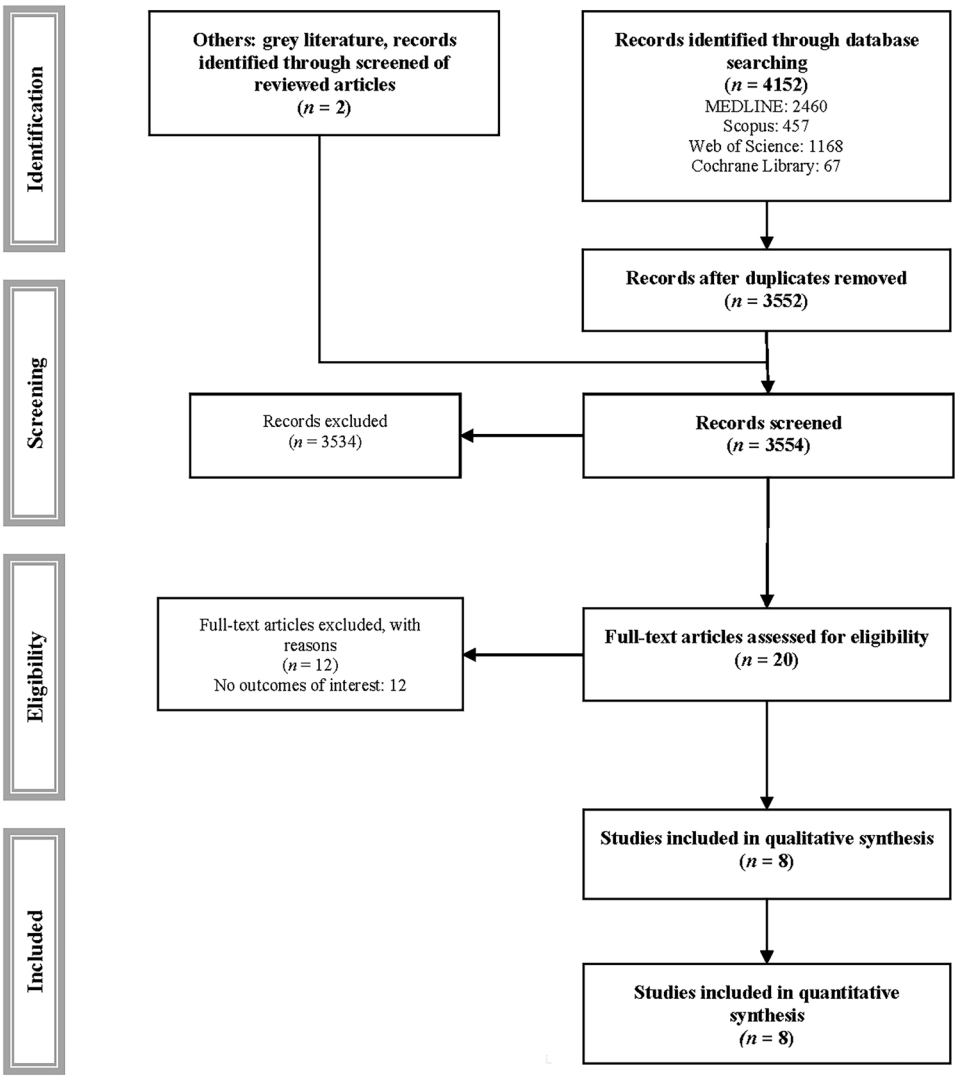

Fig. 1 PRSIMA flowchart of study selection

out of 8 studies (12.5%) regarding the number of participants who eventually participated in the study. Three domains were not eligible for assessment, based on sample size justification, whether exposure was assessed more than once over time, and whether the outcome assessor was blinded. No significant risk of bias was observed in the remaining domains. The risk of bias assessment is described in Supplementary Table S3.

Meta-analysis

The pooled prevalence showed the following estimates. In BMD, 0.07 (0.03, 0.11); in DMD, 0.05 (0.02, 0.08); and in BMD + DMD, 0.03 (0.02, 0.05). The overall prevalence of epilepsy in BMD/DMD dystrophies was 0.05 (0.03, 0.07). There were no statistically significant differences between the groups or between the groups and the overall prevalence (Fig. 3).

Heterogeneity was substantial in DMD and in overall prevalence, with $I^2 = 73.79\%$ ($p = 0.00$) and $I^2 = 60.37\%$ ($p = 0.01$), respectively (Fig. 3). Heterogeneity in BMD and BMD + DMD could not be calculated. However, in BMD, a high homogeneity was observed between the results obtained, while in BMD + DMD, a moderate inconsistency could be observed. Finally, the funnel plot showed no publication bias (Supplementary Figure S1). Sensitivity analyses with study-by-study exclusion did not show a statistically significant effect.

Discussion

Main findings

This systematic review and meta-analysis provide an estimate of the prevalence of epilepsy in the population

Table 1 Baseline characteristics of the participants in the included studies

References	Country	Design	Population			Outcome	
			Disease	Sample	Age	Prevalence	Genotype
Goodwin et al. [24]—1	UK	Case series	BMD	53	NA	✓	✓
Latimer et al. [25]—1	US	Cross-sectional	BMD	28	NA	✓	–
Mori-Yoshimura [26]	Japan	Cross-sectional	BMD	76	38.8 ± 13.3	✓	✓
Etemadifar et al. [27]	Irán	Retrospective	DMD	57	NA	✓	–
Goodwin et al. [24]—2	UK	Case series	DMD	201	NA	✓	✓
Hendriksen [28]	Australia Belgium Ireland Italy Netherlands UK US	Cross-sectional	DMD	228	13.3 ± 7.6	✓	✓
Latimer et al. [25]—2	US	Cross-sectional	DMD	164	NA	✓	–
Pane M et al. [29]	Italy	Case series	DMD	222	NA	✓	✓
Cuijie et al. [30]	China	Retrospective	BMD + DMD	307	NA	✓	–
Nakamura et al. [31]	Japan	Retrospective	BMD + DMD	200	NA	✓	–

UK: United Kingdom, US: United States; DMD: Duchenne muscular dystrophy, BMD: Becker muscular dystrophy

Table 2 Prevalence of epileptic disorders in each study

References	Disease	Outcome	
		Prevalence	95% CI
Goodwin et al. [24]—1	BMD	0.08	(0.03, 0.18)
Latimer et al. [25]—1	BMD	0.07	(0.02, 0.23)
Mori-Yoshimura [26]	BMD	0.07	(0.03, 0.14)
Etemadifar et al. [27]	DMD	0.13	(0.06, 0.24)
Goodwin et al. [24]—2	DMD	0.02	(0.01, 0.05)
Hendriksen [28]	DMD	0.08	(0.05, 0.12)
Latimer et al. [25]—2	DMD	0.03	(0.01, 0.07)
Pane et al. [29]	DMD	0.06	(0.04, 0.10)
Cuijie et al. [30]	BMD + DMD	0.02	(0.01, 0.05)
Nakamura et al. [31]	BMD + DMD	0.06	(0.03, 0.10)

BMD Becker muscular dystrophy, *DMD* Duchenne muscular dystrophy

with BMD and/or DMD. The prevalence was 7% in BMD participants and 5% in DMD participants, with an overall prevalence of 5% among participants with Becker/Duchenne dystrophinopathies. Since the inconsistency of the individual results was not especially high, it was confirmed that there is a particularly high prevalence of this disorder in this population, higher than that observed in the general population. Finally, although a deleterious effect cannot be ruled out when Dp140 is absent in DMD, the data are inconclusive, and further research is needed.

Interpretation

Our findings showed a prevalence of epilepsy of 7% in BMD, 5% in DMD, and 3% in BMD + DMD participants. These results were higher than the prevalence in general cohorts, which is estimated at 0.5–1.0% in children and adolescents and 0.5–1.6% in the total population [32–37]. Moreover, some authors [26, 28] suggest that the prevalence could be even higher due to the designs of their studies, which included interviews without questions for parents [26], or because some patients who reported epilepsy that could not be verified with clinical data were excluded from the prevalence estimates [28]. However, the data from these studies were consistent with the estimate from our meta-analysis. Otherwise, some variability in the results was observed, which could be due to small sample size (e.g., the study with the highest prevalence had a relatively small sample size) [27], selection bias, recall bias, or study design (i.e., data collection).

Regarding the genotype–epilepsy prevalence association, the available data are very limited, and therefore, no clear conclusions can be drawn. On the basis of the two studies with available prevalence ratios, a harmful trend was observed for deleterious Dp140 in BMD [26] and for mutations between exons 31–62 in DMD [29]. Interestingly, a mechanism by which the alterations of Dp140 might increase the risk of epilepsy has not yet been proposed since Dp140 mainly influences fetal development [38–40]. Conversely, no association with epilepsy has been found for Dp71 [26, 29], in which there might be a justifying mechanism, as

Table 3 Association of epileptic disorders with the genotype of the participants

References	Disease	Genotype	Association
Goodwin et al. [24]—1	BMD	–	Three participants with available genotype, 1 was Dp140 + /Dp71 + , and 2 Dp140-/Dp71 +
Mori-Yoshimura [26]—1	BMD	Dp140 + vs Dp140-	PR = 0.48 (0.03, 8.71)
Mori-Yoshimura [26]—2	BMD	Dp71 + vs Dp71-	PR = 0.46, (0.03, 7.44)
Goodwin et al. [24]—2	DMD	–	Two participants with available genotype: 1 was Dp140-/Dp71 + , and 1 Dp140 + /Dp71 +
Hendriksen [28]	DMD	–	Fifteen participants with available genotype: 6 were Dp140 + /Dp71 + , and 9 Dp140-/Dp71 +
Pane et al. [29]	DMD	Upstream 31 vs Exon 31–62	PR = 0.50 (0.11, 2.15)
Pane et al. [29]	DMD	Dp71 + vs Dp71-	PR = 1.07 (0.07, 16.46)

BMD Becker muscular dystrophy, *DMD* Duchenne muscular dystrophy

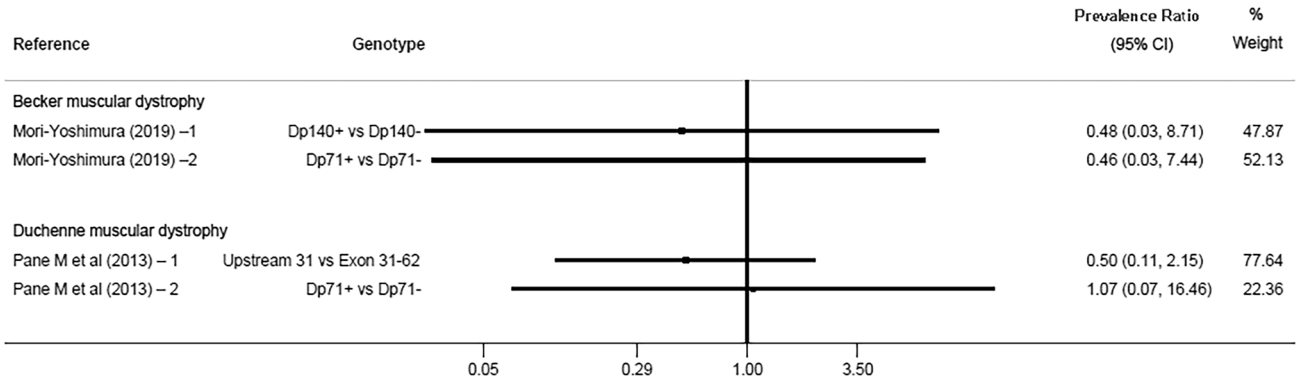

Fig. 2 Forest plot of the prevalence ratio and 95% confidence interval by genotype-outcome of each study

previously proposed [15, 16]. With the present results, the most plausible hypothesis is that Dp427 is the most relevant isoform in the development of epileptic disorders. However, to determine the roles and possible influences of Dp140 and Dp71, more research is needed.

Our findings have some direct and indirect implications for the care of these patients and for research into these diseases. First, because of the high prevalence of epilepsy in BMD/DMD, a high use of anticonvulsant treatments is expected, which together with glucocorticoids may further increase the risk of bone demineralization, requiring special monitoring [41, 42]. Second, there is an association between epilepsy and neuropsychiatric disorders, including autism spectrum disorder, attention deficit hyperactivity disorder, and emotional disorders, and this is an aspect that should be considered in the evaluation of these patients [28, 43–47]. Third, it is suggested that some types of epilepsy (i.e., absences) may be underdiagnosed. Some studies [28, 29] showed that 29–39% of epileptic episodes are "absences". Interestingly, in one study [29], two of the four patients who were diagnosed as absences did so after EEG following parent-reported staring episodes, which they misinterpreted as a sign of poor attention. Conversely, other studies did not report patients with absences, either because they did not include them or because they did not differentiate the type of epilepsy. Therefore, epilepsy should be actively sought by the neurologist or pediatrician treating patients with BMD/DMD. Fourth, the included studies that reported information showed partially or totally refractory epilepsy in 14–38% of patients, which poses a challenge for the management of these patients [24, 28, 29]. Fifth, the future development of treatments that cross the blood–brain barrier and that restore dystrophin expression at the brain level could [48], theoretically, improve the control of epilepsy in DMD. Fifth, although dystrophin is produced in BMD, the prevalence of epilepsy in BMD is similar to that in DMD, which might indicate that it is not only the presence of full-length dystrophin that is essential to avoid developing this disorder but that the correct length and structure is also required.

Limitations

Some limitations of this study should be considered. First, the limited number of studies and participants for BMD could limit the validity of the results for this group of

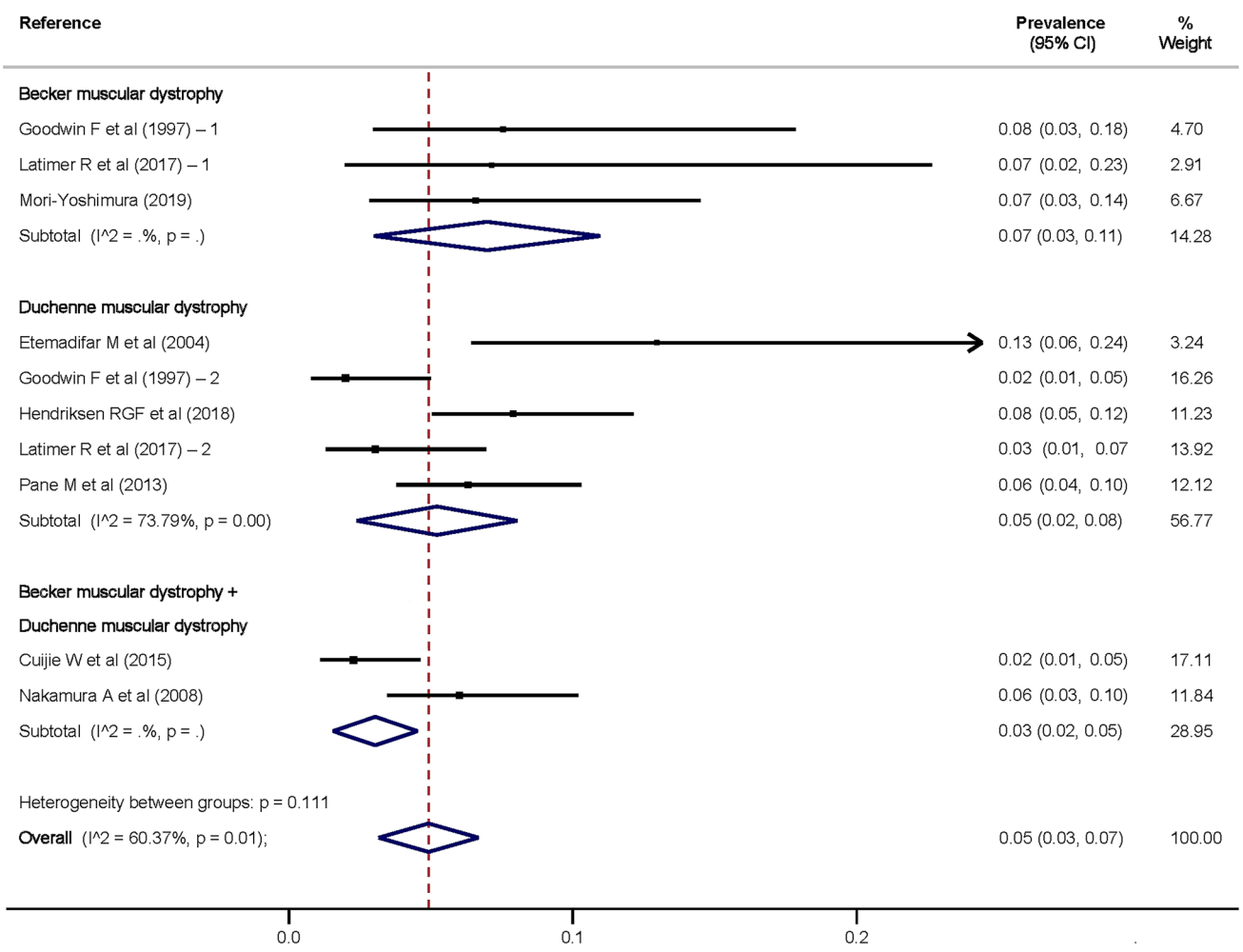

Fig. 3 Meta-analysis of prevalence of epilepsy in Becker muscular dystrophy, Duchenne muscular dystrophy, and Becker muscular dystrophy/Duchenne muscular dystrophy

patients. Moreover, only four studies considered epilepsy as the main outcome, and only two studies included genotype–prevalence association. This especially limited the interpretation of the results of prevalence ratios. Second, there was substantial heterogeneity in the results of DMD studies. Although the results of the sensitivity analyses were satisfactory, the estimates of the meta-analysis should be considered with caution. Third, due to the selection criteria and nonresponses in observational studies, selection or recall bias cannot be ruled out, which could slightly affect the individual estimates obtained. Fourth, to observe and correctly interpret the associations of interest, a large national database with diagnosis-based codes may be a better method than a cross-sectional cohort of 300 patients at most, or retrospective series. Fifth, some seizure disorders (i.e., absences) may be underdiagnosed due to confusion of some signs with other neuropsychiatric disorders.

Conclusions

BMD and DMD are disorders strongly associated with a higher prevalence of epilepsy compared to the general population, with a prevalence of 5–7%, although some authors suggest that it could be somewhat higher. However, genotype was not clearly associated with epilepsy risk, although further studies are needed because of the detrimental trend observed for patients with Dp140− and because of the notional risk of Dp71−. The possible relationship between epilepsy and other neuropsychiatric disorders, such as autism spectrum disorder, attention deficit hyperactivity disorder, and emotional disorders, which occur in patients with epilepsy but without BMD/DMD, awaits further research. Finally, the use of anticonvulsants in this population could affect bone quality, requiring strict medical control.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s00415-022-11040-y.

Author contributions Conceptualization: CP-M; methodology: CP-M and IC-R; data curation and investigation: CP-M and IC-R; formal analysis: CP-M, AS-L, JFL-G, and JF-B-R; validation and visualization: AS-L, JFL-G, and JF-B-R; writing—original draft preparation: CP-M, IC-R, and VM-V; writing—review and editing: all authors; supervision: IC-R and VM-V; funding acquisition: VM-V; project administration: VM-V. All authors have read and agreed to the published version of the manuscript.

Funding This study was funded by the European Regional Development Fund (SBPLY/17/180501/000533). C.P.-M. is supported by a grant from the Universidad de Castilla-La Mancha (2018-CPUCLM-7939).

Data statement The original contributions presented in the study are included in the article/supplementary material, and further inquiries can be directed to the corresponding author/s.

Declarations

Conflicts of interest The authors declare that they have no conflict of interest.

Ethical approval The manuscript does not contain clinical studies or patient data.

References

1. Holland A, Carberry S, Ohlendieck K (2014) Proteomics of the dystrophin-glycoprotein complex and dystrophinopathy. Curr Protein Pept Sci 14:680–697. https://doi.org/10.2174/1389203711314660083
2. Warner LE, DelloRusso CT, Crawford RW et al (2002) Expression of Dp260 in muscle tethers the actin cytoskeleton to the dystrophin-glycoprotein complex and partially prevents dystrophy. Hum Mol Genet 11:1095–1105. https://doi.org/10.1093/hmg/11.9.1095
3. Becker muscular dystrophy | Genetic and Rare Diseases Information Center (GARD)—an NCATS program. https://rarediseases.info.nih.gov/diseases/5900/becker-muscular-dystrophy. Accessed 2 Nov 2021
4. Mah JK, Korngut L, Dykeman J et al (2014) A systematic review and meta-analysis on the epidemiology of Duchenne and Becker muscular dystrophy. Neuromuscul Disord 24:482–491. https://doi.org/10.1016/j.nmd.2014.03.008
5. Birnkrant DJ, Bushby K, Bann CM et al (2018) Diagnosis and management of Duchenne muscular dystrophy, part 1: diagnosis, and neuromuscular, rehabilitation, endocrine, and gastrointestinal and nutritional management. Lancet Neurol 17:251–267. https://doi.org/10.1016/S1474-4422(18)30024-3
6. Bushby K, Finkel R, Birnkrant DJ et al (2010) Diagnosis and management of Duchenne muscular dystrophy, part 2: implementation of multidisciplinary care. Lancet Neurol 9:177–189. https://doi.org/10.1016/S1474-4422(09)70272-8
7. Pascual-Morena C, Cavero-Redondo I, Saz-Lara A et al (2021) Genetic modifiers and phenotype of Duchenne muscular dystrophy: a systematic review and meta-analysis. Pharmaceuticals. https://doi.org/10.3390/PH14080798
8. Goemans N (2018) How glucocorticoids change life in Duchenne muscular dystrophy. Lancet 391:406–407. https://doi.org/10.1016/S0140-6736(17)32405-4
9. Pascual-Morena C, Cavero-Redondo I, Álvarez-Bueno C et al (2020) Restorative treatments of dystrophin expression in Duchenne muscular dystrophy: a systematic review. Ann Clin Transl Neurol 7(acn3):51149. https://doi.org/10.1002/acn3.51149
10. Ricotti V, Roberts RG, Muntoni F (2011) Dystrophin and the brain. Dev Med Child Neurol 53:12–12. https://doi.org/10.1111/J.1469-8749.2010.03836.X
11. Sekiguchi M, Zushida K, Yoshida M et al (2009) A deficit of brain dystrophin impairs specific amygdala GABAergic transmission and enhances defensive behaviour in mice. Brain 132:124–135. https://doi.org/10.1093/brain/awn253
12. Doorenweerd N (2020) Combining genetics, neuropsychology and neuroimaging to improve understanding of brain involvement in Duchenne muscular dystrophy—a narrative review. Neuromuscul Disord 30:437–442. https://doi.org/10.1016/J.NMD.2020.05.001
13. Daoud F, Candelario-Martínez A, Billar JM et al (2008) Role of mental retardation-associated dystrophin-gene product Dp71 in excitatory synapse organization, synaptic plasticity and behavioral functions. PLoS ONE. https://doi.org/10.1371/JOURNAL.PONE.0006574
14. Doorenweerd N, Mahfouz A, van Putten M et al (2017) Timing and localization of human dystrophin isoform expression provide insights into the cognitive phenotype of Duchenne muscular dystrophy. Sci Rep 7:12575. https://doi.org/10.1038/s41598-017-12981-5
15. Hendriksen RGF, Hoogland G, Schipper S et al (2015) A possible role of dystrophin in neuronal excitability: a review of the current literature. Neurosci Biobehav Rev 51:255–262. https://doi.org/10.1016/j.neubiorev.2015.01.023
16. Hendriksen RGF, Schipper S, Hoogland G et al (2016) Dystrophin distribution and expression in human and experimental temporal lobe epilepsy. Front Cell Neurosci 10:174. https://doi.org/10.3389/fncel.2016.00174
17. Stroup DF, Berlin JA, Morton SC et al (2000) Meta-analysis of observational studies in epidemiology: a proposal for reporting. J Am Med Assoc 283:2008–2012. https://doi.org/10.1001/jama.283.15.2008
18. Higgins JP, Green S (2008) Cochrane handbook for systematic reviews of interventions: Cochrane book series. Wiley, Hoboken
19. Study Quality Assessment Tools | NHLBI, NIH. https://www.nhlbi.nih.gov/health-topics/study-quality-assessment-tools. Accessed 29 Nov 2021
20. Tufanaru C, Munn Z, Stephenson M, Aromataris E (2015) Fixed or random effects meta-analysis? Common methodological issues in systematic reviews of effectiveness. Int J Evid Based Healthc 13:196–207. https://doi.org/10.1097/XEB.0000000000000065
21. DerSimonian R, Laird N (1986) Meta-analysis in clinical trials. Control Clin Trials 7:177–188. https://doi.org/10.1016/0197-2456(86)90046-2
22. Higgins JPT, Thompson SG (2002) Quantifying heterogeneity in a meta-analysis. Stat Med 21:1539–1558. https://doi.org/10.1002/sim.1186
23. Egger M, Smith GD, Schneider M, Minder C (1997) Bias in meta-analysis detected by a simple, graphical test measures of funnel plot asymmetry. BMJ 315:629–634. https://doi.org/10.1136/bmj.315.7109.629
24. Goodwin F, Muntoni F, Dubowitz V (1997) Epilepsy in Duchenne and Becker muscular dystrophies. Eur J Paediatr Neurol EJPN Off J Eur Paediatr Neurol Soc 1:115–119. https://doi.org/10.1016/s1090-3798(97)80042-6
25. Latimer R, Street N, Conway KC et al (2017) Secondary conditions among males with Duchenne or Becker muscular dystrophy. J Child Neurol 32:663–670. https://doi.org/10.1177/0883073817701368
26. Mori-Yoshimura M, Mizuno Y, Yoshida S et al (2019) Psychiatric and neurodevelopmental aspects of Becker muscular dystrophy. Neuromuscul Disord 29:930–939. https://doi.org/10.1016/j.nmd.2019.09.006

27. Etemadifar M, Molael S (2004) Epilepsy in boys with Duchenne muscular dystrophy. J Res Med Sci 9:116–119
28. Hendriksen RGF, Vles JSH, Aalbers MW et al (2018) Brain-related comorbidities in boys and men with Duchenne Muscular Dystrophy: a descriptive study. Eur J Paediatr Neurol EJPN Off J Eur Paediatr Neurol Soc 22:488–497. https://doi.org/10.1016/j.ejpn.2017.12.004
29. Pane M, Messina S, Bruno C et al (2013) Duchenne muscular dystrophy and epilepsy. Neuromuscul Disord 23:313–315. https://doi.org/10.1016/j.nmd.2013.01.011
30. Cuijie W, Haipo Y, Xiaona F et al (2015) Duchenne and Becker muscular dystrophy complicated with epilepsy. Zhonghua Er Ke Za Zhi 53:274–279. https://doi.org/10.3760/cma.j.issn.0578-1310.2015.04.009
31. Nakamura A, Miyazaki Y, Kumagai T et al (2008) Various central nervous system involvements in dystrophinopathy: clinical and genetic considerations. No To Hattatsu 40:10–14. https://doi.org/10.11251/ojjscn1969.40.10
32. Cowan LD, Bodensteiner JB, Leviton A, Doherty L (1989) Prevalence of the epilepsies in children and adolescents. Epilepsia 30:94–106. https://doi.org/10.1111/j.1528-1157.1989.tb05289.x
33. Fiest KM, Sauro KM, Wiebe S et al (2017) Prevalence and incidence of epilepsy: a systematic review and meta-analysis of international studies. Neurology 88:296–303. https://doi.org/10.1212/WNL.0000000000003509
34. Owolabi LF, Owolabi SD, Taura AA et al (2019) Prevalence and burden of epilepsy in Nigeria: a systematic review and meta-analysis of community-based door-to-door surveys. Epilepsy Behav 92:226–234. https://doi.org/10.1016/j.yebeh.2018.12.017
35. Owolabi LF, Adamu B, Jibo AM et al (2020) Prevalence of active epilepsy, lifetime epilepsy prevalence, and burden of epilepsy in Sub-Saharan Africa from meta-analysis of door-to-door population-based surveys. Epilepsy Behav 103:106846. https://doi.org/10.1016/j.yebeh.2019.106846
36. Song P, Liu Y, Yu X et al (2017) Prevalence of epilepsy in China between 1990 and 2015: a systematic review and meta-analysis. J Glob Health 7:20706. https://doi.org/10.7189/jogh.07-020706
37. Sridharan R, Murthy BN (1999) Prevalence and pattern of epilepsy in India. Epilepsia 40:631–636. https://doi.org/10.1111/j.1528-1157.1999.tb05566.x
38. Lidov HGW, Selig S, Kunkel LM (1995) DP140—a novel 140-Kda CNS transcript from the dystrophin locus. Hum Mol Genet 4:329–335. https://doi.org/10.1093/hmg/4.3.329
39. Morris GE, Simmons C, Nguyen TM (1995) Apo-dystrophins (Dp140 and Dp71) and dystrophin splicing isoforms in developing brain. Biochem Biophys Res Commun 215:361–367. https://doi.org/10.1006/bbrc.1995.2474
40. Hoogland G, Hendriksen RGF, Slegers RJ et al (2019) The expression of the distal dystrophin isoforms Dp140 and Dp71 in the human epileptic hippocampus in relation to cognitive functioning. Hippocampus 29:102–110. https://doi.org/10.1002/hipo.23015
41. Compston J (2018) Glucocorticoid-induced osteoporosis: an update. Endocrine 61:7–16. https://doi.org/10.1007/s12020-018-1588-2
42. Pack A (2008) Bone health in people with epilepsy: is it impaired and what are the risk factors? Seizure 17:181–186. https://doi.org/10.1016/j.seizure.2007.11.020
43. Liu X, Sun X, Sun C et al (2021) Prevalence of epilepsy in autism spectrum disorders: a systematic review and meta-analysis. Autism. https://doi.org/10.1177/13623613211045029
44. Strasser L, Downes M, Kung J et al (2018) Prevalence and risk factors for autism spectrum disorder in epilepsy: a systematic review and meta-analysis. Dev Med Child Neurol 60:19–29. https://doi.org/10.1111/dmcn.13598
45. Ashjazadeh N, Sahraeian A, Sabzgolin I, Asadi-Pooya AA (2019) Attention-deficit hyperactivity disorder in adults with epilepsy. Epilepsy Behav 101:106543. https://doi.org/10.1016/j.yebeh.2019.106543
46. Wang M, Zhao Q, Kang H, Zhu S (2020) Attention deficit hyperactivity disorder (ADHD) in children with epilepsy. Ir J Med Sci 189:305–313. https://doi.org/10.1007/s11845-019-02042-3
47. Błaszczyk B, Czuczwar SJ (2016) Epilepsy coexisting with depression. Pharmacol Rep 68:1084–1092. https://doi.org/10.1016/j.pharep.2016.06.011
48. Goyenvalle A, Griffith G, Babbs A et al (2015) Functional correction in mouse models of muscular dystrophy using exon-skipping tricyclo-DNA oligomers. Nat Med 21:270. https://doi.org/10.1038/nm.3765