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Respiratory dysfunction in myotonic dystrophy type 1: A systematic review

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Abstract

Myotonic dystrophy type 1 (DM1) is one of the most common muscular dystrophies in adults. This review summarises the current literature regarding the natural history of respiratory dysfunction in DM1, the role of central respiratory drive and peripheral respiratory muscle involvement and its significance in respiratory function, and investigates the relationship between genetics (CTG repeat length) and respiratory dysfunction. The review included all articles that reported spirometry on 10 or more myotonic dystrophy patients. The final review included 55 articles between 1964 and 2017. The major conclusions of this review were (1) confirmation of the current consensus that respiratory dysfunction, predominantly a restrictive ventilatory pattern, is common in myotonic dystrophy and is associated with alveolar hypoventilation, chronic hypercapnia, and sleep disturbance in the form of sleep apnoea and sleep related disordered breathing; (2) contrary to commonly held belief, there is no consensus in the literature regarding the relationship between CTG repeat length and severity of respiratory dysfunction and a relationship has not been established; (3) the natural history and time-course of respiratory functional decline is very poorly understood in the current literature; (4) there is a consensus that there is a significant involvement of central respiratory drive in this alveolar hypoventilation however the current literature does not identify the mechanism for this.

Keywords: Myotonic dystrophy type 1; Cytosine-Thymine-Guanine (CTG); Respiratory dysfunction; Myotonic dystrophy; Spirometry.

Take home message

Systematic review of respiratory dysfunction, alveolar hypoventilation and chronic hypercapnia in myotonic dystrophy.

1. Introduction

Myotonic dystrophy type 1 (DM1) is one of the most common muscular dystrophies in adults [1]. It is an autosomal dominant condition caused by a trinucleotide cytosine-thymine-guanine (CTG) repeat expansion in the 3′ region of the DPMK gene on chromosome 19q13.3 [2]. The condition is characterised by progressive muscle weakness and myotonia along with involvement of multiple organ systems including respiratory, cardiac, endocrine, ophthalmologic, and the central nervous system [3].

Respiratory dysfunction is the most common cause of death in patients with DM1, usually resulting from respiratory failure or aspiration [4]. Symptoms related to respiratory dysfunction in DM1 also have a significant negative impact on quality of life [5,6]. As new and exciting treatments for myotonic dystrophy are beginning to emerge, it is becoming increasingly important that a clear and accurate natural history of the disease is established, allowing clinical trials to accurately measure their success.

Respiratory disease in DM1 has a complex aetiology, combining both peripheral respiratory dysfunction (respiratory muscle weakness and myotonia) and central respiratory drive dysfunction as well as upper airway muscle dysfunction

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leading to obstructive sleep apnoea and aspiration [7]. This combination of factors leads to alveolar hypoventilation, chronic hypercapnia and restrictive lung disease [7–9]. The role of peripheral respiratory muscle weakness and central respiratory drive in the pathogenesis of respiratory disease in these individuals has been the subject of some debate over the last two decades. There is increasing evidence of dysregulation of ventilation at a central level [10], however a consensus has yet to be reached.

While there is a well-established consensus that myotonic dystrophy patients often develop a restrictive ventilatory pattern, there is no consensus on a number of aspects of respiratory involvement in the disease including the role of central respiratory drive, the relationship of CTG repeat length with severity of respiratory dysfunction, and the long-term clinical course of respiratory functional decline.

This review aims to summarise the current literature regarding the natural history of respiratory dysfunction in DM1, the role of central respiratory drive and peripheral respiratory muscle involvement and its significance in respiratory function, and investigate the relationship between CTG repeat length and respiratory dysfunction. In addition, this review will summarise what research has been published and what gaps in the literature are present, as well as attempt to investigate any potential bias in the current literature.

2. Method

2.1. Article selection

Articles were included in this review if they met all of the following criteria: published peer-reviewed journal articles which included ten or more participants diagnosed with DM1 who underwent respiratory function testing in the form of spirometry. Articles were excluded if they met any of the following criteria: case reports or case series, randomised control trials for interventions or treatments, conference proceedings, or articles published only in abstract form.

Foreign language articles (six Japanese, one Spanish, one Portuguese and one French) which included an original English abstract were partially included in the review. Rather than completely excluding them, what information could be gathered from the English language abstract was included. The articles were, however, excluded from the quality assessment given the lack of full text article.

2.2. Literature search

The included articles were found using a literature search of the databases PubMed, Embase, Cochrane, Web of Science and Scopus. Search included keywords "myotonic dystrophy", "MD1", or "DM1" and the addition of one of the following keywords: "respiratory", "pulmonary", "lung", "RFT", "respiratory function test", "pulmonary function test", "spirometry", "hypercapnia", "hypoventilation", "apnoea", "apnea" or "sleep". This was carried out in November 2017, yielding 1432 results after duplicates were removed (see supplementary Table 1). The titles and abstracts were then reviewed, with articles failing to meet the above criteria removed where possible. A breakdown of the excluded articles (case reports, reviews/book chapters, etc.) can be seen in Fig. 1. While some articles would have fallen into more than one category, they were recorded in only one based on the first confirmed reason for exclusion. Full texts of the remaining articles were then obtained to further determine their appropriateness for inclusion. Articles were again removed as appropriate. Reference lists of included articles were then reviewed to cross-check for missing articles. The literature search was carried out by two investigators independently and the findings cross-checked to reduce the risk of missed articles.

2.3. Data collection

Data from each article was then recorded for quantitative analysis. Basic information about each article was recorded, including location and year of publication. Methodology was then recorded, including number of participants, participants mean age and gender distribution, the source of participants for the study (e.g. consecutive patients to a tertiary neurology clinic, or tertiary respiratory centre referred for non-invasive ventilation work-up), and the types of investigations included in the study in addition to respiratory function tests (RFTs) (e.g. arterial blood gas, genetic analysis, polysomnography, etc.). Finally, the results of the investigation were recorded, including mean values of spirometry and other investigations where available, statistical correlations reported by the investigators and significant conclusions drawn by respective investigators.

2.4. Quality assessment

This systematic review was carried out in accordance with the PRISMA checklist for systematic reviews and meta-analyses by two investigators independently [11]. The quality of each included English language article was assessed using a critical appraisal tool developed by Kmet et al. [12]. This tool has a series of checklist points for different aspects of the study. A rating of either 0, 1 or 2 is given to each point. Each article was given a score out of the total possible points which was converted into a percentage. Studies scoring a value >85% were classified as "strong", 50–85% classified as "adequate" and <50% classified as "poor". A protocol for this review was registered with PROSPERO (the international prospective registry for systematic reviews) on 9th November 2017 [13]. This can be accessed at http://www.crd.york.ac.uk/PROSPERO/display_record.php?ID=CRD42017081108.

3. Results

3.1. Literature search results

Fifty-five articles met the criteria for inclusion in this systematic review, ranging from 1964 to 2017. The majority

Table 1
Summary of articles included in the review.

Reference	Design	No. of Participants	Source of Participants/ Inclusion Criteria	Summary of Respiratory Function Test Results	Other Inclusions in the Method					Quality Score [12]	Quality Assessment
					MIP/ MEP	ABG	Sleep Study	Muscle Weakness	CTG Length		
Gillam et al., 1964 [14]	PCS	10	Unreported/variable disease severity	3 of 10 participants had abnormal VC	Yes	–	–	–	–	19	Strong
Lee et al., 1964 [15]	PCS	19	General neurology clinic/variable disease severity	17 of 19 participants had abnormal RFTs, VC and TLC were the most commonly affected parameters.	–	–	–	–	–	19	Strong
Leygonie et al., 1977 [16]	PCS	15	Unreported/variable disease severity	9 of 10 participants had RFTs with restrictive pattern	–	Yes	Yes	–	–	–	–
Begin et al., 1980 [17]	PCS	12	Unreported/healthy, young participants (ages 11–26)	Chemosensitivity is well preserved in DM1, impaired response to hypercapnia is likely due to impaired respiratory muscles, rather than a central chemoreceptor abnormality	–	–	–	–	–	20	Strong
Griggs et al., 1981 [18]	PCS	10	Unreported/variable disease severity	5 of 10 participants had FVC <80% predicted	Yes	–	–	–	–	19	Strong
Begin et al., 1982 [19]	PCS	10	Unreported/variable disease severity	Ventilatory output was altered predominantly by weakness and fatiguability of the respiratory muscles	–	–	–	–	–	20	Strong
Serisier et al., 1982 [20]	PCS	19	General neurology clinic/known respiratory disease excluded	Significant respiratory muscle weakness was found in almost all the patients and was often present without significant muscle impairment. Impaired ventilatory response to CO_2 was present in the cohort, but cause was unclear (could not rule out central respiratory drive abnormality)	Yes	–	–	–	–	20	Strong
Begin et al., 1983 [21]	PCS	11	Unreported/variable disease severity	Mean FVC 82% predicted. Fatigue of the respiratory muscles can be readily induced during maximal ventilatory output or when oxygen delivery is reduced	–	–	–	–	–	20	Strong
Jammes et al., 1985 [22]	PCS	10	Gen. neurol. Clinic /no history of respiratory disease/symptoms	6 of 10 with abnormal VC%, TLC, and hypoxaemia	Yes	Yes	–	–	–	19	Strong
Matsumoto et al., 1990 [23]	PCS	12	Unreported/patients with no known respiratory disease	Significantly impaired VC% in both sitting and supine position. Mean VC% was 64% in sitting position and 55% in supine.	–	Yes	Yes	–	–	–	–
Bogaard et al., 1992 [24]	PCS	17	Unreported/variable disease severity	DM1 participants had sig-nificantly impaired overall spirometry compared to controls, even in early stage of disease. Impairment was in a restrictive lung disease pattern. 10 of 17 had FVC <80%	–	Yes	–	–	–	20	Strong
Horikawa et al., 1992 [25]	PCS	11	Unreported/no history of respiratory disease/symptoms	Overall reduced FRC in DM1, more reduced in supine position than sitting.	–	Yes	–	–	–	–	–
Yoneyama et al., 1992 [26]	PCS	15	Unreported/variable disease severity	RFTs not reported	–	Yes	Yes	–	–	–	–
Rimmer et al., 1993 [27]	PCS	11	Unreported/variable disease severity	3 of 11 had mildly impaired FVC % predicted. Myotonia of the respiratory muscles was inducible with large voluntary breathing	–	Yes	–	–	–	19	Strong

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Table 1 (*continued*)

Reference	Design	No. of Participants	Source of Participants/ Inclusion Criteria	Summary of Respiratory Function Test Results	Other Inclusions in the Method					Quality Score [12]	Quality Assessment
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Howard et al., 1993 [28]	ROCS	13	Tertiary respiratory clinic/Referred for evaluation of respiratory symptoms	2 of 13 had impaired FVC and a significant postural change. Global respiratory muscle weakness in 7 of 13 and diaphragm weakness in 4 of 13.	–	Yes	–	–	–	15	Adequate
Igo M., 1993 [29]	PCS	12	Unreported/significant muscle impairment–10 of 12 were non-ambulatory	Abnormal VC% in all patients which was gradually progressive over time. VC% inversely correlated with age.	–	Yes	–	–	–	–	–
Clague et al., 1994 [30]	PCS	12	General neurology clinic/known respiratory muscle weakness	Mean values: FVC 70.2%, MIP 41.3% No difference in perception of respiratory effort or ventilatory response to CO_2 with respiratory muscle weakness	Yes	–	–	–	–	21	Strong
Ahlström et al., 1994 [5]	PCS	30	All known DM1 patients in a town in Sweden	13 of 32 DM1 participants had FVC <70%	–	Yes	–	–	–	21	Strong
Finnimore et al., 1994 [31]	PCS	12	General neurology clinic/variable disease severity	Mild impairment to all parameters except MIP. Mean FEV1 was 74%, FVC 80%, MIP 84% and MEP 32%.	Yes	Yes	Yes	–	–	20	Strong
Johnson et al., 1995 [32]	POLS	92	General neurology clinic/variable disease severity	Mean FVC 75% and Mean FEV1 76%. 58% of DM1 participants had mild to severe RLD	yes	–	–	–	–	20	Strong
Ververs et al., 1996 [33]	PCS	11	Tertiary respiratory clinic/referred for evaluation of daytime sleepiness	Mean Values: VC 78%, TLC 86%, RV 94%. Abnormalities predominantly restrictive pattern	Yes	Yes	Yes	–	–	20	Strong
Zifko et al., 1996 [8]	PCS	25	General neurology clinic/variable disease severity	Mean FVC was 75% and 15 of 20 participants had FVC <80%. Participants with abnormal electro-ophysiological parameters had a lower FVC%	Yes	Yes	–	Yes	–	21	Strong
Begin et al., 1997 [7]	PCS	134	General neurology clinic/majority of affected individuals in the area	Significantly impaired FVC, worsening with severity of muscle weakness. Reduced FVC also predicted hypercapnia	Yes	Yes	–	Yes	–	22	Strong
Abe et al., 1998 [34]	PCS	10	Tertiary respiratory centre/patients referred for spirometry	Restrictive respiratory defect is common in this cohort. Correlation between VC and MIP indicated respiratory muscle weakness involvement in respiratory dysfunction	Yes	–	–	–	–	19	Strong
Nitz et al., 1999 [35]	POLS	36	General neurology clinic/variable disease severity	Significant decline in FVC and FEV1 over two years of follow up	–	–	–	Yes	–	21	Strong
Phillips et al., 1999 [36]	PCS	35	General neurology clinic/variable disease severity	Significant daytime somnolence in this cohort but no correlation with respiratory function tests	–	–	–	–	–	21	Strong
Dahlbom et al., 1999 [37]	POLS	26	All known DM1 patients in a town in Sweden	VC declined over the 5 years to varying degrees.	–	–	–	Yes	–	21	Strong
Kinoshita et al., 1999 [38]	ROCS	40	Unreported/variable disease severity	VC inversely correlated with CTG repeat length	–	–	–	Yes	Yes	–	–
Marchini et al., 2000 [39]	ROCS	24	General neurology clinic/variable disease severity	Respiratory insufficiency (not specifically defined in the article) had no correlation with CTG repeat length	Yes	Yes	–	–	Yes	21	Strong

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Table 1 (*continued*)

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					MIP/ MEP	ABG	Sleep Study	Muscle Weakness	CTG Length		
Oliveri et al., 1999 [40]	PCS	10	Unreported/variable disease severity	Mean values for VC and PEF were abnormal overall. No relationship between spirometry values and P300 latency	–	Yes	–	–	–	20	Strong
López-Esteban et al., 2000 [41]	PCS	11	Tertiary respiratory clinic/referred for evaluation of respiratory symptoms	Moderate to severe ventilatory impairment of primarily restrictive type was found in all participants	–	–	Yes	–	–	–	–
Ugalde et al., 2001 [42]	PCS	10	General neurology clinic/variable disease severity	Significantly impaired MEP in this cohort. Abdominal accessory muscles recruited at lower pressures in DM1 cohort.	Yes	–	–	–	–	21	Strong
Nugent et al., 2002 [43]	PCS	13	Tertiary respiratory clinic/all participants commencing home non-invasive ventilation	All participants had significantly impaired spirometry in a restrictive pattern prior to commencing NIV. No significant change in spirometry at reassessment was noted, suggesting a potential slowing of disease progression	Yes	Yes	Yes	–	Yes	20	Strong
Laud et al., 2006 [44]	ROCS	29	Selection of patients commencing home NIV from a database of NMD patients in Sweden	Most common reason for commencing home NIV in DM1 patients was daytime sleepiness, followed by daytime hypercapnia on ABG	–	Yes	–	–	–	19	Strong
Kumar et al., 2007 [45]	PCS	25	Tertiary respiratory clinic/referred for evaluation of daytime sleepiness	Sensitivity of FVC <60% in predicting SRDB was 67%, specificity 85% Concluded daytime spirometry poor predictor of SRDB	Yes	Yes	Yes	–	–	21	Strong
Terzi et al., 2008 [46]	POLS	61	General neurology clinic/variable disease severity	VC% mean 63.4% at baseline, no significant decline in VC% over the year follow up	Yes	–	–	–	–	22	Strong
Nozaki et al., 2008 [47]	PCS	10	General neurology clinic/variable disease severity	No change in respiration associated with swallowing	–	–	–	–	–	20	Strong
Araujo et al., 2010 [6]	PCS	23	Unreported/variable disease severity	Mean values: FVC 77%, FEV1 77%. Loss of expiratory muscle strength associated with increasing MIRS score	Yes	–	–	–	–	–	–
Kiyan et al., 2010 [48]	ROCS	17	Tertiary respiratory clinic/referred for routine pulmonary workup	9 of 16 participants had an apparent restrictive ventilator pattern. Both FVC and FEV1 correlated with daytime $PaCO_2$. Mean values: FVC 68%, FEV1 71.4%, FEV1/FVC 87.8%	–	Yes	Yes	–	–	20	Strong
Kaminsky et al., 2011 [9]	ROCS	106	General neurology clinic/variable disease severity	VC and TLC <80% predicted observed in 60% of participants. Restrictive lung disease in 33% of participants. VC, TLC and FEV1 was related to BMI, CTG repeat length and severity of muscle weakness.	–	Yes	–	Yes	Yes	22	Strong
Pruna et al., 2011 [49]	ROCS	69	General neurology clinic/variable disease severity	More severe muscle weakness was associated with higher risk of respiratory insufficiency	–	Yes	–	Yes	Yes	–	–
Kierkegaard et al., 2011 [50]	PCS	70	General neurology clinic/variable disease severity	Respiratory dysfunction (impaired FVC or FEV1) present in 40% of participants. More severe respiratory dysfunction associated with MIRS 4 & 5	–	–	–	Yes	–	21	Strong

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Table 1 (*continued*)

Reference	Design	No. of Participants	Source of Participants/ Inclusion Criteria	Summary of Respiratory Function Test Results	Other Inclusions in the Method					Quality Score [12]	Quality Assessment
					MIP/ MEP	ABG	Sleep Study	Muscle Weakness	CTG Length		
Kaminsky et al., 2013 [51]	ROCS	107	General neurology clinic/variable disease severity, participants with pacemakers excluded	40% of participants presented with restrictive ventilator pattern. VC and TLC both correlated with severity of muscle weakness. Mean values: VC 72.6%, TLC 78.3%. Presence of restrictive lung disease predicted cardiac events.	–	Yes	–	Yes	Yes	22	Strong
Monteiro et al., 2013 [52]	ROCS	42	Tertiary respiratory clinic/referred for evaluation for home NIV	Ventilated participants had lower FVC. FVC decreased with age. Mean values: FVC 74%, FEV1 77%, MIP 52%, MEP 35%	Yes	Yes	Yes	–	yes	21	Strong
Bianchi et al., 2014 [53]	PCS	71	General neurology clinic/variable disease severity	FVC was <80% predicted in 9 of the 61 DM1 participants, with none showing severe restrictive pattern	Yes	–	Yes	–	Yes	21	Strong
Poussel et al., 2014 [54]	PCS	58	General neurology clinic/all patients ambulatory	36% of participants presented with a restrictive ventilatory pattern, which was associated with BMI, CTG repeat length and severity of muscle impairment.	Yes	Yes	–	Yes	–	22	Strong
Fregonezi et al., 2015 [55]	PCS	25	General neurology clinic/variable disease severity	Found a predominantly expiratory muscle weakness in the cohort. Mean values: FVC% 77%, FEV1 75.1%, FEV1/FVC 0.82	Yes	–	–	–	–	22	Strong
Poussel et al., 2015 [10]	PCS	69	General neurology clinic/variable disease severity, excluding patients on home NIV.	FVC was correlated to MIP and CTG repeat length, TLC decline correlated to hypoxaemia and hypercapnia.31 of 69 participants presented with restrictive ventilatory pattern which was associated with higher BMI and greater CTG repeat length	yes	yes	–	yes	yes	21	Strong
Leonardis et al., 2015 [56]	PCS	25	General neurology clinic/variable disease severity	Daytime sleepiness and respiratory dysfunction was more prominent in DM1 participants than in DM2	Yes	Yes	–	Yes	Yes	22	Strong
Carrié et al., 2016 [57]	PCS	12	Tertiary respiratory clinic/referred for routine pulmonary evaluation	Spirometry reported as aggregate data of multiple NMD (ALS, DMD, DP, POEMS and DM1). Strong correlation between ultrasound measured diaphragmatic excursion and FVC.	Yes	–	–	–	–	20	Strong
Cho et al., 2016 [58]	ROCS	21	Tertiary respiratory clinic/all participants commencing home non-invasive ventilation	At the point of requiring commencement of NIV, DM1 had better respiratory muscle function than DMD and ALS participants – concluded that this suggested a central respiratory drive involvement. Mean values: FVC (sit) 39.9%, FVC (supine) 34.7%	Yes	–	–	–	–	20	Strong
Seijger et al., 2016 [59]	ROCS	105	Tertiary respiratory clinic/referred for routine pulmonary evaluation	BMI significant predictor of TLC independently of respiratory muscle weakness. Mean values: VC 83.9%, FEV1 82.9%, FRC 72.3%, RV 71.1%, TLC 79%, MEP 55.7%, MIP 65.0%	–	–	–	Yes	–	21	Strong

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Table 1 (*continued*)

Reference	Design	No. of Participants	Source of Participants/ Inclusion Criteria	Summary of Respiratory Function Test Results	Other Inclusions in the Method					Quality Score [12]	Quality Assessment
					MIP/ MEP	ABG	Sleep Study	Muscle Weakness	CTG Length		
Evangelista et al., 2017 [60]	PCS	18	General neurology clinic/variable disease severity	Respiratory function showed a predominantly restrictive ventilatory pattern.	Yes	–	–	–	–	22	Strong
O'Donoghue et al., 2017 [61]	PCS	12	Tertiary respiratory clinic/patients stable on NIV already	No change in any parameter of spirometry after withdrawal of NIV for a month. Mean values (baseline): VC 80.67%, FEV1 82.10%, TLC 96.13%, RV 113%, FRC 102%, FEV1/VC 0.81	–	Yes	Yes	–	–	20	Strong
Thil et al., 2017 [62]	ROCS	80	General neurology clinic/variable disease severity	Slow change in RFTs over time compared to both normal population and other NMD. Faster rate of decline was reported in participants who initially had no evidence of RLD but developed it during the follow up period, compared to participants who started with RLD as well as participants who never developed RLD. Mean Values: FVC (Δ/year in % predicted) -0.72, FEV1 (Δ in % predicted/year) -1.07, TLC (Δ in % predicted/year) -1.15, RV (Δ in % predicted/year) -1.49	–	–	–	–	–	21	Strong

Key: PCS: prospective cross-sectional study, POLS: prospective observational longitudinal study, ROCS: retrospective observational cross-sectional study, RFTs: respiratory function tests, FVC: forced vital capacity, VC: vital capacity, FEV1: forced expiratory volume in the first second, TLC: total lung capacity, RV: residual volume, FRC: functional residual capacity, MIP: maximal inspiratory pressure, MEP: maximal expiratory pressure, SRDB: sleep-related disordered breathing, PEF: peak expiratory flow, RLD: restrictive lung disease, NIV: non-invasive ventilation at home, BMI: body mass index, NMD: neuromuscular disease, DMD: Duchenne's muscular dystrophy, ALS: amyotrophic lateral sclerosis, DP: demyelinating polyradiculoneuropathy, POEMS: polyneuropathy organomegaly endocrinopathy monoclonal gammopathy and skin change.
Spirometry values reported as % of predicted value unless otherwise stated.

were published in English, while five were published in Japanese, one in Spanish, one in Portuguese and two in French. France was the most common country of publication (n=11), with the United Kingdom second most common (n=8). Forty-two of the studies (76%) were prospective observational cross-sectional studies or prospective observational longitudinal studies. The other thirteen (24%) were retrospective cohort studies.

3.2. Quality assessment

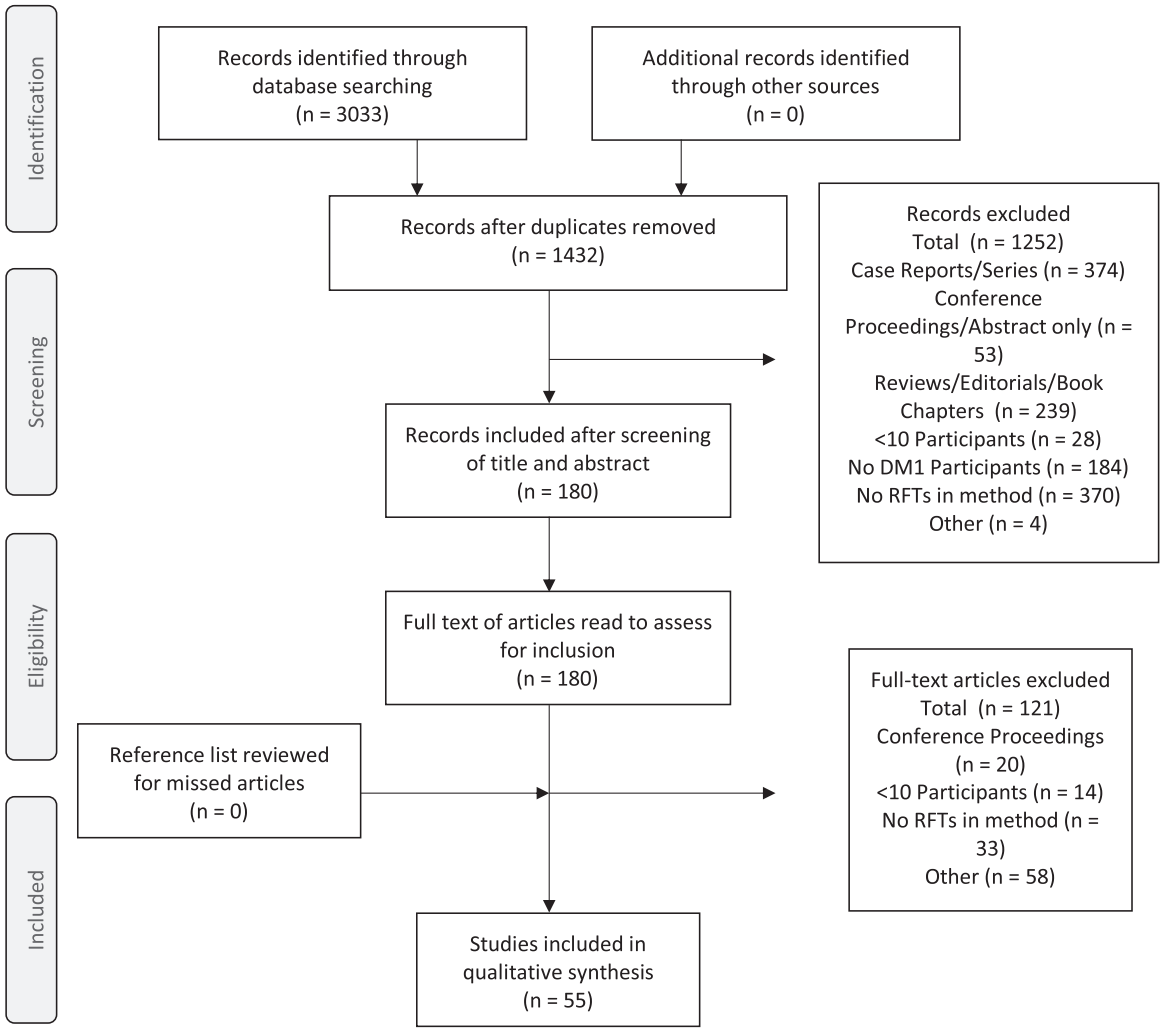
All included English language articles (n=46) were assessed for their quality using the critical appraisal tool described by Kmet et al. [12]. 45 of 46 articles were classified as "strong" quality. Only one article was classified as "adequate", and none were classified as "poor". Each individual quality assessment score can be seen in Table 1.

3.3. Participants

The number of participants included in the studies ranged from 10 to 134, with a median of 19 participants (mean=33). Reported mean ages of the participants ranged from 22 to 56. Both genders were fairly equally represented. Participants included a majority of males in 47% (n=26) of the articles. Of the aggregate participants in all articles that reported the gender distribution, there were 741 male and 737 female participants.

3.4. Methodology of the articles

Inclusion criteria for the participants of each study varied greatly. Two studies included all known myotonic dystrophy patients in a specified area [5,37]. The majority of other studies recruited patients from a general neurology clinic or similar with no specific inclusion criteria based on disease severity [8–10,15,22,29–32,35,36,39,42,46,47,49,51,53–56,60,62], while two studies specifically recruited participants with no respiratory symptoms [20,25]. Fourteen studies recruited from a tertiary respiratory clinic or specifically recruited for presence of respiratory dysfunction [28,30,33,34,41,43–45,48,52,57–59,61]. There was significant variation in the characteristics of each cohort, ranging from no respiratory symptoms to patients commencing home non-invasive ventilation (refer to Table 1). The method of investigation also varied



greatly between studies. Inclusion of various tests including postural RFTs, maximal inspiratory pressure (MIP)/maximal expiratory pressure (MEP), arterial blood gas (ABG) and sleep studies can be seen in Table 1.

3.5. Respiratory function test results

Almost all the studies found overall abnormal respiratory function tests in a large proportion of their participants. The predominant respiratory function abnormality was a restrictive ventilatory pattern. Forced vital capacity (FVC) and vital capacity (VC) were the most commonly impaired parameters, while total lung capacity (TLC), residual volume (RV), and forced expiratory volume in the first second (FEV1) were also commonly affected. Summaries of the main spirometry findings for each article are recorded in Table 1. Abnormal RFTs were found to be associated with various other factors, including severity of muscle disease [6,9,49–51], age [32], BMI [9,59], duration of muscle symptoms [29,32], hypercapnia [7,45,48,49], pulmonary complications [32], cardiac conduction abnormalities [9,51], CTG repeat length [9,10,38], and risk of mortality [51].

Twenty-six of the included articles measured the MIP and/or MEP of participants. The majority found a significantly lower MEP in DM1 patients than MIP. Significant statistical relationships were found between MIP or MEP and severity of muscle weakness [7], FVC [34,45,57] and poor quality of life [6]. Both Kumar et al. [45] and Bianchi et al. [53] concluded there was no significant relationship between MIP/MEP and sleep apnoea.

Postural changes in spirometry parameters is one method of measuring diaphragmatic weakness. This was measured in six of the included studies. Poussel et al. [54] investigated a large cohort of 58 participants and found a significant change in both FVC and FEV1 between sitting and supine positions. The findings of Matsumoto et al. [23] and Horikawa et al. [25] also supported this, while Howard et al. [28] and Finnimore et al. [31] found postural change in only 2 and 1 participants respectively. Bogaard et al. [24] found no postural change at all. Poussel et al. [54] found that postural change in FEV1 was the only significant predictor of daytime hypercapnia.

Arterial blood gases were measured in twenty-eight of the included studies. Eight studies found daytime hypercapnia in a significant portion of participants [5,9,26,27,31,43,48,51,54].

Hypercapnia was found to be associated with severity of muscle weakness in three studies [7,9,51]. While there were conflicting results about the relationship between hypercapnia and baseline respiratory function tests, a correlation was found between spirometry parameters and hypercapnia in five studies [5,7,29,45,48]. CTG repeat length was associated with hypercapnia in one study [10] while another study found no correlation [52]. There were similarly conflicting findings for postural changes in spirometry results; a positive correlation in one study [54] and no correlation in another [23].

3.6. Genetic associations

Ten of the included studies measured the CTG repeat length of the patients [9,10,38,39,43,49,51–53,56]. Four of these studies found a correlation between CTG repeat length and some aspect of respiratory dysfunction, three studies found no correlation between CTG repeat length and any respiratory function parameters, and three studies did not comment on the relationship. Numbers of participants in these studies were between 13 and 106 with a mean of 58 participants.

CTG repeat length was found to have an association with VC (% predicted) by two of the studies [9,38]. Kaminsky et al. [9] also found that CTG was an independent risk factor for restrictive lung disease (defined as both VC and TLC below 70% predicted) [9]. Poussel et al. found a correlation between FVC (% predicted) and CTG repeat length, but no correlation between ventilatory response to CO_2 and CTG repeat length [10]. Monteiro et al. found a relationship between CTG repeat length and SpO_2, MEP (% predicted) and home NIV requirement, but not with FVC, FEV1 or MIP. Those relationships were also lost in multivariate analysis [52]. Three studies specifically reported that no relationship between CTG repeat length and respiratory parameters were found [39,49,53]. The remaining three studies made no comment on any relationship [43,51,56].

3.7. Progressive changes over time

Seven of the studies investigated the natural progression of respiratory dysfunction over time. Follow up periods ranged from 1 to 10 years. Four studies found clear declines in spirometry over time [29,35,37,62], while three studies did not find statistically significant changes [46,52] or did not comment on any change over time [32]. Thil et al. reported the annual decline in FVC, FEV1 and TLC of −0.73 (% predicted), −1.07 (% predicted) and −1.15 (%predicted) respectively [62]. They also reported that annual decline in TLC was faster for patients who did not have restrictive lung disease at commencement of the study but developed it during the follow up period. They concluded that this may imply a non-linear decline in lung function. Both Igo et al. and Dahlbom et al. reported significant and gradual decline in VC (% predicted) over time [29,37].

3.8. Central respiratory drive

The question of the involvement of central respiratory drive in respiratory disease of DM1 patients was explored in ten of the studies. Five of them used ventilatory response to CO_2 in an attempt to demonstrate the central involvement. Gillam et al. [14], were the first to investigate in a very small group of 3 patients compared to 3 controls, however found no significant difference in ventilatory response to CO_2. Clague et al. [30] also found no significant difference in ventilatory response to CO_2 between DM1 patients and controls. Bogaard et al. [24] and Poussel et al. [10] all found a significant reduction in ventilatory response to CO_2 independent of spirometry results, implying a central cause for CO_2 insensitivity. The findings of Zifko et al. [8], Begin et al. [7] and Cho et al. [58] also supported some degree of central involvement. In contrast, Begin et al. [17] concluded that chemosensitivity in DM1 is preserved and that the impaired response to CO_2 is likely a result of muscle weakness only. Serisier et al. [20] were also reserved in their conclusions, stating that while their evidence appeared to point to ventilatory response to CO_2 being a result of peripheral muscle weakness, they could not rule out defective central respiratory control.

3.9. Sleep disorders and respiratory dysfunction

Twelve studies investigated the relationship between sleep and respiratory dysfunction using overnight sleep studies. The majority found a significant proportion of sleep apnoea, sleep disordered breathing or significant overnight oxygen desaturations in DM1 patients [16,23,26,31,33,41,45,48,52,53]. The apnoeas observed were both obstructive and central in origin. There were mixed findings when looking at any statistical relationship between daytime respiratory function and sleep abnormalities. Leygonie et al. [16] and Kiyan et al. [48] found an association between abnormal sleep and restrictive lung disease and daytime hypoxaemia, respectively. Finnimore et al. [31] found only BMI to be significantly predictive of sleep abnormalities, with no relationship between sleep and daytime RFTs nor $PaCO_2$ observed. Ververs et al. [33] also found no relationship between daytime respiratory parameters and sleep disordered breathing.

4. Discussion

This review has identified a large base of literature describing the respiratory dysfunction associated with myotonic dystrophy. The aims of this review were to summarise the current literature regarding the natural history of DM1, to investigate whether there is a consensus in the current literature regarding the question of central versus peripheral origin of respiratory dysfunction in DM1, summarise the current literature regarding genetic correlations with respiratory disease severity, and finally to identify gaps in the current literature to guide future direction of research.

4.1. Summary of current literature

The predominant finding of the majority of the publications was a strong prevalence of restrictive lung disease in DM1 patients. FVC, FEV1 and TLC were all commonly impaired to varying degrees. Restrictive lung disease is a common result of many types of neuromuscular disease, and this consensus in DM1 is not surprising [63,64]. Both MEP and MIP were found to be consistently impaired (MEP often reportedly more severely affected than MIP). Respiratory function was also commonly found to be further impaired in the supine position compared to sitting. These findings both indicate the presence of significant respiratory muscle weakness in DM1 patients [65]. This finding is consistent with the findings in other neuromuscular diseases, including Duchenne's muscular dystrophy (DMD) and amyotrophic lateral sclerosis (ALS) [55,66]. These findings show that the respiratory disease in DM1 can, at least partly, be directly attributed to weakness of respiratory muscles.

Progression of respiratory dysfunction over time is an important part of the characterisation of the disease, especially as new treatments are finally emerging. A clear natural history of respiratory dysfunction in DM1 will aid in clinic trials in the near future. Only 6 studies investigated change in respiratory function with time. The largest and most comprehensive study was published by Thil et al. [62], reporting annual declines in all respiratory function parameters over a follow up period of 5 years. Dahlbom et al. [37] and Igo et al. [29] also had similar findings, albeit through less comprehensive study designs. While Terzi et al. [46] and Monteiro et al. [52] both found no significant change over time, the follow-up period was limited to 1 year for both, hence these studies are likely to be too short to detect any meaningful changes. While the majority of studies indicate a progressive decline in respiratory function over time, the trajectory of decline (e.g. linear or non-linear) remains unclear. Thil et al. [62] suggested that the course may be non-linear, based on their finding that the rate of decline varied between groups of patients. When they separated the groups into participants with restrictive disease at commencement, participants who developed restrictive disease during the follow-up period, and participants who never developed restrictive disease, they found that the second group had a significantly higher rate of decline. While this implies that there may be a point in the disease progression that the respiratory dysfunction deteriorates rapidly, further investigation is needed to confirm this.

Since the discovery of the CTG repeat expansion as the basis of myotonic dystrophy, the length of the CTG repeat has been found to be associated with severity of disease. There has been shown to be a clear association between CTG repeat length and muscle weakness [67]. It appears there is also a clear relationship with cardiac involvement [68]. The relationship between CTG repeat length and respiratory dysfunction has not been so clearly demonstrated. Of the ten studies that measured CTG repeat length, only 4 showed a clear relationship with respiratory dysfunction. Two studies with large participant numbers, Kaminsky et al. [9] and Poussel et al. [10], both showed a correlation with restrictive ventilatory patterns on spirometry. Neither study, however, reported a multivariate statistical analysis. Monteiro et al. [52] found a relationship with SpO_2, MEP and requirement for home NIV therapy, however these relationships were lost in multivariate analysis. Marchini et al. [39] and Bianchi et al. [53] all reported no relationship between respiratory dysfunction and CTG repeat length. The latter study had a large sample population of 71, and both studies were specifically investigating clinical correlates of CTG repeat length in multiple organ systems. Pruna et al. [49] also concluded no relationship, however the study was designed to investigate a new muscular involvement rating system rather than specifically CTG repeat length clinical correlations and interpretation was limited by the original French language of the article. While there is no consensus in the current literature regarding the relationship between CTG repeat length and respiratory dysfunction, the studies have been largely underpowered. Given the strong correlation of CTG repeat length with other aspects of the disease, a large scale study is needed to assess for any potential association. Further investigation is required in this area to further elucidate the details of this relationship.

Myotonic dystrophy is known to be associated with hypercapnia, as well as symptoms of daytime sleepiness, irregular breathing patterns and other indicators of alveolar hypoventilation [69,70]. These abnormalities appear to be independent of both respiratory muscle weakness and sleep disturbance, leading to the suggestion that there is involvement of the respiratory centre in the brain stem or another abnormality of central respiratory drive. While multiple studies have suggested this, there is still neither a consensus nor a proven mechanism. A common method of attempting to differentiate the cause of alveolar hypoventilation from respiratory muscle weakness was to assess ventilatory response to CO_2. By showing that an impaired response to CO_2 is independent of respiratory muscle involvement, it can be implied that there must be an abnormality in the central respiratory drive. While initial investigations by Gillam et al. [14] and Begin et al. [17] suggested that the findings could be explained by respiratory muscle weakness alone, both conclusions were based on very small sample sizes and were performed solely on participants without any clinical respiratory symptoms or daytime hypercapnia. Since then, multiple studies have found that DM1 patients have an impaired ventilatory response to CO_2 which is independent of respiratory muscle weakness or restrictive lung disease. The largest study investigating this question was carried out by Poussel et al. [10], finding significant impairment in ventilatory response to CO_2 which was independent of respiratory muscle weakness in a large group of 58 DM1 patients of variable disease severity. The consensus among the majority of articles assessed indicates alveolar hypoventilation as a central cause of respiratory dysfunction in DM1, though the phenomenology is not fully explained by peripheral respiratory muscle involvement. An

alternative theory was suggested by Serisier et al. [20] that the abnormalities of respiratory control may be a result of abnormal afferent signalling by the respiratory muscles. Further investigation into the mechanism of the central respiratory drive involvement in alveolar hypoventilation is required.

There is a significant body of literature investigating sleep disorders in myotonic dystrophy. This review did not specifically include all of this literature, however twelve of the included studies did investigate the relationship between sleep and respiratory dysfunction. Results were mixed, with several studies finding a correlation between abnormal respiratory function tests or restrictive lung disease and abnormal sleep studies. It is likely that respiratory sleep abnormalities in DM1 are multifactorial, and while respiratory muscle weakness may play a role, central respiratory drive and upper airway obstruction are likely to be involved [71–73]. A comprehensive conclusion on sleep abnormalities is beyond the scope of this review.

ABG was measured in a significant number of the studies, usually measured at rest during the daytime. Unsurprisingly, a significant portion of participants were found to be hypercapnic at rest. This is consistent with restrictive lung disease commonly described in DM1, as well as the prevalence of sleep apnoea and sleep disordered breathing [72–74]. The aetiology of the hypercapnia is likely a complex combination of respiratory muscle weakness, abnormalities in central respiratory drive and sleep disordered breathing.

4.2. Significance in clinical practice

Three important aspects of the clinical management of respiratory disease in DM1 patients are screening for respiratory disease at time of initial assessment, predicting progression of disease and monitoring the progression of respiratory dysfunction over time. Each of these require different tools and biomarkers for assessment. At the time of initial assessment in patients with a new diagnosis of DM1, early screening for respiratory disease is crucial. This assessment can be based on both symptoms and early investigations. In 2014, the 207th ENMC Workshop on chronic respiratory insufficiency in myotonic dystrophies outlined a recommendation for initial evaluation of pulmonary function in DM1 patients [75]. The first part of recommended screening is a comprehensive review of symptoms of respiratory disease. These include, but are not limited to, orthopnoea, dyspnoea on exertion, sleep disturbance, morning headaches, apnoeas, decreased cognitive performance, excessive daytime sleepiness, fatigue and history of chest infections. In addition to symptom screening, the initial assessment was recommended to include spirometry (including FVC and FEV1), overnight oximetry and peak cough expiratory flow (PCEF). Additionally, maximum inspiratory pressure (MIP), maximum expiratory pressure (MEP) and arterial blood gas testing should ideally be performed as well. The aim of these investigations is to identify key aspects of respiratory dysfunction in these patients, including respiratory muscle weakness, restrictive lung disease and chronic hypercapnia. Many of these biomarkers, including spirometry and PCEF, can be tested in the outpatient clinic setting making them ideal and convenient tools for assessment.

Respiratory disease progression in DM1 can be monitored with a similar approach, combining symptom screening, respiratory function testing and other investigations. Central to management of respiratory disease in DM1 is the introduction of non-invasive ventilation (NIV) and identifying the point at which to commence NIV is central to monitoring disease progression in these patients. The slow progression of respiratory function, over years to decades, creates difficulties in identifying the decline in function early as well as the identifying the appropriate time to initiate NIV. The 207th ENMC workshop recommended commencement of NIV therapy when symptomatic chronic respiratory insufficiency is combined with daytime hypercapnia ($PaCO_2 > 50$ mmHg), FVC $<50\%$ predicted plus MIP $<60 cmH_2O$ over 3 measurements, or evidence of nocturnal hypoventilation (including a rise in $PaCO_2$ of >8 mmHg between evening and morning ABG or overnight oximetry demonstrating significant hypoxia). The emergence of symptoms of sleep disordered breathing, including sleep disturbance, daytime hypersomnolence and fatigue, should prompt overnight polysomnography to assess for obstructive sleep apnoea or sleep hypoventilation.

Predicting progression of disease has generally been based on the assessments discussed above combined with the CTG repeat length, allowing clinicians to give patients some idea of what to expect for the future. The findings of this review highlight the difficulties in the use of CTG repeat length in the clinical setting. While an understanding of the relationship between genetics and disease severity is important, its relevance to an individual patient in the clinical setting is not so clear. At a population level there is a broad correlation between CTG repeat length and disease severity, and as discussed in this review, a large-scale study would likely confirm a correlation with respiratory dysfunction. On an individual level, the relevance is not so clear, with marked discrepancies between genetics and clinical severity commonly seen in clinical practice. A recent Scottish study of DM1 patients revealed several patients with large interruptions in their CTG repeat length associated with a milder form of the disease [76]. This study concluded that disease severity is related to at least two properties, length of the CTG repeat plus the instability of the length (which can be affected by a number of factors, including interruptions in the repeat). Further investigation into this is required. It is important to keep in mind the limitations of CTG repeat length as a prognostic indicator in the clinical setting for an individual patient.

4.3. Future research directions

This systematic review has identified several areas where further research is required. Progression of respiratory

dysfunction over time and the natural history of this aspect of the disease is an area significantly lacking in the current body of literature. This will become crucial as new treatments reach the final stages of clinical trials. An accurate assessment of the effect of any new treatments cannot be completed without an accurate and complete understanding of the normal progression of the disease. Only six studies have reported progression of respiratory dysfunction over time, only one in significant detail, and the findings were not all consistent with each other. Additionally, the relationship between CTG repeat length and respiratory dysfunction has not yet been shown conclusively. This is vital for management planning and prognostic information for the patient. Large studies have found inconsistent and contradictory results, and a consensus on the relationship between genetics and respiratory dysfunction is yet to be reached. Finally, the question of what (if any) involvement the central respiratory drive has on alveolar hypoventilation in myotonic dystrophy has not yet been answered. While this review has shown that the majority of recent, large investigations found that central respiratory drive is at least a significant contributor to alveolar hypoventilation, the mechanism for this is still largely unknown.

4.4. Quality assessment and potential biases

While this systematic review reports a significant body of research into respiratory dysfunction in myotonic dystrophy, there are some significant limitations to the findings. Many of the investigations had very small numbers of participants (commonly between 10 and 20), so the conclusions we can draw from each is limited. Additionally, the source of participants and level of both muscle weakness and respiratory dysfunction in each cohort was highly variable between studies, ranging from studies comprising asymptomatic young healthy patients to studies which specifically included participants commencing home non-invasive ventilation. While this provides a wide range of results, the generalisability of each investigation is difficult to assess. Without large studies involving all levels of disease severity, it is difficult to make accurate conclusions. The majority of articles were cross-sectional studies, which provides some good insight into disease at a specific point but does have many limitations as a research design. These include inability to differentiate causation from correlation, difficulty accounting for compounding factors, and the inherent difficulties with interpreting data at an aggregate level.

Quality assessment of the articles produced overall good scores, however there were common downfalls present in almost all articles. Confounding factors were often not adequately controlled when making conclusions regarding clinical correlations. This is important in a condition such as DM1, where the multisystem involvement means outcomes are often multifactorial in aetiology. Additionally, the selection process for participants was often not reported, and the method of arriving at the final number of participants unknown to the reader. Generally, however, the overall quality of the included articles was acceptable.

4.5. Justification and limitations

The inclusion criteria were developed to account for a number of factors. Articles published in a journal, as opposed to conference presentations and abstract-only publications, have undergone full peer-review assessment by the appropriate discipline prior to publication, ensuring the methodology and conclusions are of a high standard. Including all articles that performed spirometry on participants was intended to allow the review to identify all publications that investigated respiratory function while still allowing for comparison with a wide array of other factors relevant to respiratory disease (e.g. ABGs, sleep studies, etc.). Limiting the inclusion criteria to studies with ten or more participants was chosen primarily because this review is limited to discussing the conclusion of each article rather than any meta-analysis. The authors felt that studies with any less than ten participants would make it difficult to make judgement on the conclusions made. While the authors acknowledge that in a rarer disease such as myotonic dystrophy many studies are conducted on a small number of patients, the limit of 10 participants was felt an appropriate compromise.

Articles published in languages other than English were included in a partial capacity in the review. While it is not ideal to assess the article without a full original translation from the authors, it was decided that the basic conclusions made by each article should be included in this review as they contribute significantly to the current body of literature. All the articles included an abstract in English written by the original authors for publication, which allowed for some degree of confidence in the interpretation of their conclusions.

This review does have some limitations. The chosen inclusion criteria, in particular to include only studies that measured respiratory function using spirometry, did exclude some studies that have contributed to the body of literature for respiratory dysfunction in myotonic dystrophy. Studies that only assessed pattern of breathing at rest, for example, were not included in this systematic review. The inclusion of only articles reporting spirometry was also the reason for this review not examining in further detail the role of non-invasive ventilation in these patients. Although this is an important part of management in these patients, this review was limited to examining the severity of respiratory dysfunction and its associations in observational studies rather than assessment of the effectiveness of intervention options. A separate review with a focus on the current evidence of NIV in these patients would be useful to collate the current literature. Additionally, while the sample of fifty-five articles was fairly large, each article was limited in its scope. As a result, the conclusions drawn by this review on some aspects of disease were based on much smaller sample sizes. The data reported in this review had a significant degree of heterogeneity. Studies varied significantly in sample size, study design and

patient characteristics. Due to this heterogeneity of the articles included in this review, a breakdown of patients into further categories of severity (e.g. congenital, childhood, juvenile, adult and late-onset) was not possible. While this is a result of a relatively small body of literature and the difficulties of conducting studies in rarer diseases, some degree of caution should be taken in the results. Finally, this review was limited to discussing the conclusions and findings of each article, without aggregation or meta-analysis of the data. A meta-analysis of the available data would be valuable in further expanding on the conclusions of this review.

5. Conclusion

The major conclusions of this systematic review into respiratory dysfunction in myotonic dystrophy are; (1) confirmation of the current consensus that respiratory dysfunction, predominantly a restrictive ventilatory pattern, is common in myotonic dystrophy and is associated with alveolar hypoventilation, chronic hypercapnia, and sleep disturbance in the form of sleep apnoea and sleep related disordered breathing; (2) contrary to commonly held belief, there is no consensus in the literature regarding the relationship between CTG repeat length and severity of respiratory dysfunction and a relationship has not been established; (3) the natural history and time-course of respiratory functional decline is very poorly understood in the current literature; (4) there is a consensus that there is a significant involvement of central respiratory drive in this alveolar hypoventilation however the current literature does not identify the mechanism for this.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.nmd.2018.12.002.

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