



A model to predict ventilator requirement in Myotonic Dystrophy Type 1

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Keywords:	Myotonic dystrophy, Repeat expansion, Obstructive sleep apnoea, Muscle Impairment Rating Scale, daytime somnolence, Nocturnal Positive Airway Pressure

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Table 1: Demographics of the DM1 patients assessed

	Number/average value (% or range in brackets)
Gender	
M	50 (39)
F	76 (61)
Age (years)	45±1.3 (20-76)
Expansion score	
Very small (1)	14 (11)
Small (2)	37 (29)
Medium (3)	50 (40)
Large (4)	25 (20)
Repeat years (age x expansion score)	118±4.2 (25-256)
Duration of disease (years)	20±1.4 (3-56)
MIRS	
1	15 (12)
2	45 (36)
3	40 (32)
4	20 (16)
5	6 (4)
ESS	10±0.9 (0-22)

MIRS = Muscle

Impairment Rating Scale; ESS = Epworth Sleepiness Score

Table 2: Multiple linear regression analysis for NPAP requirement

Variable	Intercept	Slope	P value
Age	-0.07	0.01	0.02
Gender	0.43	0.006	0.95
Repeats group	0.34	0.03	0.48
Duration of symptoms	0.14	0.01	0.1
Repeat years	0.03	0.003	<0.01
MIRS	0.02	0.23	<0.01
FVC	0.84	-0.112	0.03

MIRS - Muscular Impairment Rating Scale; FVC – Forced Vital Capacity

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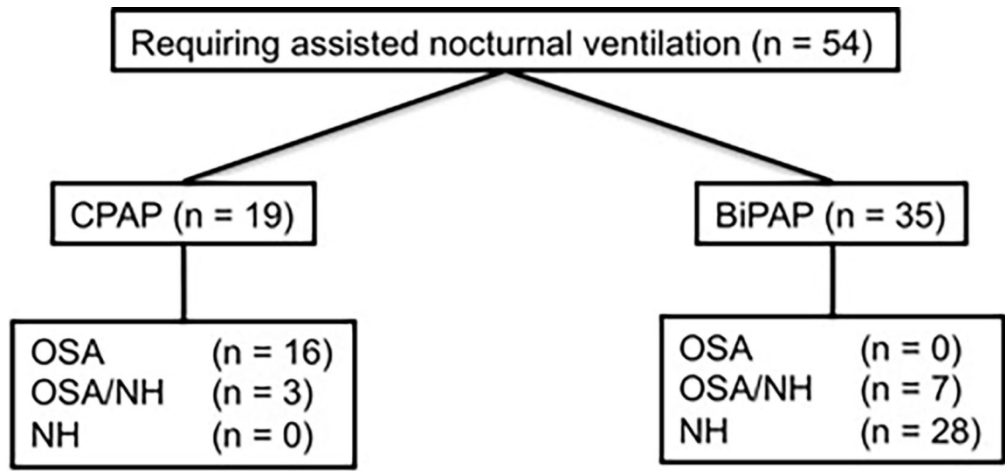


Figure 1

140x66mm (300 x 300 DPI)

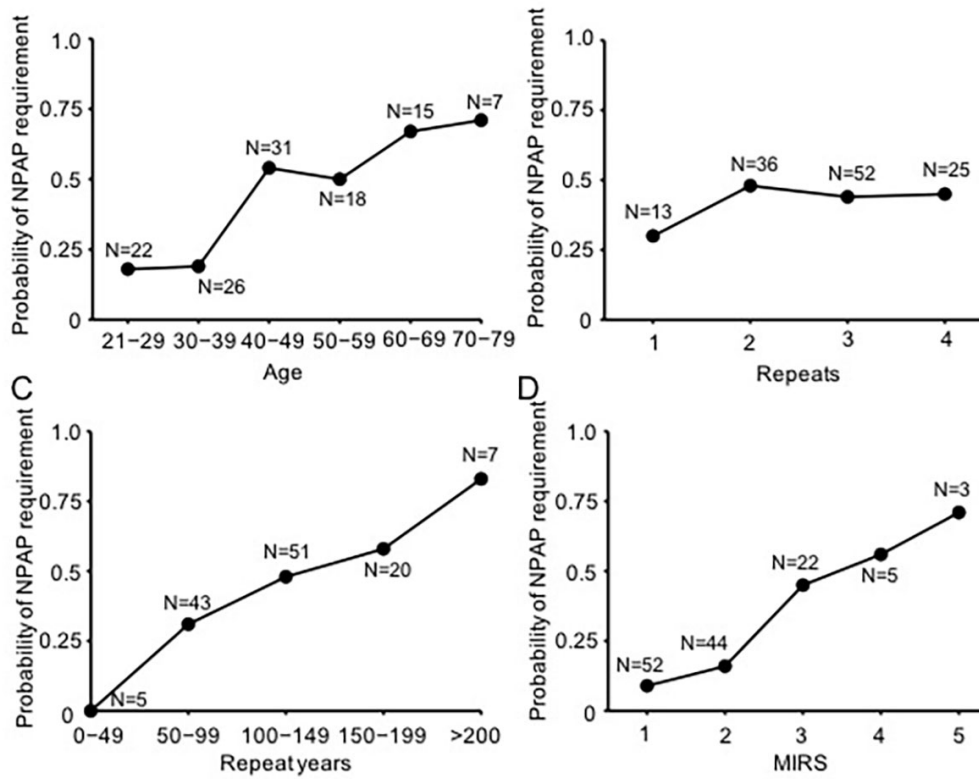


Figure 2

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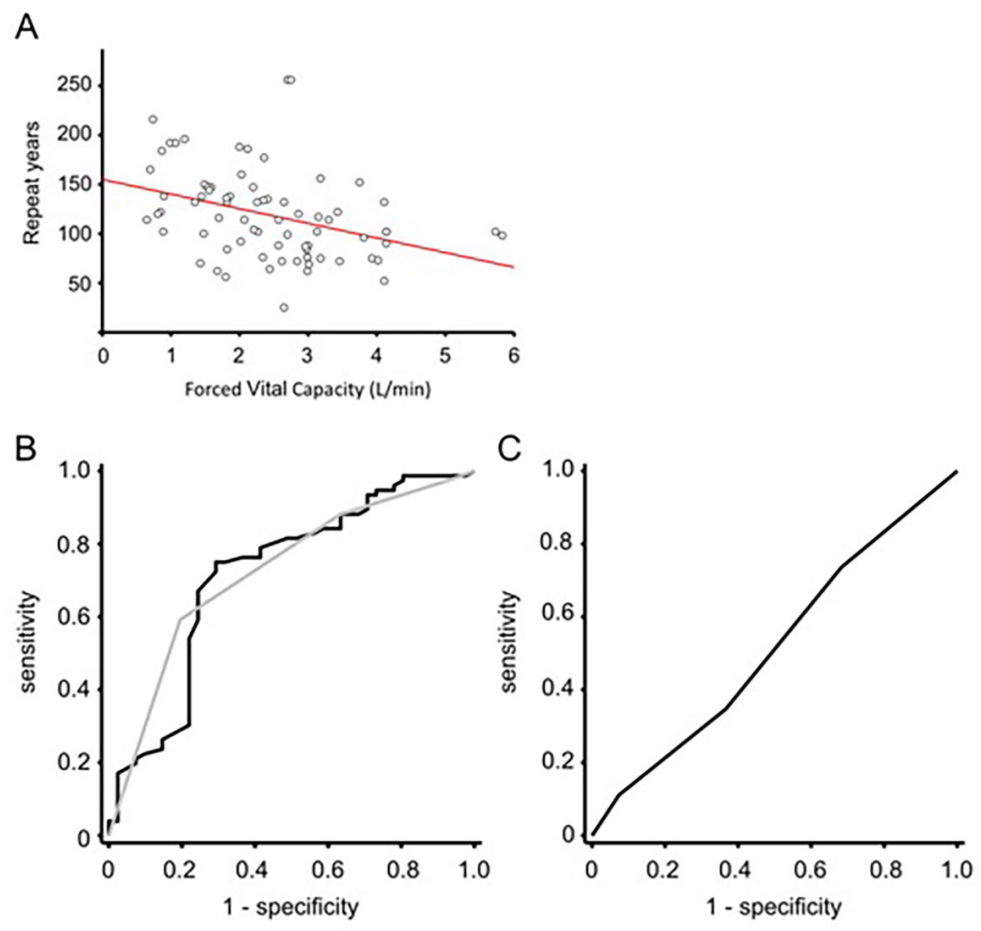


Figure 3

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38 Running Title: DM ventilation prediction model
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42 We confirm that we have read the Journal's position on issues involved in ethical
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44 publication and affirm that this report is consistent with those guidelines. None of the
45
46 authors has any conflict of interest to disclose
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Abstract

Introduction: Respiratory failure is one of the commonest causes of mortality in myotonic dystrophy type 1 (DM1). The variation in the DM1 phenotype causes difficulty in clinically predicting the severity of respiratory involvement, and parameters such as daytime somnolence are insensitive for identifying patients who require continuous or bi-level Nocturnal Positive Airway Pressure (NPAP).

Methods: We have retrospectively analysed a cohort of 126 adult onset DM1 patients at the point of their first respiratory assessment to identify significant factors in predicting ventilator requirement.

Results: Triplet repeat years score and Muscle Impairment Rating Scale were significantly linearly related to NPAP, and so formed the model.

Discussion: We have devised a simple model to aid clinicians in predicting on first visit those DM1 patients who are likely to require NPAP. We also describe the causes of failure to tolerate NPAP in DM1.

Keywords: Myotonic dystrophy, Daytime somnolescence, Nocturnal Positive Airway Pressure, Repeat expansion, Muscle Impairment Rating Scale, Obstructive sleep apnoea

Introduction

Myotonic dystrophy is the commonest form of adult-onset muscular dystrophy with a European prevalence of 3-15 per 100 000¹. Myotonic dystrophy type 1 (DM1) is caused by an unstable trinucleotide repeat (CTG) in the 3'UTR of the DMPK gene, located on chromosome 19q3.3². Regular assessment of ventilation is important in DM1 as respiratory failure accounts for almost 40% of mortality³ at an average age of 53 years. Respiratory failure is caused by dysfunction in the central control of ventilation causing alveolar hypoventilation^{4,5}, weakness of the respiratory muscles, weakness of pharyngeal muscles causing dysphagia and aspiration pneumonia⁶, and concurrent obstructive apnoea⁷. Nocturnal Positive Airway Pressure (NPAP) is currently recommended when there is evidence of nocturnal hypoventilation or obstructive sleep apnoea (OSA) on overnight sleep study testing. NPAP may improve symptoms of chronic hypoventilation and OSA. It has also been shown to reduce the frequency of hospitalisation and improve survival in other neuromuscular disorders such as Duchenne muscular dystrophy⁸ and spinal muscular atrophy⁹. Many DM1 patients who are prescribed NPAP are unable to tolerate it due to poorly defined factors. Understanding these factors may enable better patient compliance and improve prognosis.

DM1 is a multisystem disease associated with wide phenotypic variation between patients. This clinical variation may in part be explained by the number of acquired triplet repeats in each organ, such as muscle, brain, lungs and heart, caused by somatic mosaicism. The variation in clinical phenotype makes it difficult to assess

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3 which clinical and laboratory parameters are predictive of respiratory involvement. For
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5 example, although an increasing number of CTG repeats is broadly associated with
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7 earlier disease onset and increased clinical severity¹⁰, there is conflicting evidence as
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9 to whether the number of CTG repeats is correlated with the development of sleep
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11 apnoea^{7,11}. The assessment of daytime somnolence with scales such as the Epworth
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13 Sleepiness score (ESS) do not reflect the severity of nocturnal hypoventilation¹².
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21 This study aimed to assess several clinical and laboratory parameters in a large DM1
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23 population, including demographic data, genetic status and skeletal muscle
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25 involvement, and develop a model that could predict requirement for NPAP in DM1 in
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27 order to prevent early complications of respiratory failure. We hypothesised that
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29 patients who present with more severe limb symptoms, especially involving the
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31 proximal muscles, would also develop respiratory muscle weakness leading to
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33 nocturnal hypoventilation and a requirement for NPAP. We also assessed the reasons
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35 why NPAP was not tolerated, in spite of being clinically indicated.
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Methods

We retrospectively reviewed the records of all patients with genetically confirmed adult onset DM1 who were seen at the Centre for Neuromuscular Diseases (National Hospital for Neurology and Neurosurgery, London) from 2008 to 2015. We collected data on their age at enrolment, gender, semi-quantitative analysis of CTG repeat expansion using Southern blot analysis, age of first symptom (muscle weakness or

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3 myotonia), forced vital capacity (FVC) measurement at first visit and Muscular
4 Impairment Rating Scale (MIRS) recorded by a neurologist. The MIRS score is an
5 ordinal five-point rating scale, established in accordance with the clinically recognized
6 distal to proximal progression of muscular involvement in DM1¹³; no muscular
7 impairment (1), minimal signs of weakness (2), distal weakness (3), mild to moderate
8 proximal weakness (4), severe proximal weakness (5). In addition we looked at the
9 Epworth Sleepiness score (scored out of 24) assessed by a neuroanaesthetist,
10 respiratory diagnosis given after sleep study testing, and adherence to NPAP. The
11 criteria for initiating NPAP was daytime hypercapnia ($\text{PaCO}_2 > 6.5\text{kPa}$), and for CPAP
12 was an apnoea hypopnoea index of greater than 15 per hour alone, decided on by two
13 sleep study experts.
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32 The influence of expansion size on disease severity is dependant on the CTG repeat
33 size and on length of patient exposure to an expanded CTG repeat ie. their age. Age
34 and repeat size are therefore two independent variables that are considered to be
35 related to disease severity. The assessment of CTG triplet repeat length using
36 Southern blot analysis does not provide a precise method of assessing CTG repeat
37 size because of the spread in the distribution of CTG repeats due to somatic
38 mosaicism. Our genetic reference laboratory defined CTG repeat expansion as very
39 small (less than 100), small (100 to 199), medium (200 to 699) and large (700 or
40 greater). We assigned a score to the size of the repeats from 1 (very small) to 4 (large).
41 From this, we derived "triplet repeat years" score by multiplying the patient's age at
42 presentation in years by their repeat expansion size. For example, a patient aged 50
43 years with a medium repeat size would have a triplet repeat score of $50 \times 3 = 150$.
44 This generated a number that reflected increasing disease duration and severity of
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3 mutation as two known independent risk factors for disease severity. We performed
4 linear multivariate and separate receiver operator characteristic (ROC) curve analyses
5 using SigmaPlot (Systat Software Inc., Chicago, USA) to assess the dependence of
6 NPAP requirement on each variable. The accuracy of the linear multivariate model
7 could then be approximated by its R squared value, which is a statistical measure of
8 how close the data fits the regression line and is a value between 0 and 1. ROC curves
9 were derived from plotting true positive rate versus false positive rate, with a p-value
10 of less than 0.05 considered significant.
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26 Results

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31 Table 1 summarises the demographics of our patient group. Of the 126 patients
32 assessed by overnight sleep study, 54 required the initiation of NPAP; either
33 Continuous Positive Airway Pressure (CPAP) or Bi-level Positive Airway Pressure
34 (BiPAP) for predominant nocturnal hypoventilation or obstructive sleep apnoea
35 respectively (Figure 1). One patient had an additional diagnosis of sarcoidosis and
36 one had an additional diagnosis of bronchiectasis.
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50 Of the 54 patients prescribed NPAP, 22 patients could not tolerate it and discontinued
51 therapy. This consisted of 9 patients who found the mask too uncomfortable, 8 who
52 were disrupted by the noise, 4 who were disrupted by the delivery of cold air in spite
53 of a humidifier, and 1 who found no positive effect. Five patients died after initial
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3 investigations and three of these were due to respiratory causes in patients in whom
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5 BiPAP had been initiated but was not tolerated.
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11 We calculated the probability of requiring NPAP in relationship to age (Figure 2a),
12 number of repeats (Figure 2b), repeat years (Figure 2c) and MIRS score (Figure 2d).
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14 To analyse this further we performed linear regression analyses with the same
15 variables as well as gender and duration of muscle symptoms (Table 2). Age, repeat
16 years and MIRS score showed significant linearity with NPAP requirement. Age and
17 repeat years also showed co-linearity, as may be predicted, and as repeat years was
18 more significant than age it was preferentially adopted. We analysed our data with
19 multivariate linear regression accounting for age and gender, and the R squared value
20 using repeat years and MIRS was 0.46, meaning that our model accounts statistically
21 for 46% of the variation in nocturnal ventilatory requirement. To validate this result we
22 performed a Pearson's correlation between repeat years, MIRS and FVC in patients
23 in whom the latter was recorded (n=75), and found a significant negative correlation
24 for both variables (-0.36, $p < 0.01$ and -0.37, $p < 0.01$ respectively) (Figure 3a).
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46 ROC curve analysis demonstrated that repeat years score (area under curve = 0.69)
47 and MIRS score (area under curve = 0.71) were significantly sensitive and specific to
48 NPAP requirement (Figure 3b.) In comparison, the ROC curve for repeat score alone
49 was not significant (area under curve = 0.51) (Figure 3c.) Moreover the optimal cut-off
50 for repeat years was 115 (with an estimated sensitivity of 64% and specificity of 72%)
51 and for MIRS score was 1.5 (with an estimated sensitivity of 60% and specificity of
52 75%).
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6 We further analysed age, gender, expansion size, repeat years, duration of muscle
7 symptoms and MIRS score separately for the patients predominantly requiring BiPAP
8 (n = 35) and those predominantly requiring CPAP (n = 19). In the BiPAP and CPAP
9 groups respectively, gender (p = 0.63; p = 0.65), duration of muscle symptoms (p =
10 0.51; p = 0.03) and repeat score (p = 0.2, p = 0.99) did not demonstrate significant
11 linearity with NPAP requirement. Age and repeat years demonstrated significant
12 linearity with BiPAP requirement (p = 0.001) and MIRS score demonstrated significant
13 linearity with CPAP requirement (p = 0.001). MIRS score did not have significant
14 linearity with BiPAP requirement (p = 0.11) and age and repeat years did not have
15 significant linearity with CPAP requirement (p = 0.15).
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33 ROC analysis demonstrated that repeat years was significantly sensitive and specific
34 to NPAP requirement for the BiPAP group (area under curve = 0.78, p < 0.001) and
35 MIRS score was significantly sensitive and specific to NPAP requirement for the CPAP
36 group (area under curve = 0.76, p < 0.001).
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53 Discussion

54 The two parameters that were significantly linearly related to NPAP requirement and
55 demonstrated no co-linearity were repeat years and MIRS scores. Repeat years has
56 been used in other triplet repeat disorders such as Huntington's disease¹⁴ as these
57 two independent variables are associated with clinical severity and will have an
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3 independent cumulative effect on disease progression. Linear regression and ROC
4 analyses suggested that cumulative effect of age at presentation and size of
5 trinucleotide repeat or “repeat years” was most sensitive and specific when predicting
6 NPAP requirement. MIRS was also significantly sensitive and specific to NPAP
7 requirement and in contrast to previous work⁷. Indeed both repeat years and MIRS
8 had a significant negative correlation with another index for respiratory failure, FVC,
9 although a limitation of the study was that FVC was recorded in only 60% of the cohort
10 on initial visit. A future study would be to prospectively assess both MIRS and repeat
11 years on stratifying ventilatory need in our increasing DM1 cohort and correlate it with
12 current respiratory measures being performed such as transcutaneous carbon dioxide
13 monitoring and full spirometry. In contrast, severity in Epworth Sleepiness Score, a
14 subjective measure of excessive daytime sleepiness and a common symptom in
15 myotonic dystrophy¹⁵, correlated poorly with requirement of NPAP. This is in
16 agreement with other studies^{16,17}.

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Contrary to our original hypothesis, the requirement for CPAP, and not BiPAP, correlated with the MIRS score and the requirement for BiPAP, and not CPAP, correlated with age and repeat years. This suggests that neuromuscular weakness is a better predictor of obstructive sleep apnoea possibly by being associated with weakness and anatomical changes in the oropharynx and increasing BMI with worsening muscle power and immobility. In contrast, the size of the repeat and the duration of exposure to a specific repeat size i.e. age, is a better predictor of nocturnal hypoventilation. This suggests that central nervous system control of nocturnal breathing, causing central apnoea, may represent a more important factor in predicting

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3 requirement for BiPAP than neuromuscular weakness, and may be a reflection of
4 cerebral progression of the disease.
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11 Of the 126 patients assessed, NPAP was recommended in 54 (42%), which is higher
12 than previous studies such as Bianchi et al.⁷ who prescribed NPAP in 28% of 85 DM
13 patients. This may be due to differences in disease severity between the cohorts. In
14 our study, 40% of patients who were recommended NPAP were unable to tolerate it.
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16 It has been suggested that this is due to irregular respiratory drive, upper airway
17 obstruction, facial muscle weakness, and intellectual and emotional problems¹⁸.
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19 Apathy is a recognised feature of myotonic dystrophy, and although not related to
20 hypersomnia, in DM1 patients¹⁹, apathy is probably a significant factor negatively
21 influencing NPAP adherence. The reasons reported by our patients included noise of
22 the machine and discomfort of the mask, in part, due to the facial myopathy.
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39 In summary, our recommendation is that any patient who has distal weakness and a
40 repeat years score of over 115 should undergo regular respiratory and swallowing
41 surveillance and if found to require NPAP should be cared for in a multidisciplinary
42 setting to achieve optimal NPAP compliance.
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3 Table 1. Demographics of the DM1 patients assessed including gender and age and
4 expansion score, repeat years, duration of disease (years), Muscle Impairment Rating
5 Scale (MIRS) and Epworth Sleepiness Score (ESS) (n=126)
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11 Table 2. Multiple linear regression analysis for NPAP requirement. Repeat group
12 between 1 and 4 dependent size of triplet repeat. MIRS – Muscular Impairment Rating
13 Scale; FVC – Forced Vital Capacity
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19 Figure 1. Nocturnal ventilatory requirement. CPAP – continuous positive airway
20 pressure ; BiPAP – bi-level positive airway pressure ; OSA – obstructive sleep apnoea,
21 NH – nocturnal hypoventilation
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27 Figure 2. Probability of Nocturnal positive airway pressure (NPAP) requirement versus
28 (A) Age, (B) Repeats, (C) Repeat years and (D) MIRS score.
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33 Figure 3a. Pearson's correlation of repeat years and forced vital capacity, with line of
34 best fit (red). 3b. Receiver Operator Characteristic (ROC) curves indicating a high
35 sensitivity and specificity for the use of repeat years (black, $p < 0.01$) and Muscular
36 Impairment Rating Scale (MIRS) score (grey, $p < 0.01$) as predictors for Nocturnal
37 Positive Airway Pressure (NPAP) requirement; 3c. In comparison the ROC curve for
38 CTG repeat score demonstrated no significance in predicting NPAP requirement
39 ($p = 0.75$).
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