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Myotonic dystrophy severity with respect to the outcome measures

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Abstract:

Progressive multisystem disorders of Myotonic dystrophy (MD) due to high number of repeats of Cytosine-Thymine-Guanine (CTG) or Cellular nucleic acid-binding protein (CCTG) in CNBP gene are one-dimensional measure of intensity of MD1, MD2 respectively. Manifestations of MD by multidimensional effects require appropriate aggregation method and validation with CTG/CCTG repeats. Management of symptoms by physical and occupational therapies and outcome measures are important for monitoring and treatment of MD. Outcome measures in ordinal scales containing K-point items like muscle impairment rating scale (MIRS) and other performance based measures in clinical trials suffer from methodological limitations. The paper suggests a method to convert ordinal item scores to continuous, equidistant scores following normal distribution and scale score (S-scores) as sum of such item scores. S-scores can be added to get battery scores (B-scores) reflecting MD severity with respect to the outcome measures. Normally distributed S-scores and B-scores satisfy desired properties, help to undertake parametric analysis to compare status and progression of patients and group of patients including assessment of effectiveness of treatment plans, equivalent scores of two scales and better estimates of reliability, validity and their relationships. The suggested B-scores reflecting MD severity with respect to the outcome measures is recommended.

Key Words: Myotonic dystrophy, Patient-reported Outcome Scale, Normal distribution; Progress path, Factorial validity, Reliability.

Introduction

Myotonic dystrophy (MD) is a multisystem condition which causes progressive disorders with respect to muscle loss, weakness, muscle stiffness (myotonia), slow and irregular heartbeat (cardiac arrhythmia), slurred speech, clouding of the eye lens (cataracts), dysphagia (problems with swallowing), bowel problems, constipation and incontinence, behavioural and personality problems, etc. Myotonic dystrophy has been abbreviated as MD and also DM in the literature. MD is used throughout this paper. Two major forms of MD are: (i) MD1 (also called Steinert disease)- Classic Form begins at age 20 to 40; Mild Form typically for people with age $\geq$ 40; Congenial Form at birth; Childhood Form begins at age around 10 years and (ii) MD2 (also called proximal myotonic myopathy)- typically for adults with median age of 48 years.

Prevalence of MD varies among nations but MD1 with high severity is more common than the MD2. While mutations in the dystrophia myotonica protein kinase (DMPK) gene result in MD1, mutations in the Cellular nucleic acid-binding protein (CNBP) gene cause MD2 [1, 2]. Among the initial symptom, leg weakness is most common in MD2, the same for MD1 is grip myotonia [3]. A segment of DNA is abnormally repeated several times in each case. MD severity is directly proportional to number of abnormal repetitions of DNA. Alleles containing 5 to 34 Cytosine-Thymine-Guanine (CTG) repeats are normal and between 35 and 50 are mutable normal alleles (permutation alleles). Demonstrating full penetrance alleles of greater than 50 CTG repeats confirms the diagnosis associated with clinical manifestations. Excess messenger RNA generated from the abnormal DNA-repeats is toxic and disturbs production of many proteins in cells, which, in turn, causes signs and symptoms in various organs in MD.

Thus, number of CTG repeats in the blood or CCTG repeats in *CNBP* gene is the *cause* and can be taken as a one-dimensional measure of intensity of MD1 or MD2 respectively. Increase in the measure of intensity is manifested by *effects* like decline in muscle strength, handgrip force, physical disability [4]; cognitive deficits such as impairments in executive function, visuospatial function, processing speed, attention [5]; emotional disturbances and personality patterns[6], etc.

Researchers have attempted to quantify the effects mostly by rating scales to describe intensity of MD[7]. For MD1, severity index with respect to the walking capabilities was suggested [8]. Clearly, quantification of relevant multidimensional effects involves appropriate aggregation method which can be validated with number of repeats of CTG or CCTG. Theoretically speaking, third approach could be evaluating the factors giving rise to increased number of CTG/CCTG repeats, aggregating those factors and finding its relationship with intensity of MD. However, pathophysiology of congenital disease MD1 are still unresolved and congenital disease does not also occur in MD2 [9]. Rapid, accurate, and cost-effective genetic testing for measuring repeat lengths are needed to establish positive relationship between repeat size and disease [10]. Thus, the third approach is ruled out.

In terms of regions of reduced brain metabolism in patients with MD1 but MD2, cognitive impairment is more pronounced in MD1 but MD2 patients have shown deficits in executive, visuospatial, episodic verbal memory, etc.[11].

Outcome measures in ordinal scales containing K-point items (K= 2, 3, 4, 5 ……) are not equidistant since distance between two successive levels of an item $d_{j,(j+1)} \neq d_{j,(j+2)}\ \forall\ j$ =1, 2, 3, 4, ….. Thus, addition of ordinal item scores are not meaningful [12] and $\bar{X}$> or <$\bar{Y}$is meaningless [13]. Non-meaningful addition makes standard deviation (SD), correlation, Cronbach α, etc. meaningless. Analysis like regression, Principal component analysis (PCA), Factor analysis (FA), etc. and testing equlity of means by t-test or ANOVA assume normal distribution

of the variables under study but, outcome scores emerging from questionnaires violates the assumption and may distort the results. Assigning equal importance to items and dimensions are un-justified due to different contributions of items/dimensions to total score, different values of inter-item correlations, item-total correlations and factor loadings [14]. Mean, SD increase with increase in number of levels and may influence mean more than the underlying variable [15]. For two variables, $X \pm Y = Z$ is meaningful if X and Y follow similar probability distribution and distribution of Z is known for further uses. Thus, knowledge of probability density function (pdf) of X and Y and their convolution are necessary.

2. Management plan:

While no treatment exists to cure MD, management of its symptoms by appropriate treatments along with physical and of the variables under study but, outcome scores emerging from questionnaires violates the assumption and may distort the results. Assigning equal importance to items and dimensions are un-justified due to different contributions of items/dimensions to total score, different values of inter-item correlations, item-total correlations and factor loadings [14]. Mean, SD increase with increase in number of levels and may influence mean more than the underlying variable [15]. For two variables, $X \pm Y = Z$ is meaningful if X and Y follow similar probability distribution and distribution of Z is known for further uses. Thus, knowledge of probability density function (pdf) of X and Y and their convolution are necessary. occupational therapies help to manage the symptoms severity. Maximizing health and functional independence of MD patients with focus on preventing cardiopulmonary complications, symptomatic treatment of myotonia, daytime sleepiness, etc. are covered in monitoring and treating the medical issues [16, 17]. Management plan of MD patients includes among others:

2.1 Medical Treatment:

Cardiac monitoring and annual monitoring of cardiac disturbances. Baseline cardiac imagings are performed every 1 to 5 years thereafter [18].

Baseline and serial pulmonary function tests for monitoring neuromuscular respiratory failure [16]

Evaluation of sleep apnea. Continuous positive airway pressure (CPAP), Neurostimulants like methylphenidate or modafinil can be useful for excessive sleepiness.

Annual eye exam including slit-lamp examination, removal of cataracts in case of vision impairment[16].

For pregnant patients, high-risk obstetrics evaluation and respiratory difficulties during pregnancy are conducted.

Baseline and monitoring of annual fasting blood glucose and hemoglobin A1C for patients who are at increased risk of diabetes mellitus from insulin resistance.

Medications to reduce sustained myotonia, sodium channel blockers like mexiletine, tricyclic antidepressants, benzodiazepines, or calcium antagonists are often used. Sodium channel blockers are contraindicated in those with second and third-degree heart block.

2.2 Therapy:

Physical and occupational therapy are undertaken for strengthening weakened muscles, evaluation for orthotics, and durable medical equipment needs. Speech-language pathology (SLP) for dysphagia, intellectual disabilities and swallowing studies or dysarthria if needed.

2.3 Outcome measures:

Selection of pertinent outcome measures is needed for designing tailored therapeutic approach[19]. To assess changes of muscular impairment in MD1 patients, operator dependent muscle impairment rating scale (MIRS) was suggested [7] involving manual muscle testing of 11 muscle groups for five different stages: MIRS-1 (no muscular impairment); MIRS-2 (myotonia, jaw and temporal wasting, facial weakness, neck flexors weakness, ptosis, nasal speech, no distal weakness except isolated digit flexor weakness); MIRS-3 (distal weakness, no proximal weakness except isolated elbow extensor weakness); MIRS-4 (mild to moderate proximal weakness); MIRS-5 (severe proximal weakness). Despite frequent uses of MIRS, functional portraits associated to each grade is not fully known and thus, prevention targets are difficult to establish.

Performance based outcome measures in clinical trials of MD patients varied. For example,[20] considered: Six-Minute Walk Test (walking capacity over longer distances); 10-meterWalk Test (walking speed over a short distance); 30-second chair-stand test (lower limb strength and dynamic balance); Nine-Hole Peg Test (upper extremity function, specifically fine dexterity and coordination). But, [21] considered hand opening time, pressure pain threshold, hand held dynamometry, scale for the assessment and rating of ataxia (SARA), quantitative motor function test, gait stairs Gowers chair, 30-s sit to stand test, functional index 2 and 6MWT and additional patient reported scales like DM1-Active-C, Rasch-built Pompe-specific activity scale, fatigue and daytime sleepiness, brief pain inventory, myotonia behavior scale, McGill pain questionnaire, etc.

However, selection of scales/tests and hence deciding the battery is important. Selection of tests to detect cognitive impairment in MD2 is not clear[11]. The same applies for MD1. Generally, tests areselected from researchers' experiences on neurological/neurodegenerative disorders and constraints of the study protocol. Disease-specific instruments like Myotonic Dystrophy Health Index (MDHI) have advantages over generic instruments in assessing outcomes during clinical trials[22].

Chosen scales differ with respect to length (number of items), width (number of levels), range and distribution of scores and are not comparable. Moreover, such scales assess different functions like strength, endurance, speed, dexterity and balance, etc. which are problematic for aggregation. In addition to selection of scales, method of aggregating scores are critical to evaluate current status, progress/decline, relapse or development of adverse reaction or a new disease entity (like infection) of patients over time[23].

Cut-off scores vary for different scales.For example, cut-off score of Stroke-Adapted Sickness Impact Profile (SA-SIP30) with 30 items covering 8 subscales is 33 and the same for Sickness Impact Profile (SIP136) with 136 "Yes–No" type items distributed over 12 domains is 22. Question arises whether 33 in SA-SIP30 is equivalent to 22 in SIP136 and vice versa?

Intra- and-inter observer reliability of ordinal five-point MIRS scale was evaluated by Cohen's weighted kappa (κ) and construct validity was obtained as correlations with the Functional Status Index (FSI) [7]. However, different methods of deciding weights may give different values of weighted kappa ($\kappa_{Weighted}$). Concepts of agreement in terms of κ or $\kappa_{Weighted}$ are different from the concept of reliability of tests/scales. Kappa and weighted kappa as reliability have limitations[24].

Use of bioelectrical impedance analysis (BIA) for monitoring progress was suggested considering poor sensitivity of MIRS to responsiveness and high correlation between BIA and handgrip strength (HGS) [25]. Improvement of health status can be achieved by addressing reduced initiative, optimizing physical activity, and alleviating reported fatigue [26].

Gait impairment in MD has been addressed [27, 28]. For analysis of gait alteration,[8] considered 16 meters of walking both at a comfortable speed and fast pace to assess motor tasks as evidence of the foot-drop behavior among MD1 patients. Walking facilitated measurement of elapsed times in both plantar-flexion (PI) (negative-angles) and dorsi-flexion (DI) (positive – angles) in Y-axis and "narrow" time interval in X-axis. The PI–DI plot helps finding (i) Area Ratio (AR) = $\frac{PI}{DI}$ where AR > 1 implied more time in plantar-flexion conditions, typical of a foot-drop behavior of the MD1 disease, and (ii) Power Ratio (PR)= $\frac{PI}{PH} = \frac{\text{0.2–1.5 Hz band−pass}}{\text{1.5–5 Hz band−pass}}$ where PR > 1 indicates foot-drop behavior of the subjects performing motor tasks. Referring AR and PR for left and right legs as AR-L, AR-R and PR-L, PR-R, respectively, two severity indices viz. *SI-1* and *SI-2* were computed where *SI-1* reveals a foot-drop issue based on (i) AR-OUT (AR-L OR AR-R) = "1" if at least one of the two feet behaves as dropping-foot; (ii) PR-Out (PR-L OR PR-R) and *SI-2* reveals a foot-drop issue based on both AR- OUT and PR-Out . The

SI-1	*SI-2*	*SI*	*Severity Grade*
0	0	0	Regular
1	0	1	Mild
1	1	2	Severe
0	1	X	Not defined

The overall severity index "SI-Norm2" (Squared Norm for Severity Index), assesses the severity of MD1 with respect to the walking capabilities in integer values between 0–16. Significant correspondence between the SI-Norm2 and clinical classification between controls and patients was found [8]. Correlation between SI-Norm2 (walking capability (specifically the foot-drop) and MIRS covering all-body evaluation of strength loss was low.

High r_{xy} may not imply linearity between *X* and *Y*. For example, if X takes values 1, 2, 3… 30, $r_{X,X^2} > 0.9$ and $r_{X,X^3} > 0.9$ even if eachof X^2, X^3 is non-linear function of *X*, due to non-satisfaction of assumptions of linear regression of *Y* on *X* where the error score $E = (Y - \hat{Y})$ did not follow normal distribution[29]. One possible solution to the above said problem areas are to transform item scores to follow normal distribution.

3. Suggested method:

This is in line with method given by [30] to transform ordinal item scores (X_i) to continuous equidistant scores (E_i) followed by standardization (Z_i) following $N(0,1)$ and further transformation to (S_i) in the score range [1, 100] following$N(\mu_i, \sigma_i)$. The method is described below.

Assume higher item score implies higher dysfunctions or impairments. Mark the response-categories as 1, 2, 3, 4, 5, etc. avoiding zero for meaningful expected values.

Let X_{ij}be the raw score of a respondent choosing the *j*-th response-category for the *i*-th item. Find maximum frequency $f_{i.Max}$and minimum frequency $f_{i\,Min}$. For *n*-number of respondents in a 5-point item find initial weights $\omega_{i1} = \frac{f_i}{Min}{n}$ and the common difference$\alpha = \frac{5f_{i.Max} - f_{i\,Min}}{4n}$.

Find other initial weights as $\omega_{i2} = \frac{\omega_{i1}+\alpha}{2}$, $\omega_{i3} = \frac{\omega_{i1}+2\alpha}{3}$, $\omega_{i4} = \frac{\omega_{i1}+3\alpha}{4}$, and $\omega_{i5} = \frac{\omega_{i1}+4\alpha}{5}$.

Clearly, for $\alpha > 0, \omega_{i1} < \omega_{i2} < \omega_{i3} < \omega_{i4} < \omega_{i5}$

Take final weights $W_{ij} = \frac{\omega_{ij}}{\sum_{j=1}^{5} \omega_{ij}}$ Here, $\sum_{j=1}^{5} W_{ij} = 1$. Here, W_{ij}'s form final SI vector taking values "0", "1" or "2" depending upon combinations of *SI-1* and *SI-2* is shown below:

an arithmetic progression.

Generated scores $E_{ij} = W_{ij}X_{ij}$ are continuous, monotonic and equidistant.

Table 1. Severity Estimation

Standardized equidistant scores (E) of each item as $Z = \frac{E - \bar{E}}{SD(E)} \sim N(0, 1)$

Convert Z-score of an item to $S_i = \frac{(99) * (Z_i - Min(Z_i))}{Max\,(Z_i) - Min(Z_i)} + 1 \sim N(\mu_i, \sigma_i)$

where $0 \leq S_i \leq 100$.

S_i score of an item can be obtained irrespective of length of scale and width of items.

Normality of item scores ($S_i's$) facilitates meaningful addition and the resultant scale scores (*S*-scores) as $\sum_i S_i$ is the convolution of $S's$. Normally distributed *S*-scores can be added to get battery score (*B*-scores) also following normal.

3.1 Properties:

- Each of *S*-scores and *B*-scores avoids equal importance to items and dimensions and represents continuous, monotonically increasing and normally distributed scores. Normality ensures meaningful admissibility of arithmetic aggregation.

- $f_{ij} = 0$ is the zero point for scoring *K*-point items as weighted sum to get *E*-scores. Items in ratio scales can be standardized and transformed to follow normal distribution in the score range [1, 100].

- Contribution of *j*-th scale to the battery can be found by $\frac{S_j}{B-\text{scores}}$.

3.2 Benefits:

Parameters of distributions of S-scores and B-scores can be estimated from data. Normality enables estimation of population mean (μ), population variance (σ^2), confidence interval of μ, testing statistical hypothesis like $H: \mu = \mu_0$ or $H: \sigma^2 = \sigma^2_0$ etc.

Evaluate progress of i-th patient in time-period (t) over the previous period by $\frac{B_{i(t)} - B_{i(t-1)}}{B_{i(t-1)}} \times 100$ Decline is indicated if $B_{i(t)} - B_{i(t-1)} <$

0For a group of patients, $\overline{B_{i(t)}} > \overline{B_{i(t-1)}}$ indicates progress. Decline if any, may be probed to find the critical scale(s) where S_(i(t))-$S_{i(t-1)} < 0$ and initiate appropriate corrective actions in the Management plan.

Normality of S-scores and B-scores facilitates testing H_0: $\mu_{B_t} = \mu_{B_{(t-1)}}$reflecting effectiveness of the treatment plans and H_0: $Progress_{(t+1)over\ t}$, reflecting progression

Graph depicting progress/decline of one patient or a group of patients with similar socio-demographic profile is analogous to hazard function and helps to identify high-risk groups and also to compare response to treatments from the start.

- For two scales X and Y with normal pdf $f(x)$and

- For standardized item scores, $FV_{Z-scores}$ of a test is $\frac{\lambda 1}{m}$ and the test variance S^2 can be written as $S^2 = \sum \lambda_i + 2\sum_{i \neq j=1}^{m} Cov(X_i, X_j) = \frac{\lambda_1}{FV} + 2\sum_{i \neq j=1}^{X} Cov(X_i, X_j)$ (1)

Thus, theoretical reliability $r_{tt(theoretical)} = \frac{S_T^2}{S_X^2} = \frac{S_T^2}{S_X^2} = \frac{S_T^2}{\frac{\lambda_1}{FV} + 2\sum_{i \neq j=1}^{m} Cov(X_i, X_j)}$ (2)

Equation (2) gives non-linear relationship between $r_{tt(theoretical)}$ and factorial validity.

- Maximum value of test reliability (α_{PCA}) derived from the correlation matrix of *m*-number of items was given by [34] as

$$\alpha_{PCA} = \left(\frac{m}{m-1}\right)\left(1 - \frac{1}{\lambda_1}\right) \quad (3)$$

Relationship between FV and α_{PCA} is:

$$\alpha_{PCA} = \left(\frac{m}{m-1}\right)\left(1 - \frac{1}{\lambda_1}\right) = \left(\frac{m}{m-1}\right)\left(1 - \frac{1}{FV.\sum \lambda_i}\right) = \left(\frac{m}{m-1}\right)\left(1 - \frac{1}{m.FV_{Z-scores}}\right) \quad (4)$$

As per (4), higher value of $FV_{Z-scores}$ increases α_{PCA}

Cronbach alpha of a battery consisting of *K*-scales can be obtained as a function of scale reliabilities by $\hat{\alpha}_{battery} = \frac{\sum_{i=1}^{K} r_{tt(i)} S_{Xi} + \sum_{i=1, i \neq j}^{K} \sum_{j=1}^{K} 2COV(X_i, X_j)}{\sum_{i=1}^{K} S_{Xi} + \sum_{i=1, i \neq j}^{K} \sum_{j=1}^{K} 2COV(X_i, X_j)}$ (5)

where $r_{tt(i)}$ and S_{xi} denote respectively reliability and SD of the *i*-th scale.

4. Discussion:

The suggested method defines meaningful scale scores and battery scores for each individual.

S-scores and *B*-scores satisfy desired properties, helps undertaking parametric analysis, comparing status and progression of patients including indication of effectiveness of treatment plans, finding equivalent scores of two patient reported scales (PROs) where area under normal curve corresponding to PRO-1 up to P^0 $_{PRO-1}$ area under normal curve corresponding to PRO-2 up to P^0. Such $_{Var.of\ group_{Score \geq P^0}^{PRO-2}}$

equivalent cut-off scores also satisfy $\frac{PRO-1}{Variance\ of\ PRO-1} = \frac{PRO-2}{Variance\ of PRO-2}$ and can be used to evaluate efficiency of

$g(y)$ respectively, equivalent score y_0 for a given value x_0 say x_0 can be found by solving the equation $\int_{-\infty}^{x_0} f(x)dx = \int_{-\infty}^{y_0} g(y)dy$ using standard normal table [31] even if the scales have different lengths and widths.

- *S*-scores and *B*-scores satisfy the assumptions of PCA, FA and enable finding Factorial (FV) = $\frac{\lambda 1}{\sum \lambda_i} = \frac{\lambda 1}{\sum S_{Xi}^2}$ where λ is the highest eigenvalue [32] indicating validity for the main factor being measured. Tracy–Widom (TW) test statistic $U = \frac{\lambda 1}{\sum \lambda_i}$ following TW-distribution helps to test significance of λ_1[33]. Such FV avoids the problems of construct validity and selection of criterion scale ensuring matching constructs and two administrations (the scale and the criterion scale).

classification, in terms of within group variance and between group variance.

Methodological novelties also include finding factorial validity (FV) reflecting the main factor being measured; maximum value of test reliability α_{PCA}; finding relationship between $FV_{Z-scores}$ and α_{PCA} and also relationship between $r_{tt(theoretical)}$ and FV. In addition, normally distributed scores help to find population estimate of Cronbach alpha for a scale and a battery.

The results may get distorted by wrong selection of constituent scales. A chosen scale may be retained if correlation of the scale scores (*S*-scores) with number of CTG repeats for MD1 and CCTG repeats for MD2 patients exceeds significantly similar correlation for normal group (control group). An alternate approach could be to find

eigenvalues for each scale and retain the scales with eigenvalues exceeding unity.

5. Conclusions:

The suggested B-scores reflecting MD severity with respect to the outcome measures is recommended with the scales chosen as per the selection criteria mentioned above. Future empirical investigations may be undertaken to evaluate properties of the suggested method and its validation as correlation with CTG repeats for MD1 and CCTG repeats for MD2 patients along with effects of sociodemographic factors.

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