Prognostic indicators of neuromuscular disorders for palliative care referral

Richard Shek-Kwan Chang¹, Yuen Kwun Wong²

¹Division of Neurology, Queen Mary Hospital, Hong Kong, China; ²Department of Medicine, University of Hong Kong, Hong Kong, China

Contributions: (I) Conception and design: RS Chang; (II) Administrative support: All authors; (III) Provision of study materials or patients: RS Chang; (IV) Collection and assembly of data: RS Chang; (V) Data analysis and interpretation: All authors; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

Correspondence to: Richard Shek-Kwan Chang. Department of Medicine, 4/F Professorial Block, Queen Mary Hospital, Pokfulam, Hong Kong, China. Email: changsk@ha.org.hk.

Background: Most of the neuromuscular disorders (NMDs) have poor prognosis and lead to various symptoms amendable to palliative care. However, the suitable time of referral is uncertain.

Methods: A retrospective study was conducted to describe the trajectories of NMDs. Early death within one year after NMD diagnosis was set as the outcome. Total of 86 adult NMD patients were recruited in a university hospital. Demographic variable including gender, age at diagnosis and early-onset symptoms including dyspnea, dysphagia, loss of mobility, constipation, mood and sleep disorders, and pain were correlated with the outcome. Prediction models for early death were tested.

Results: Age at NMD diagnosis, early-onsets dyspnea, dysphagia, constipation and impaired mobility were found to have statistically significant correlation with early death. A prediction model consisted of these four factors had area under receiver operating characteristic (ROC) curve of 0.919.

Conclusions: Elder age at NMD diagnosis, early-onset dyspnea, dysphagia, constipation and impaired mobility within the first year after NMD diagnosis may predict mortality within the first year after diagnosis. It may provide guidance to clinicians for early palliative care referral in this patient group.

Keywords: Palliative care; neurology; neuromuscular disorders (NMDs); prognosis; triggers


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Introduction

Neuromuscular disorders (NMDs) refer to diseases that affect the nervous system from the lower motor neuron to the muscle. They can involve the anterior horn cell, for example the motor neuron disease (MND); the myelin and axon of the neuron, as exemplified by various neuropathies; the neuromuscular junction, such as the myasthenia gravis; and the muscle, namely both acquired and congenital myopathies. Some of them are curable or controllable by specific therapies, hence projecting favorable outcomes. However, a large portion has no effective treatment and run an intractable course, having grave prognosis. These cases, including MND and muscular dystrophies, could be ideal candidates for palliative care (1). Symptom relief, psychosocial support and end-of-life planning are needed. Despite that, the timing of palliative service referral is uncertain (2). Few studies have been done to investigate the trajectories of incurable NMDs in palliative medicine perspective. This study is aimed to investigate various symptoms and their predictive values in early mortality. It is hope to help clinicians to identify NMD cases that need early referral to palliative service.

Methods

Study design and data collection

A single center and retrospective study was conducted. The computerized database of a university hospital in Hong
Kong was searched to identify patients with diagnostic labels of NMD in the period of 2009 to 2016. The diagnosis should be made at adult age of 18-year-old or above. Demographic data and clinical profiles were extracted.

Data analysis

Outcome was defined as early death from any causes within the first year after the NMD diagnosis. Early-onset of a symptom was defined as the presentation of the symptom within the first year after the NMD diagnosis. Impaired mobility was defined as modified ranking scale of 4 or below. Age, gender and early-onset symptoms were correlated with the outcome using Pearson’s correlation coefficient. Prediction models for early death were formulated and their performance was assessed. Chi-square test and binary logistic regression were employed for analysis. Area under the receiver operating characteristic (ROC) curve was used to test the model performance. Statistical analysis was performed with SPSS version 24. Statistical significance was defined as P<0.05.

Results

Total of 86 patients were recruited for analysis. There were 67 MND cases (78%) (Table 1). Other myopathies accounted for 19 cases (22%). They included mitochondrial myopathies, myotonia dystrophica, facioscapulohumeral muscular dystrophy, etc. Mean age at NMD diagnosis was 59 years (range, 20–93 years). Male to female ratio was about 3:2. The mean follow-up duration was 4.15±4.26 years. Mean survival time was 3.13±3.02 years after diagnosis. Different symptoms were documented (Table 2).

Variables of gender, age of diagnosis and early-onset symptoms were correlated with early death individually by t-test and Chi’s square (or Fisher’s exact test) (Table 3). NMD onset age, early-onset dyspnea, dysphagia, impaired mobility and constipation were found to have significant correlation with early death.

Logistic regression model was used to investigate the effects of early-onset dyspnea, dysphagia, impaired mobility and constipation on the likelihood of early death. Male and age at diagnosis were also included in the analysis. Linearity of the continuous variable with respect to the logit of the dependent variable was verified by the Box-Tidwell procedure with application of Bonferroni correction. Age was linearly related to the logit of the dependent variable. The logistic regression model was statistically significant, $\chi^2[9] = 54.08$, P<0.001. The model explained 66.1% (Nagelkerke $R^2$) of the variance in the outcome and correctly classified 85% of cases. Sensitivity was 76.92%, specificity was 88.33%, positive
predictive value was 74.07% and negative predictive value was 89.83%. Of the nine variables, four were statistically significant: age of NMD onset, early-onset dyspnea, dysphagia and constipation (Table 4).

Three models were established, trying to associate different variable combinations with the outcome of early death (Table 5). Area under ROC curve was used to assess the accuracy of prediction. Model 3, which includes variables of age on NMD onset, early onsets of dyspnea, dysphagia, constipation and impaired mobility, has the best performance in predicting early death within one year of NMD diagnosis.

Discussion

The results show the age of NMD diagnosis and early emergence of certain symptoms are associated with early death. They may serve as predictors of early mortality and hence indicators of palliative care referral in this group of patients. This is consistent with the previous study findings (3). Age itself is correlated with life expectancy and also related to general morbidity state. Bulbar onset MND has been found to have poorer prognosis (4). Dysphagia can directly threaten a patient’s life by choking with suffocation and aspiration pneumonia. Also, dysphagia can result in malnutrition (5,6). Dyspnea is related to poor respiratory muscles and weakened diaphragm (7,8). In fact, the emergence of dyspnea may signify the final state of prolonged respiratory failure (9). Neuromuscular diseases typically complicated by type II respiratory failure with carbon dioxide retention. Constipation has multifactorial causes, such as autonomic failure, immobility and side effects of medications (10-12). Importantly, it may reflect poor abdominal and diaphragmatic muscles (13). This symptom may be easily overlooked. Attention should be paid to this symptom as it may predict early mortality especially if it is presented early in the course of disease. Mobility depends on limb muscle power and so as the respiratory function. Although early-onset pain, sleep and mood disorders are not found to have correlations with short-term mortality, these symptoms are could be ignored. Mood and sleep symptoms are not uncommon and have great implication in the patient’s quality of life (14-16). Despite, motor system is predominantly involved in NMDs, pain and other sensory symptoms are common in this patient group (17,18). These symptoms could be major treatment goals of palliative care.

There are several limitations in the study. This was a retrospective study with recall bias. The study group mainly consisted of patients with MND. MND has faster progression than other NMDs in general. Symptom occurrence depended on reporting rather than systemic questioning and may cause reporting bias. Symptoms were only interpreted as either presence or absence but not graded in established severity scores.

Conclusions

This study describes the symptomatology of NMDs which may serve as triggers for palliative care. It shows that onset

<table>
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<tr>
<th>Table 4</th>
<th>Logistic regression predicting likelihood of early death</th>
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<tr>
<td>Variables</td>
<td>Multivariate, OR (95% CI)</td>
</tr>
<tr>
<td>Male</td>
<td>1.84 (0.35–9.64)</td>
</tr>
<tr>
<td>Age</td>
<td>1.09 (1.02–1.16)</td>
</tr>
<tr>
<td>Early-onset dyspnea</td>
<td>7.32 (1.48–36.25)</td>
</tr>
<tr>
<td>Early-onset dysphagia</td>
<td>9.24 (1.45–58.92)</td>
</tr>
<tr>
<td>Early-onset impaired mobility</td>
<td>1.98 (0.45–8.62)</td>
</tr>
<tr>
<td>Early-onset constipation</td>
<td>1.98 (0.45–8.62)</td>
</tr>
<tr>
<td>Early-onset mood disorders</td>
<td>0.22 (0.02–3.27)</td>
</tr>
<tr>
<td>Early-onset sleep disorders</td>
<td>0.12 (0.01–2.94)</td>
</tr>
<tr>
<td>Early-onset pain</td>
<td>3.06 (0.29–32.53)</td>
</tr>
</tbody>
</table>

OR, indicates odds ratio; 95% CI, 95% confidence interval.

<table>
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<th>Table 5</th>
<th>Performance of different models in predicting early death based on area under the ROC curve</th>
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<tbody>
<tr>
<td>Models</td>
<td>Variable included</td>
</tr>
<tr>
<td>Model 1</td>
<td>Early onsets of dyspnea, dysphagia and constipation</td>
</tr>
<tr>
<td>Model 2</td>
<td>Age of NMD onset, early onsets of dyspnea, dysphagia and constipation</td>
</tr>
<tr>
<td>Model 3</td>
<td>Age of NMD onset, early onsets of dyspnea, dysphagia, constipation and impaired mobility</td>
</tr>
</tbody>
</table>

ROC, receiver operating characteristic; AUC, area under ROC curve.
age and certain early-onset symptoms including dyspnea, dysphagia, impaired motility and constipation could predict early mortality.

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None.

**Footnote**

*Conflicts of Interest:* The authors have no conflicts of interest to declare.

*Ethical Statement:* The Ethical approval is by the Institutional Review Board of the University of Hong Kong/Hospital Authority Hong Kong West Cluster (No. UW-16-187). This was a retrospective study, all subjects were anonymous, written consent was not applicable.

**References**


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