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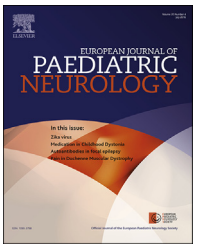

Original article

Why are some patients with Duchenne muscular dystrophy dying young: An analysis of causes of death in North East England

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ABSTRACT

Introduction: Duchenne muscular dystrophy (DMD) is the most common inherited muscle disease in children. Recent years have seen an increase in age of survival into adulthood following the introduction of proactive standards of care. We reviewed mortality in DMD in our population in order to identify potential underlying risk factors for premature death and improve clinical care.

Method: A retrospective case note review of all deaths in the DMD population over the last 10 years in North East England. We identified 2 groups of patients: patients who died from underlying cardiac and/or respiratory failure (group 1) and patients who died unexpectedly in the absence of underlying cardio-respiratory failure (group 2).

Results: Detailed information was available on 21 patients. Mean age of death in group 1 (17 patients) was 23.9 (14.4–39.5) years, in group 2 (4 patients) 14 (12.7–14.9) years. Causes of death in group 2 were acute pneumonia, cardiac arrest, acute respiratory distress and multi-organ failure. Across both groups we identified concerns regarding respiratory failure, inadequate nutrition, non-attendance at appointments, suboptimal coordination of care and decreased psychological wellbeing. In group 2, fat embolism, cardiac arrhythmia and adrenal insufficiency were also potential contributing factors.

Conclusions: The main cause of death in DMD in our population remains cardio-respiratory failure. Four patients (19%) died in their teenage years in the absence of severe cardiorespiratory failure. A more thorough understanding of the impact of DMD and its treatment on all organs systems is required to minimise the risk of an untimely death.

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1. Introduction

Duchenne muscular dystrophy (DMD) is the most common inherited muscle disease in children. The incidence is between 1 and 2.8 cases per 10.000 newborns in the UK.[1] It is an X-linked recessive condition although the spontaneous mutation rate is high, with new mutations in approximately one third of cases.[2] DMD is caused by a mutation in the dystrophin gene, which leads to a relentless progression of muscle weakness and wasting of skeletal and cardiac muscle. Affected patients display the first signs of muscle weakness around preschool age, most become wheel chair users in their teens and respiratory and cardiac failure occurs in late teens/early twenties. Death is mostly due to end stage cardiac and/or respiratory failure.

The last 10 years have seen an exponential rise in scientific research to find disease-modifying drugs to alter the devastating course of DMD. Parallel to the scientific development has been continuous improvement in clinical care for DMD, based on early and long term use of corticosteroids and a comprehensive and anticipatory multidisciplinary approach to cardiac and respiratory impairment. Corticosteroids have been shown to prolong ambulation and delay the onset of respiratory complications in DMD.[3] In addition, corticosteroids have been shown to have cardio protective properties and prevent or reduce the need for spinal (scoliosis) surgery.[4,5]

All of these and other improvements are encapsulated in the NICE accredited International Care Recommendations for Duchenne muscular dystrophy[6,7]; these provide a guideline for clinicians to optimise and standardise care for patients with DMD. At a time when new therapies are on the horizon patients remain ambulant for longer, develop cardiac and respiratory complications later and have an increased life expectancy with a net improvement of the survival curve and quality of life over the last decades.[8–11] The current mean age of survival in DMD is between 23 and 27.8 years of age.[8–11] However, despite the significant advances in the scientific and clinical fields, there are still a small number of patients with DMD who die younger than expected and from causes other than cardiorespiratory failure.

The John Walton Muscular Dystrophy Research Centre (Newcastle University and The Newcastle upon Tyne Hospitals NHS Foundation Trust) is one of three MDUK recognised Centres for research and clinical excellence for neuromuscular disorders in the UK and part of the MRC Centre for Neuromuscular Diseases. Our current DMD population includes 163 patients (67% under 18 years of age).

The aim of this retrospective review is to gain a more detailed understanding of mortality in DMD. We reviewed the causes of death in our DMD population over the last 10 years and analysed the events leading up to these deaths. We focused particularly on patients who died younger than expected and in the absence of end stage cardiorespiratory failure to identify potential predictors of early mortality. The hope is that these predictors will help us to refine care in more vulnerable patients and improve life expectancy.

2. Methods

A retrospective case note review was performed. We reviewed all deaths that occurred in the DMD population in North East England between 2004 and 2014 and who were under our care at the time of death. We collected data from clinic letters (up to two years prior to death), hospital notes and intensive care notes and liaised closely with all subspecialities involved in their care. Patients who died were divided into two groups; Group 1 included patients who had known moderate to severely impaired cardiorespiratory function leading up to death. Group 2 included patients who died in the absence of underlying moderate to severe cardiorespiratory failure; their death was considered to be "unexpected". Cardiac function was classified according to left ventricular ejection fraction (LVEF) as normal (LVEF > 55%), mildly impaired (LVEF 45–54%), moderately impaired (LVEF 30–44%) or severely impaired (LVEF < 30%).[12] Respiratory failure was classified as measured by forced vital capacity (FVC); severely impaired respiratory function was defined by an FVC<30% of predicted value for age and height and a history of either an abnormal sleep study or symptoms of nocturnal hypoventilation.[6,7]

Information collated included: ambulation status, corticosteroid regimen, respiratory status (latest FVC, sleep studies, oxygen saturations, presence of symptoms of nocturnal hypoventilation), cardiac clinical status (latest LVEF, cardiac medications), concomitant medications, weights (including weight loss), symptoms of dysphagia, nutritional assessments, history of depression/anxiety and attendance at appointments.

This review was deemed to be an audit of patient outcome with no identifiable data and so formal Ethical Committee approval was not required.

3. Results

In the 10-year period from 2004 to 2014 we identified a total of 24 deaths in our DMD population. Three patients were excluded from the analysis; they died in another hospital or at home, we had insufficient information regarding the events leading up to their death. Of the remaining 21 patients, all were non ambulant at the time of their death. Seventeen patients had known moderate to severe cardio-respiratory failure leading up to their death (group 1). In four patients the cardiorespiratory function was not considered to be significantly impaired and they did not die of end stage cardiorespiratory failure (group 2).

3.1. *Group one*

The mean age of death in the 17 patients in this group was 23.9 years (range 14.4–39.5 years). The cause of death was recorded as following; end stage cardiac failure (CF) (7 patients), end stage respiratory failure (RF) (6 patients) and combined cardiorespiratory failure (CRF) (4 patients) (Fig. 1). Loss of ambulation varied between 7.2 and 11.9 years. All patients were on cardiac treatment, two patients were on

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