Outcomes of Enteral Feeding in Motor Neurone Disease

By

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"When [no therapy] avails to ward off the fatal ending, it is still no small portion of [the physician's] art to rid his patient's path of thorns if he cannot make it bloom with roses."

—Alfred Stille, "An address delivered to the medical classes of the University of Pennsylvania on withdrawing from his chair, April 10, 1884." Medical News. 1884; 44:433-38.

DECLARATION

This thesis is an original piece of work. No portion of the work referred to in the thesis has been submitted in support of an application for another degree or qualification of this or any other university.

Signed

ABSTRACT

Motor Neurone Disease (MND) is a fatal neurodegenerative disease of unknown aetiology characterised by the degeneration of motor neurones leading to progressive wasting and weakness of the bulbar, limb and respiratory muscles. Symptomatic treatment remains the cornerstone of management. Malnutrition is a common occurrence and an independent risk factor for worse prognosis. Clinical guidelines recommend enteral feeding when there is deterioration in nutritional status and/or dysphagia. However, it remains unclear whether enteral feeding offers any survival advantage. Moreover, the impact of enteral feeding on patients' quality of life remains unknown. This study was undertaken to assess the impact of enteral feeding on survival and quality of life of patients with MND and describe the clinico-demographic characteristics of MND in Lancashire and South Cumbria in North West England.

The study has both retrospective and prospective arms. The retrospective study was undertaken by reviewing the Preston MND database and case notes to examine the demographic, clinical and survival characteristics of MND in Lancashire and South Cumbria. The prospective study was undertaken over a period of three years to explore the perspectives of 21 patients with enteral feeding and its impact on their quality of life.

The overall crude incidence of MND was 3.15 per 100,000. The mean age of onset was 67.28 (S.D. 11.06; range 22.78-93.06) years. Median overall illness duration was 1.98 (range 1.18-3.05) years. The presentation was limb onset in 62.1% cases and bulbar onset in 37.9% cases. A total of 91 (26.8%) patients received enteral feeding of which 67.0% were bulbar onset. Enteral feeding was not associated with a statistically significant survival advantage ($\chi 2$ (1) = 1.73, p = 0.19).

Enteral feeding was associated with improved quality of life, despite the attendant inconveniences. Enteral feeding was perceived as being essential to survival by some participants while others reported a sense of relief and security that their nutritional needs were met. The body mass index stabilised following enteral feeding. A key finding, relevant for clinical practice, is that most study subjects acknowledged the importance of enteral feeding and a vast majority did not wish for the feeding tube to be removed, indicating a positive attitude towards enteral feeding.

In conclusion, this study demonstrates a positive impact of enteral feeding on quality of life but not on survival. The lack of survival advantage should however, not dissuade clinicians from offering enteral feeding to patients with MND who manifest dysphagia and/or malnutrition. Even if enteral feeding does not add months to life, this study provides preliminary evidence that that it helps to add life to months.

TABLE OF CONTENTS

LIST OF APPENDICES

LIST OF FIGURES

LIST OF TABLES

LIST OF ABBREVIATIONS

AAN	American Academy of Neurologists
ALS	Amyotrophic Lateral Sclerosis
ALSFRS-R	Amyotrophic Lateral Sclerosis Functional Rating Scale-Revised
ALSAQ – 40	Amyotrophic Lateral Sclerosis Assessment Questionnaire - 40
ALSSQOL-R	Amyotrophic Lateral Sclerosis Specific Quality of Life Instrument-Revised
BMI	Body Mass Index
C9orf72	Chromosome 9 open reading frame 72
EF	Enteral Feeding
EFNS	European Federation of Neurological Societies
EMG	Electromyography
FVC	Forced Vital Capacity
LMN	Lower Motor Neurone
MND	Motor Neurone Disease
MQOL	McGill Quality of Life
MQOL-SIS	Single item McGill Quality of Life Scale
NIV	Non-invasive ventilation
PEG	Percutaneous Endoscopic Gastrostomy
PIG	Per-oral Image-guided Gastrostomy
PLS	Primary Lateral Sclerosis
PMA	Progressive Muscular Atrophy
QOL	Quality of Life
RIG	Radiologically Inserted Gastrostomy
RIP	Rest in Peace
SEIQoL-DW	Schedule for the evaluation of individual QOL-Direct Weighting

SF-12	Short Form-12
SIP	Sickness Impact Profile
SMiLE	Schedule for Meaning in Life Evaluation
SOD1	Superoxide Dismutase 1
SPSS	Statistical Package for the Social Sciences
TDP-43	Transactive response DNA-binding Protein 43 kDa
UMN	Upper Motor Neurone

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I am also grateful for the enthusiasm and valuable time of the study participants – the study could not have taken place without their generous participation and support. They have very kindly allowed me to use their photographs in the thesis. This thesis is a fitting tribute to all the study participants and my patients who have inspired me with their courage in dealing with this cruel illness.

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CHAPTER ONE

GENERAL INTRODUCTION

1.1 Background

Motor Neurone Disease (MND) is a fatal neurodegenerative disease of unknown aetiology characterised by the degeneration of motor neurones in the primary motor cortex, corticospinal tracts, brainstem and anterior horn cells of the spinal cord (Hardiman, 2000; Miller et al., 2009). The clinical presentation results from progressive wasting and weakness of the bulbar, limb and respiratory muscles (Kiernan et al., 2011). The condition can be sporadic or familial (Wijesekera and Leigh, 2009).

The median survival from symptom onset to death varies from 20 to 48 months (Beghi et al., 2011). In the absence of a cure, symptomatic and palliative treatment remains the mainstay of management (Andersen et al., 2012). Malnutrition is a major concern and an independent prognostic factor for survival (Desport et al., 1999; Marin et al., 2011).

Treatment guidelines recommend consideration of enteral nutrition through a feeding tube in patients at risk of malnutrition or dysphagia (Andersen et al., 2012; Miller et al., 2009). However, the evidence for survival advantage with enteral feeding is inconclusive (Katzberg and Benatar, 2011). Furthermore, there is little evidence to support or refute enteral feeding for improving quality of life (QOL) of patients with MND (Katzberg and Benatar, 2011).

The aims of the thesis were to assess the outcomes of enteral feeding and describe the demographic and clinical characteristics of MND in Lancashire and South Cumbria in North West England. The thesis begins with an overview of MND and its management, thereby setting the scene for use of enteral feeding in MND.

This thesis is divided into five chapters. Chapter 1 begins with a review of relevant literature and rationale for the research and further discusses the nomenclature,

epidemiology, aetio-pathogenesis, clinical characteristics, diagnosis and management of MND. Chapter 2 systematically reviews all retrospective and prospective studies investigating the impact of enteral feeding on survival, nutritional status and QOL of patients with MND. Chapter 3 describes the demographic, clinical and survival characteristics of MND in Lancashire and South Cumbria. Chapter 4 presents the findings of a prospective study aimed at investigating the impact of enteral feeding on QOL of MND patients. Chapter 5 discusses the results in the broader context of extant literature, draws conclusions and proposes recommendations for clinical practice and future research. These chapters are followed by scope for future studies and references.

1.2 History and Nomenclature

The nomenclature of motor neurone disease has evolved over a century reflecting advances in clinico-pathological concepts of the disorder (Rowland, 2001). In 1850, Aran described patients with muscle weakness and atrophy and termed the condition 'atrophie musculaire progressive' or progressive muscular atrophy (Aran, 1850). However, Duchenne (1883) claimed that the publication by Aran was based on the data from electrical stimulation studies that he had undertaken and communicated to Aran. As a compromise, contemporary neurologists credited both by referring to the condition as Aran-Duchenne disease or Duchenne-Aran disease (Visser et al., 2008).

Amyotrophic lateral sclerosis (ALS), the classical variant of MND was initially described by Jean-Martin Charcot, the French neurobiologist and physician, as a distinct neurological disorder with characteristic pathological findings (Charcot, 1881). In a series of lectures, he described the clinical and pathological features of the condition based upon his clinico-pathological observations of patients with muscle wasting and weakness (Charcot, 1881).

‘Amyotrophy’ refers to muscle atrophy, weakness and fasciculations secondary to the degeneration of anterior horn cells, reflecting lower motor neurone (LMN) involvement (Rowland and Shneider, 2001). The lower motor neurones originate in the cranial nerve motor nuclei of brainstem or the anterior horn cells of spinal cord and innervate skeletal muscles (Damjanov, 2000). They are the final common pathway through which the nervous system transmits neural information to the skeletal muscles (Figure 1.1). Lower motor neurone syndrome results from damage to the LMN cell bodies or their peripheral axons.

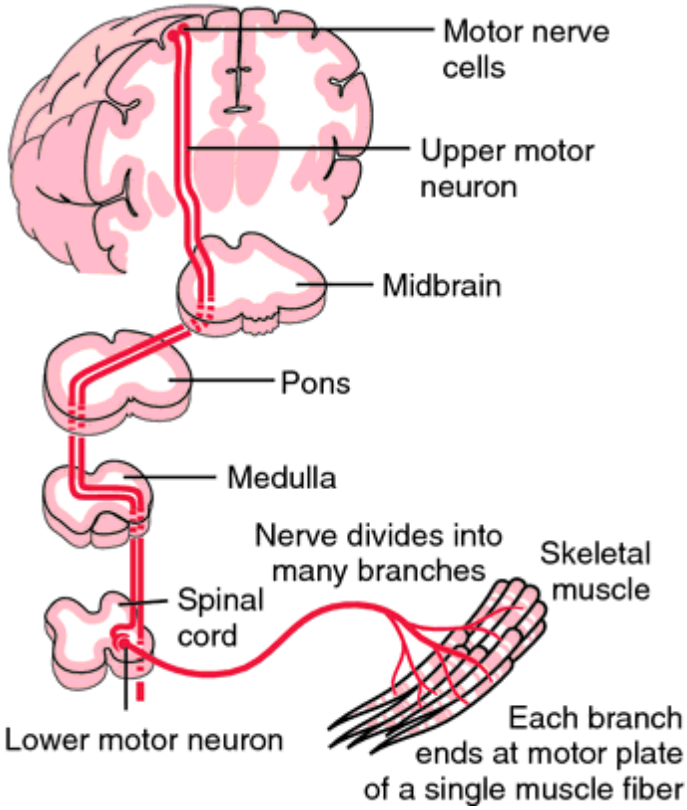

Figure 1.1: The pathways of upper and lower motor neurones (Taken from Damjanov, 2000)

‘Lateral sclerosis’ refers to the hardening or sclerosis of the lateral corticospinal tracts secondary to degeneration and replacement of these upper motor neurone (UMN) tracts by gliosis (Rowland and Shneider, 2001). The neurones that originate from the motor

cortex of brain and project to the lower motor neurones in brainstem or spinal cord through various descending pathways including corticobulbar and corticospinal tracts are called upper motor neurones (Damjanov, 2000). Damage to the neural pathway anywhere along this trajectory gives rise to UMN syndrome. Primary lateral sclerosis, a progressive pure UMN syndrome was first described by Spiller in 1904 (Spiller, 1904).

Recognising the variable involvement of upper and lower motor neurones in these syndromes, Lord Russell Brain introduced the term motor neurone disease to encompass a spectrum of disorders including amyotrophic lateral sclerosis, primary lateral sclerosis, progressive bulbar palsy and progressive muscular atrophy (Brain, 1962). The condition is known colloquially as Lou Gehrig's disease, particularly in the United States, after the famous New York Yankees baseball player who acquired the disease (Brennan, 2012; Kasarskis and Winslow, 1989). In the United Kingdom, motor neurone disease is adopted as an umbrella term to refer to all these variants of the illness (Swash and Desai, 2000). The common trend internationally is to use the terms amyotrophic lateral sclerosis and motor neurone disease interchangeably (Bak and Hodges, 2004).

1.3 Epidemiology

Sporadic MND predominantly affects middle-aged and elderly individuals with the mean age of onset varying from 55 to 65 years (Wijesekera and Leigh, 2009). The incidence ranges from 1.5 to 2.5 cases per 100,000 per year (Hoppitt et al., 2011; Logroscino et al., 2010; Mehal et al., 2013; Traynor et al., 1999). However, the incidence rate varies significantly in different age groups. The age adjusted incidence rate is less than 1.5 cases per 100,000 per year in the first four decades and increases sharply around 40 years of age, reaching its peak of 10 to 15 cases per 100,000 per year

between ages 60 and 79. The incidence declines rapidly after 80 years of age (Logroscino et al., 2010; Sorenson et al., 2002; Traynor et al., 1999).

The point prevalence varies from 2.7 to 7.4 per 100,000 (Worms, 2001). The estimated lifetime risk of developing MND is approximately 1 in 350 for men and 1 in 472 for women (Alonso et al., 2009). For reasons that are not clear, males are affected more than females with a male to female ratio of 1.5 (Beghi et al., 2006; McCombe and Henderson, 2010; Wijesekera and Leigh, 2009).

1.4 Clinical Presentation

Motor neurone disease demonstrates marked phenotypic heterogeneity (Table 1.1). The presentation may be with progressive weakness and wasting of limb, bulbar or respiratory muscles (Chio et al., 2011a; Kiernan et al., 2011). The four major clinical phenotypes include amyotrophic lateral sclerosis, progressive bulbar palsy, progressive muscular atrophy and primary lateral sclerosis (Kiernan et al., 2011).

Table 1.1: Table showing the six Motor Neurone Disease Phenotypes

1. Amyotrophic lateral sclerosis (classic variant)
2. Progressive bulbar palsy
3. Progressive muscular atrophy
4. Primary lateral sclerosis
5. Other rare variants
    a. Flail arm variant
    b. Flail Leg Variant
6. Familial motor neurone disease

Extraocular and sphincter muscles are typically spared, although they may rarely be involved in the later stages of the illness (Hardiman et al., 2011). Subtle ocular abnormalities including slowing of saccadic eye movements and ocular fixation abnormalities can occur and may indicate sub-clinical frontal lobe dysfunction (Donaghy et al., 2009; Donaghy et al., 2010). Sensory examination is almost always normal and an abnormal sensory examination in the absence of a neurological comorbidity should raise suspicion about an alternative diagnosis (Mitchell and Borasio, 2007). The usual cause of death is respiratory failure (Kiernan et al., 2011).

1.4.1 Amyotrophic Lateral Sclerosis (ALS)

Approximately 61-70% of patients with MND present with limb onset of the illness, characteristic of ALS (Kiernan et al., 2011; Logroscino et al., 2010). The clinical diagnosis of ALS rests on the demonstration of LMN and UMN signs (Figure 1.2), which spread both within and between four different body regions, and exclusion of other mimic syndromes (Brooks, 1994; Brooks et al., 2000). The four body regions include bulbar, cervical, thoracic and lumbosacral segments of the central nervous system. However, signs may be absent early in the course of the illness leading to diagnostic delays (Cellura et al., 2012; Mitchell et al., 2010).

Limb clumsiness and muscle weakness of insidious onset may start either distally or proximally in the upper or lower limbs (Eisen, 2009; Mitchell and Borasio, 2007; Zoccolella et al., 2006). The symptoms are usually asymmetrical at onset and spread contiguously over months to become bilateral (Ravits and La Spada, 2009; Vejjajiva et al., 1967). Uncommonly, patients may present with wasting before weakness becomes evident (Wijesekera and Leigh, 2009). Patients may notice cramps, muscle twitching or fasciculations prior to the onset of weakness but these are rarely the presenting

symptoms (Eisen, 2009; Gubbay et al., 1985; Kiernan et al., 2011). Upper limb onset illness presents with reduced muscle strength, poor grip and/or impaired hand dexterity. Lower limb onset illness manifests as difficulty in walking, foot drop, tendency to trip and heaviness of one or both legs (Eisen, 2009; Kiernan et al., 2011; Norris et al., 1993).

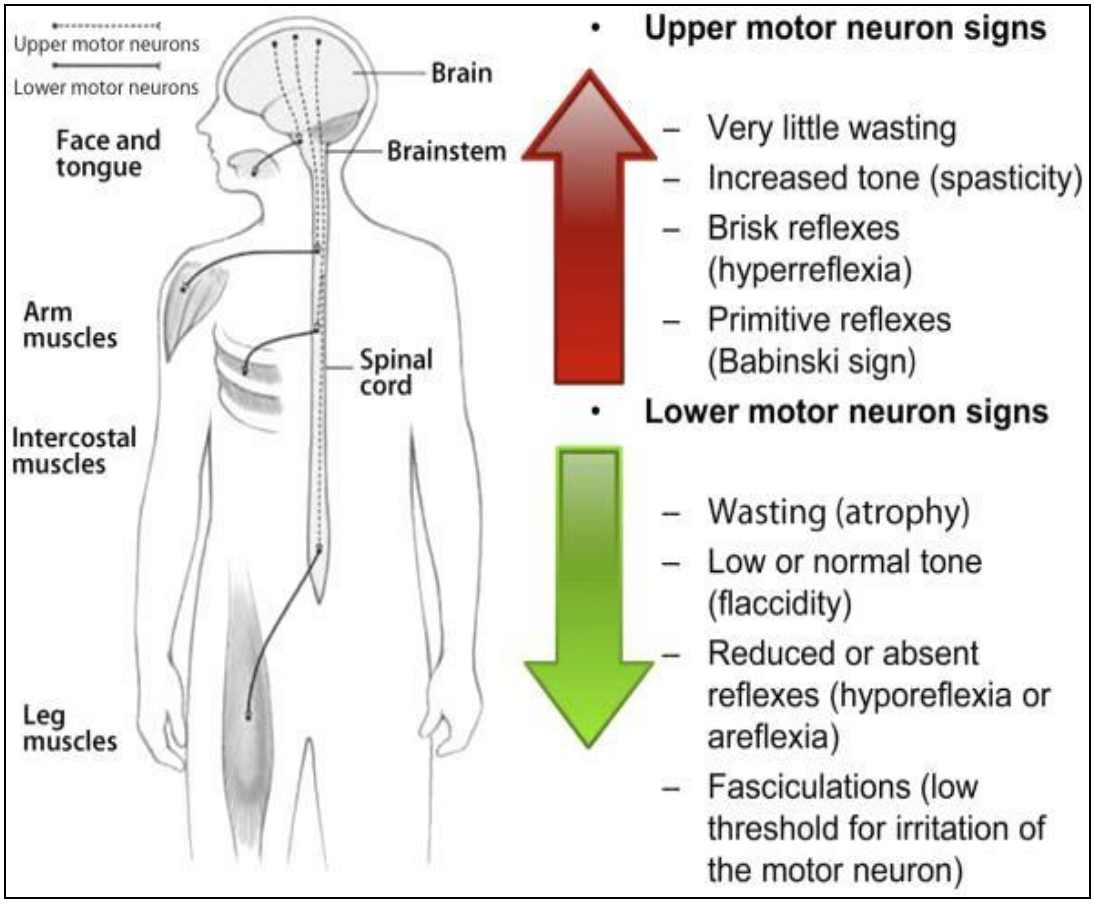

Figure 1.2: Both upper and lower motor neurones degenerate in ALS (Taken from Tiryaki and Horak, 2014).

Progressive bulbar involvement affects a vast majority of patients resulting in dysarthria and difficulty in swallowing (Gubbay et al., 1985). With disease progression, 70% - 81% of patients with MND develop dysarthria and dysphagia (Caroscio et al., 1987; Greenwood, 2013). The respiratory muscles are commonly involved in the disease course leading to respiratory failure (Hardiman et al., 2011). Respiratory onset of the

illness occurs in 3 to 5% of the patients and may present with shortness of breath and respiratory failure (Gautier et al., 2010; Shoesmith et al., 2007; Wijesekera and Leigh, 2009). Median survival is approximately 2.6 years with a 10 year survival rate of 13% (Chio et al., 2011a).

Examination may disclose signs of UMN and LMN degeneration (Brooks, 1994; Brooks et al., 2000). UMN signs include spasticity, pyramidal pattern of weakness with the limb flexors being more involved than the extensors, brisk deep tendon reflexes or preservation of reflexes in a wasted extremity, sustained clonus and extensor plantar reflex.

LMN features include muscle wasting (Figures 1.3 – 1.5), weakness and fasciculations (Brooks et al., 2000; Hardiman et al., 2011; Wijesekera et al., 2009). Fasciculations in the presence of weakness, particularly if multifocal, is a strong evidence of LMN degeneration (Eisen, 2009; Kiernan et al., 2011). Weakness of neck extensors may manifest as head drop (Umapathi et al., 2002).

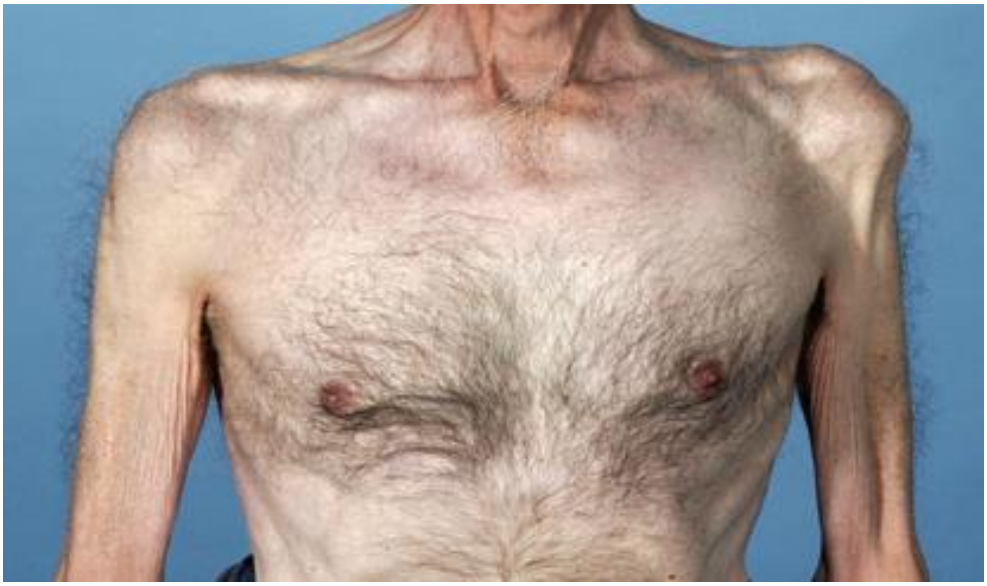

Figure 1.3: Photograph showing marked bilateral wasting of the shoulder girdles, pectoral muscles and upper limbs (Taken from Hardiman et al., 2011).

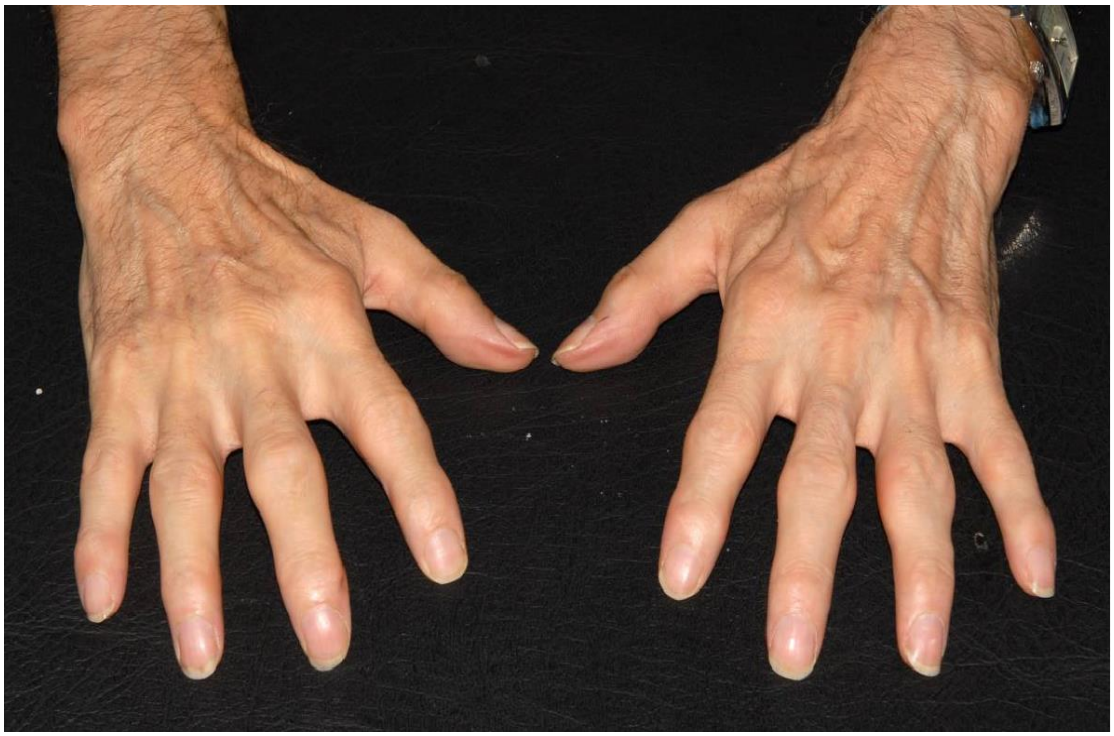

Figure 1.4: Photograph showing wasting of the dorsal interossei muscles of the hand (printed with patient's consent).

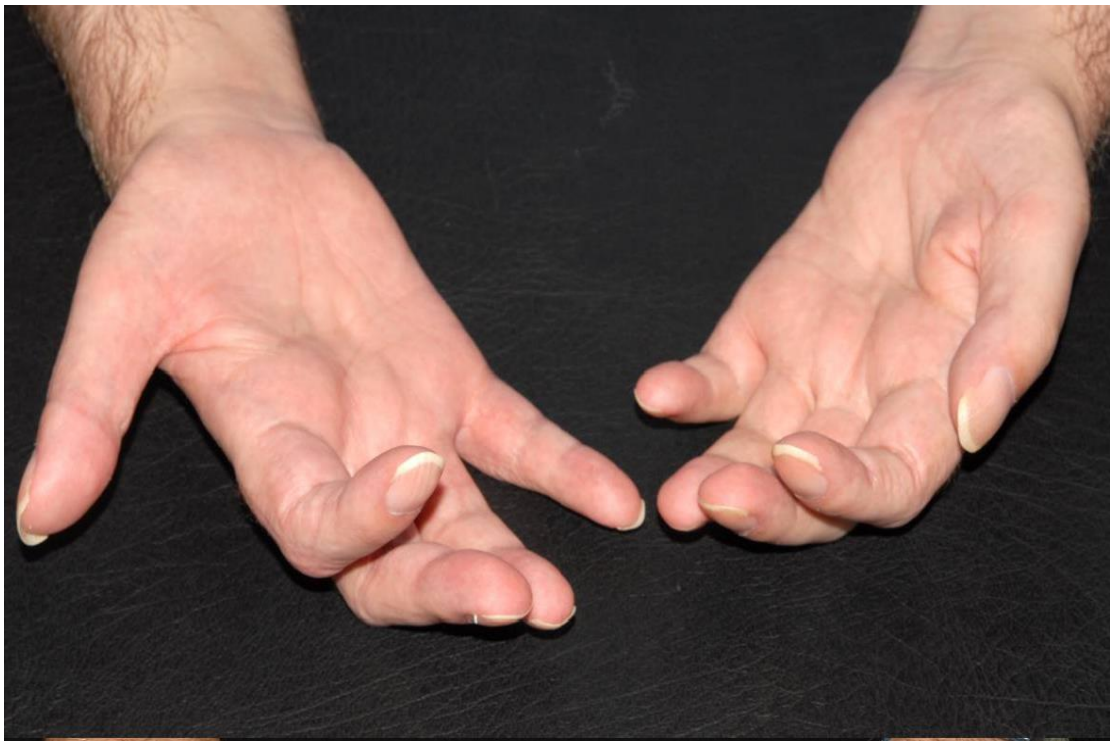

Figure 1.5: Photograph showing wasting of the thenar and hypothenar eminences (printed with patient's consent).

Some cases may demonstrate the 'split hand syndrome' (Figure 1.6) with preferential wasting of the muscles of the lateral border of hand which includes the first dorsal interosseous and abductor pollicis brevis (Eisen and Kuwabara, 2012). ALS may rarely present as a clinical syndrome of progressive hemiplegia that may ascend from the leg or descend from the arm. This phenotype is referred to as the Mills variant or hemiplegic ALS (Baumer et al., 2014; Mills, 1900).

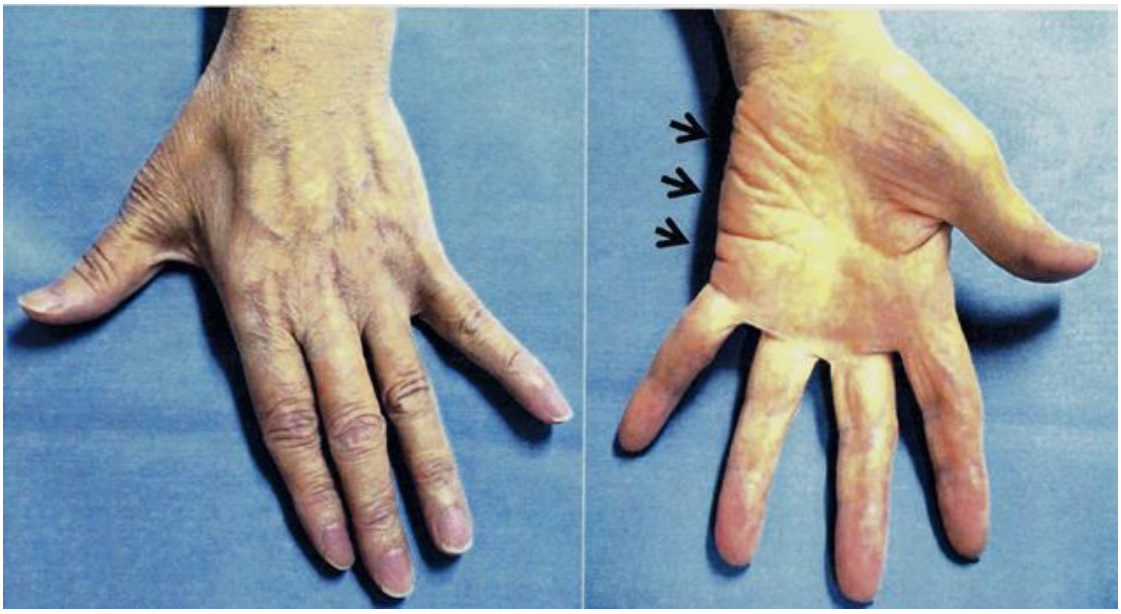

Figure 1.6: Photograph showing the 'split hand' syndrome. There is wasting of the first dorsal interosseous and thenar complex but sparing of the hypothenar muscles (black arrows) (Taken from Eisen and Kuwabara, 2012).

1.4.2 Progressive Bulbar Palsy

Bulbar onset illness presenting with dysarthria and dysphagia occurs in approximately 20 - 25% of the patients (Haverkamp et al., 1995; Logroscino et al., 2010; Turner et al., 2010). Females are more commonly affected and the proportion of patients with bulbar onset illness increases with advancing age (Traynor et al., 2000). The initial presenting

symptom is usually dysarthria followed by dysphagia (Eisen, 2009; Traynor et al., 2000). Similar to limb onset illness, progressive bulbar palsy may manifest with clinical features of UMN dysfunction, LMN dysfunction or combination of both (Norris et al., 1993; Vejjajiva et al., 1967).

Bulbar UMN dysfunction results in pseudobulbar palsy which presents with spastic dysarthria characterised by slow, strained and effortful speech, slow tongue movements, brisk jaw jerk, emotional lability and excessive yawning (Eisen, 2009; Kiernan et al., 2011; Vejjajiva et al., 1967). Bulbar LMN dysfunction results in bulbar palsy presenting with flaccid dysarthria characterised by nasal speech, weakness, fasiculations and wasting of the tongue (Figure 1.7).

A vast majority of patients with bulbar dysfunction develop sialorrhoea due to difficulty swallowing saliva. Bulbar onset illness tends to have a worse prognosis than limb onset MND with a median survival of 27 months (Wijesekera and Leigh, 2009).

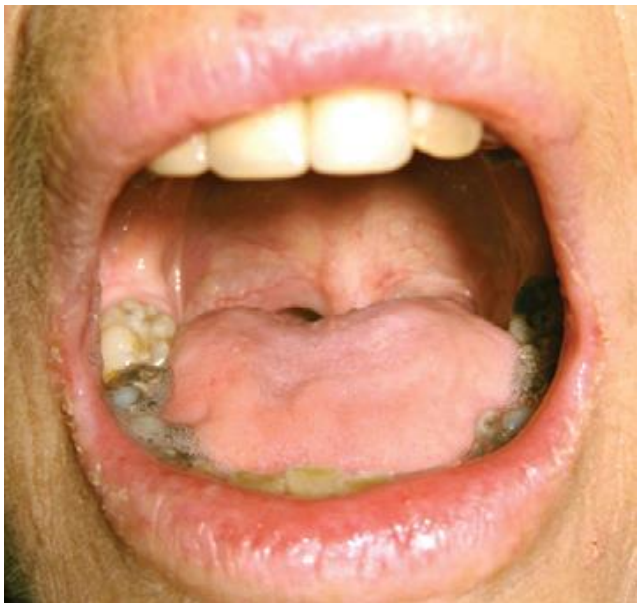

Figure 1.7: Photograph showing wasting of the tongue muscles in bulbar palsy (Taken from Kiernan et al., 2011).

1.4.3 Primary Lateral Sclerosis

Primary lateral sclerosis (PLS) is characterized clinically by a progressive pure upper motor syndrome in the absence of an alternative disease process (Pringle et al., 1992; Singer et al., 2007). PLS is rare, accounting for 1.6 to 4.4% of patients with MND (Le Forestier et al., 2001; Pringle et al., 1992).

Patients present with spastic paresis of insidious onset, usually beginning in the legs, but occasionally can manifest with pseudobulbar palsy and UMN features in the arms (Gordon et al., 2006; Pringle et al., 1992). The clinical manifestations may remain asymmetric for several years (Strong and Gordon, 2005). Patients report stiffness and clumsiness rather than weakness as compared to ALS; when limb weakness occurs, it is generally mild and noticed later in the course of illness (Singer et al., 2007).

The diagnosis rests on demonstration of UMN signs, absence of LMN signs and no evidence of denervation on electromyography (EMG), 4 years from the onset of symptoms (Gordon et al., 2006). 77% of patients develop clinical or EMG features of LMN involvement and hence the diagnosis of PLS should be made only after four years of disease duration (Gordon et al., 2006). The prognosis is significantly better than other MND phenotypes with a median survival of 13.1 years and a 10 year survival rate of 71.1% (Chio et al., 2011a; Gordon et al., 2006).

Neuropathological features of motor neurone degeneration typical of ALS such as ubiquitinated inclusions are described in patients with PLS (Tan et al., 2003). It therefore remains unclear whether PLS is a distinct nosological entity or a different phenotypic manifestation of ALS, as most patients show clinical and/or electrophysiological signs of denervation (Le Forestier et al., 2001; Strong and Gordon, 2005).

1.4.4 Progressive muscular atrophy

Progressive muscular atrophy (PMA) is clinically characterised by signs of LMN dysfunction and no signs of UMN involvement (Visser et al., 2008). It is almost always of limb onset, but patients may eventually develop bulbar dysfunction (Wijesekera et al., 2009). PMA is identified in only 2.4 to 7.6% of cases with sporadic MND (Norris et al., 1993; Kim et al., 2009). Patients are more likely to be males with a male to female ratio of 2:1 (Kim et al., 2009; Visser et al., 2008). The median survival of 48 to 56 months is approximately 12 months longer than that of ALS (Kim et al., 2009; Visser et al., 2008).

UMN signs develop in 22 to 35% of patients at some point in the illness, of which 50% develop within a year of symptom onset. These patients are then considered to have LMN onset ALS (Kim et al., 2009; Visser et al., 2008). Corticospinal tract degeneration is present in post mortem pathology in up to 50% of patients with an initial diagnosis of PMA indicating that most, if not all, cases of PMA may represent a form of ALS (Ince et al., 2003; Kim et al., 2009).

1.4.5 Other Rare Variants

Flail Arm Variant

This is a regional LMN variant characterised by bilateral, progressive, predominately proximal wasting and weakness of the upper limbs at presentation (Hu et al., 1998; Wijesekera et al., 2009). The condition has been described under various names including ‘Vulpian-Bernhardt syndrome’ (Gamez et al., 1999), ‘neurogenic man-in-the-barrel syndrome’ (Katz et al., 1999), ‘flail arm syndrome’ (Hu et al., 1998) and ‘Brachial amyotrophic diplegia’ (Katz et al., 1999).

There may be severe wasting of the shoulder girdle muscles (Figure 1.8) and the arms may hang flaccidly by the sides (Wijesekera et al., 2009). There is little or no functional involvement of the bulbar musculature and lower limbs in the early stage of the illness. Tendon reflexes in the upper limbs are typically reduced or absent, but the lower limbs may demonstrate UMN signs (Hu et al., 1998).

With disease progression, patients may manifest bulbar and lower limb symptoms (Hu et al., 1998; Katz et al., 1999). The condition remains restricted to the upper limbs for a mean of 20 months after onset (Chio et al., 2011a). The syndrome is significantly more common in men with a male to female ratio of 4:1 (Chio et al., 2011a; Wijesekera et al., 2009). The median survival is 65 months with a five year survival of 52% (Wijesekera et al., 2009).

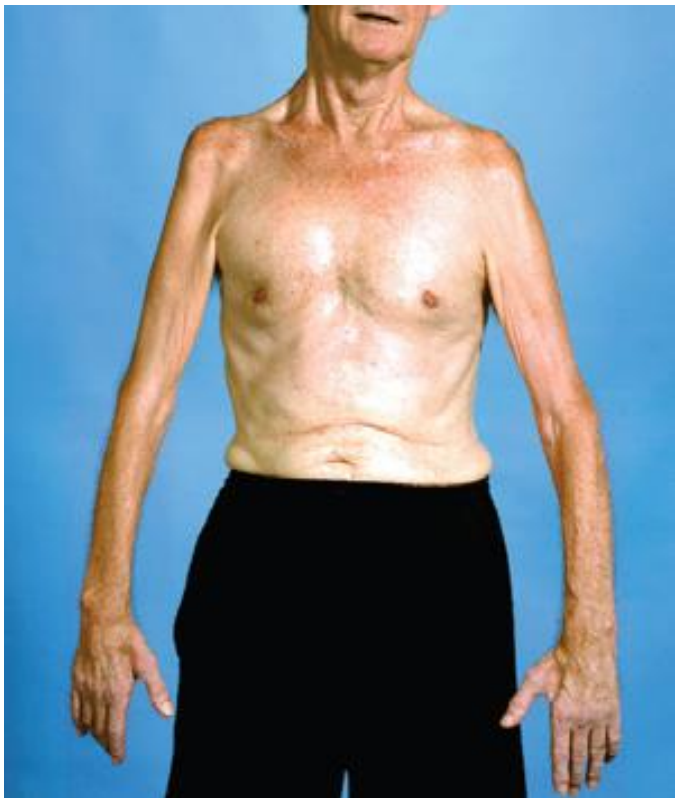

Figure 1.8: Photograph showing flail arm variant presenting with proximal and symmetrical upper limb wasting (Taken from Kiernan et al., 2011).

Flail Leg Variant

This is a lower extremity, regional LMN variant characterised by progressive distal onset weakness and wasting (Wijesekera et al., 2009). The condition has been variously termed the pseudopolyneuritic variant, the Marie-Patrikios form or the peroneal form of MND (Wijesekera et al., 2009). UMN signs are absent in the earlier stages of the illness but may develop with disease progression. Similarly, functional impairment of the bulbar musculature and upper limbs is uncommon and may emerge late in the course of illness. The condition remains restricted to the lower limbs for a mean of 16 months (Chio et al., 2011a). Males and females are equally affected (Chio et al., 2011a; Wijesekera et al., 2009). The median survival is 69 months with a five year survival of 64% (Wijesekera et al., 2009).

1.4.6 Familial Motor Neurone Disease

A positive family history of the condition is present in up to 5 to 10% of patients with MND (Renton et al., 2014; Rowland and Shneider, 2001). Similar to sporadic MND, there is heterogeneity in phenotypic expression and rate of progression, both within and between different genes (Ravits et al., 2013; Renton et al., 2014). Most cases are inherited in an autosomal dominant pattern, although autosomal recessive forms have been described (Renton et al., 2014). The age of onset of familial MND is roughly a decade earlier than the sporadic cases (Wijesekera and Leigh, 2009; Williams et al., 2013).

The genetic aetiology of two thirds of familial pedigrees has been identified (Renton et al., 2014). Major genes underlying familial MND includes chromosome 9 open reading frame 72 (C9orf72), Superoxide Dismutase 1 (SOD1), Transactive response DNA-binding protein (TARDBP), Fused in sarcoma (FUS), Optineurin (OPTN), Valosin-

containing protein (VCP), Ubiquilin 2 (UBQLN2), Sequestosome 1 (SQSTM1) and Profilin 1 (PFN1) (Ravits et al., 2013; Renton et al., 2014). Mutations in C9orf72, SOD1, TARDBP and FUS genes underline approximately two-thirds of familial cases (Figure 1.9) (Chio et al., 2014).

Mutation in C9orf72 gene is responsible for 39% of cases of familial and 7% of sporadic MND (Majounie et al., 2012). The identification of hexanucleotide repeat expansion in the C9orf72 gene in 7% of patients without a family history of MND challenges the traditional nomenclature of sporadic and familial MND and should not be viewed as absolute (Majounie et al., 2012; Renton et al., 2014).

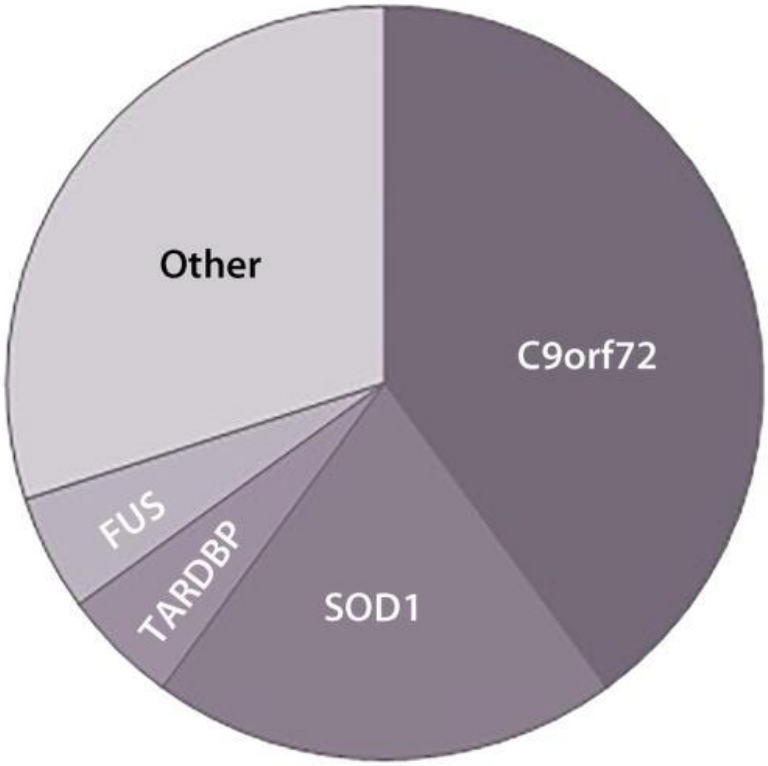

Figure 1.9: Pie chart showing genetics of familial Motor Neurone Disease. C9orf72 = chromosome 9 open reading frame 72; SOD1 = superoxide dismutase 1; TARDBP = transactive response DNA binding protein; FUS = fused in sarcoma (Taken from Tiryaki and Horak, 2014).

1.5 Aetiology

The cause of sporadic MND remains unknown. However, given the significant clinical, prognostic and genetic heterogeneity (Figure 1.10), the condition is believed to result from a complex interplay of genetic and environmental factors (Ravits et al., 2013). For reasons that are unclear, substantially increased risk of MND has been reported in Italian professional football players (Chio et al., 2005) and military personnel (Weisskopf et al., 2005).

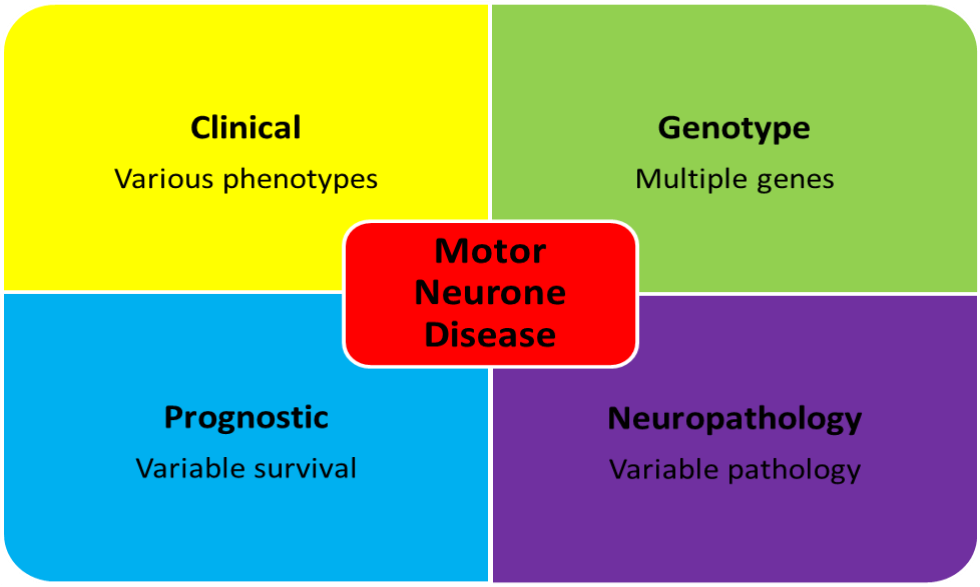

Figure 1.10: Flow chart showing the heterogeneity of Motor Neurone Disease

A range of risk factors including environmental toxins (Malek et al., 2014), occupation (Sutedja et al., 2007), physical activities (Veldink et al., 2005), alcohol (de Jong et al., 2012) smoking and a combination of these risk factors (Pamphlett and Ward, 2012; Wang et al., 2011) have been analysed in number of neuroepidemiological studies. The findings of these studies have demonstrated little consensus and this may be due to a number of factors including small sample sizes, methodological issues and use of referral or prevalent cohorts rather than population-based incident cohorts (Hardiman et al., 2011; Sutedja et al., 2009).

1.6 Pathogenesis

The pathophysiological mechanisms underlying motor neurone degeneration remains unknown but is presumed to be multifactorial (Figure 1.11), with complex interactions between genetic and molecular pathways (Pasinelli and Brown, 2006). The possible mechanisms of motor neurone death includes glutamate excitotoxicity, oxidative stress, mitochondrial dysfunction, formation of inflammatory cascades, derangement of cytoskeletal elements, impaired axonal transport, deficits in neurotrophic factors, aberrant ribonucleic acid (RNA) metabolism, glial cell pathology, apoptosis, neurofilament and protein aggregation (Cleveland and Rothstein, 2001; Rothstein, 2009; Swarup and Julien, 2011).

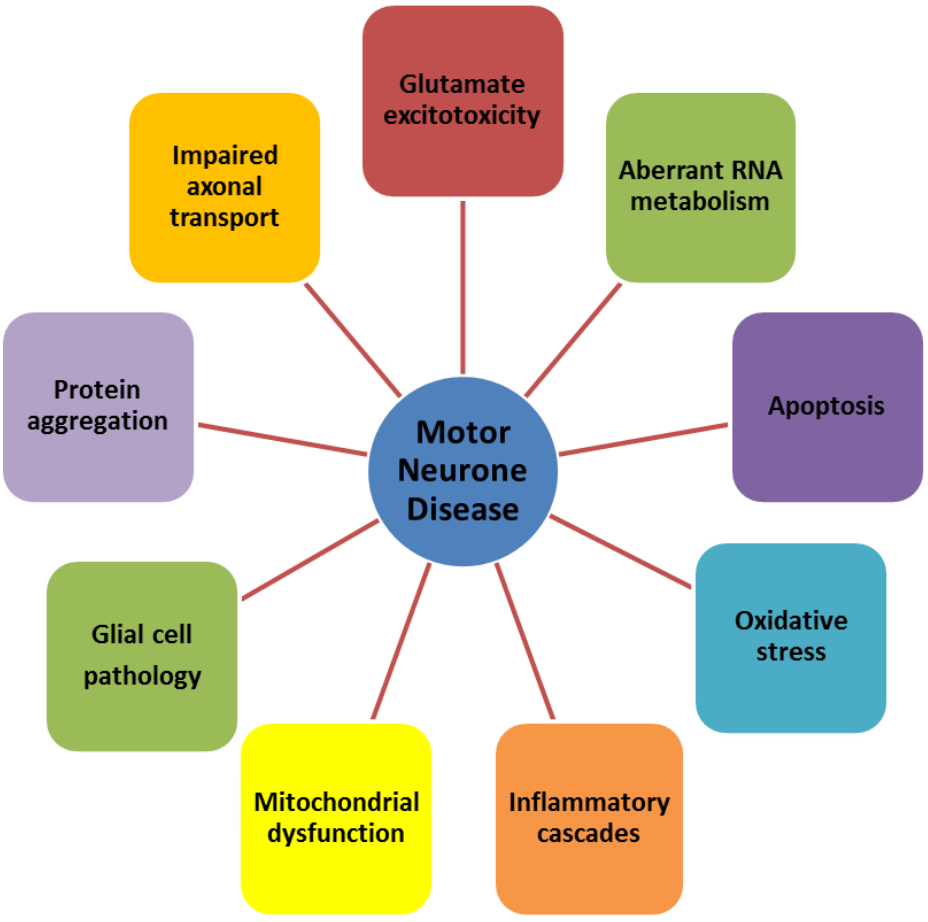

Figure 1.11: Diagram showing the mechanisms underlying neurodegeneration in MND.

The selective vulnerability of the motor neurones to neurodegeneration also remains a mystery. However, it is increasingly becoming obvious from the clinical, prognostic and genetic heterogeneity that MND may be a syndrome rather than a single disease entity (Ravits et al., 2013).

1.7 Histopathological features

Motor neurone disease has a distinctive neuropathological signature. The pathological hallmarks include loss of motor neurones with astrocytic gliosis and presence of intraneuronal inclusions in degenerating neurones and glia (Hirano, 1996; Wijesekera and Leigh, 2009). UMN loss is demonstrated by loss of Betz cells in the motor cortex and axonal loss in descending motor pathways including the lateral corticospinal tracts (lateral sclerosis). There is also loss of lower motor neurones within the anterior horns of the spinal cord and brainstem leading to muscle denervation and atrophy (amyotrophy) (Hirano, 1996; Wijesekera and Leigh, 2009).

The neuronal cytoplasmic inclusions include Bunina bodies which are small eosniophilic granular inclusions in the anterior horn cells and ubiquitinated protein aggregates. Cytoplasmic inclusions of transactive response DNA binding protein 43 kDa (TDP-43) are found in a majority of cases of sporadic MND (Geser et al., 2010; Majounie et al., 2012). However, TDP-43 is absent in MND associated with pathogenic mutations of SOD1 indicating pathogenic heterogeneity (Mackenzie et al., 2007).

For reasons that are not understood, there is selective sparing of the motor nucleus of Onufrowicz in the sacral spinal segment (Wijesekera and Leigh, 2009). There is also sparing of the nuclei of the oculomotor, trochlear and abducens nerve (Hirano, 1996; Wijesekera and Leigh, 2009).

1.8 Diagnostic criteria

In the absence of a definitive diagnostic test or biomarker, the diagnosis of MND is based on typical clinical findings and exclusion of "mimic" syndromes with appropriate investigations (Kiernan et al., 2011; Wijesekera and Leigh, 2009). The diagnostic criteria for MND have evolved over time and include the following:

1.8.1 El Escorial criteria

The World Federation of Neurology (WFN) subcommittee on MND proposed the "El Escorial" criteria (Table 1.2) for diagnosis of MND after meeting in El Escorial, Spain in 1990 (Brooks, 1994).

Table 1.2: The El Escorial criteria for diagnosis of Motor Neurone Disease/ Amyotrophic Lateral Sclerosis (Taken from Brooks, 1994).

The diagnosis of Motor Neurone Disease/Amyotrophic Lateral Sclerosis requires:

The presence of:

1. Evidence of lower motor neurone degeneration by clinical, electrophysiological or neuropathological examination
2. Evidence of upper motor neurone degeneration by clinical examination
3. Progressive spread of signs within a region or to other regions

Together with the absence of:

1. Electrophysiological evidence of other disease processes that might explain the signs of lower motor and/or upper motor neurone degeneration
2. Neuroimaging evidence of other disease processes that might explain the clinical and electrophysiological signs.

Clinical evaluation should aim to identify signs of UMN and LMN degeneration in the four regions (bulbar, cervical, thoracic and lumbosacral) of central nervous system. Clinical features of LMN degeneration include weakness, wasting and fasciculations. Features of UMN degeneration include spasticity, brisk deep tendon reflexes and extensor plantar response (Brooks, 1994). Progression of signs within a region or to other regions is crucial to the diagnosis and six monthly clinical reviews are recommended to assess progression (Brooks, 1994).

Based on the El Escorial criteria, patients can be classified into the following categories depending on the clinical probability of diagnosis (Brooks, 1994):

a. ***Definite amyotrophic lateral sclerosis/motor neurone disease:***

Clinical evidence of UMN and LMN signs in the bulbar region and at least two of the other spinal regions or the presence of UMN and LMN signs in three spinal regions.

b. ***Probable amyotrophic lateral sclerosis/motor neurone disease:***

Clinical evidence of UMN and LMN signs in at least two regions with some UMN signs rostral to the LMN signs.

c. ***Possible amyotrophic lateral sclerosis/motor neurone disease:***

Clinical evidence of UMN and LMN signs in only one region or UMN signs only in 2 or more regions or LMN signs are rostral to UMN signs.

d. ***Suspected amyotrophic lateral sclerosis/motor neurone disease:***

Clinical evidence of LMN signs in 2 or more regions. However, there may be pathological evidence of UMN involvement at autopsy.

1.8.2. Revised El Escorial or Airlie House diagnostic criteria

The increasing recognition of the importance of electrophysiological data and the need to improve diagnostic sensitivity led to revision of the ‘El Escorial’ criteria (Brooks et al., 2000). Following a meeting in Airlie House, Virginia in 1998, electrophysiological data were incorporated into the diagnostic algorithm and the revised criteria were renamed the ‘revised El Escorial’ diagnostic criteria (Brooks et al., 2000). Based on the revised criteria, patients can be classified into 'Clinically definite', 'Clinically probable', 'Clinically probable-laboratory supported' and 'Clinically possible' categories (Table 1.3).

All categories except the 'Clinically probable-Laboratory supported' are defined in the same way as in the El Escorial criteria. A diagnosis of 'Clinically probable-laboratory supported' MND can be made in the presence of UMN and LMN signs in only one region or UMN signs in only one region and LMN signs defined by EMG in at least 2 regions.

EMG should show evidence of active and chronic denervation (Brooks et al., 2000). Signs of acute denervation include fibrillation potentials and positive sharp waves. Signs of chronic denervation include fasciculation potentials, reduced interference pattern with firing rates higher than 10 hertz and unstable motor unit potentials. These changes must be present in at least two or more muscles innervated by different nerve roots and peripheral nerves in cervical and lumbosacral regions and in one muscle in the brainstem and thoracic regions (Brooks et al., 2000).

The ‘suspected amyotrophic lateral sclerosis’ category has been deleted in the revised criteria as the diagnosis of MND may not be necessarily certain for entry into a research study (Brooks et al., 2000).

Table 1.3: The revised El Escorial criteria for diagnosis of Motor Neurone Disease/ Amyotrophic Lateral Sclerosis: categories of diagnostic certainty (Taken from Brooks et al., 2000).

Clinically Definite

- Upper and lower motor neurone signs in the bulbar region and at least two spinal regions or
- Upper and lower motor neurone signs in three spinal regions.

Clinically Probable

- Upper and lower motor neurone signs in at least two regions with some upper motor neurone signs rostral to the lower motor neuron signs.

Clinically probable-laboratory supported

- Upper and lower motor neurone signs in only one region, or
- Upper motor neurone signs in only one region and lower motor neurone signs defined by electromyography in at least 2 regions.

Clinically Possible

- Upper motor and lower motor neurone signs in only one region, or
- Upper motor neurone signs alone in 2 or more regions, or
- Lower motor neurone signs are rostral to upper motor neurone signs, and
- The diagnosis of 'clinically Probable – Laboratory supported' category cannot be proven with investigations.

1.8.3. Awaji criteria

The revised El Escorial diagnostic criteria have been criticised for being too stringent and 22% of patients with MND may die without achieving a diagnostic category higher

than clinically possible (Traynor et al., 2000). Moreover, the clinical and EMG abnormalities cannot be combined in a single limb and many muscles do not show fibrillation potentials and positive sharp waves leading to diagnostic delays (de Carvalho et al., 2008).

In order to determine the efficient use of electrophysiological data, an international consensus meeting was held in Awaji Island, Japan in 2006 (de Carvalho et al., 2008). The 'Awaji criteria' proposed that electrophysiological evidence for LMN dysfunction should be assigned equal diagnostic significance to the clinical signs of LMN degeneration. Although the revised El Escorial diagnostic criteria noted fasciculation potential as a characteristic feature of MND, they were not acknowledged as evidence of active denervation (Brooks et al., 2000). In the Awaji criteria, fasciculation potentials associated with signs of reinnervation are considered equivalent to fibrillation potentials and positive sharp waves as evidence of acute denervation (de Carvalho et al., 2008). This has rendered the 'clinically probable – laboratory supported ALS' category redundant, and is based on the observation that EMG is an extension of clinical examination (de Carvalho et al., 2008). Based on the Awaji criteria, the diagnostic categories include 'clinically definite', 'clinically probable' and 'clinically possible' motor neurone disease.

A systematic review of eight studies comparing the Awaji criteria with revised El Escorial diagnostic criteria suggests improvement in diagnostic sensitivity from 62.2% to 81.1% with no change in specificity, which remains at 98% (Costa et al., 2012). However, many studies evaluating the Awaji criteria have various methodological limitations and report conflicting findings (Benatar and Tandan, 2011). For instance, one of the papers included in the systematic review reported increase in diagnostic sensitivity from 57% to 87% by using the Awaji criteria (Chen et al., 2010). However

this increase is apparent rather than real and resulted from exclusion of the 'clinically probable-laboratory supported' category as defined by the revised El Escorial as genuine cases of MND. The Awaji criteria has also been criticised for being developed on the basis of expert opinion rather than empirical or high quality data and the revised El Escorial criteria continues to be widely used in clinical and research studies (Benatar and Tandan, 2011).

1.9 Differential diagnosis

Differential diagnostic considerations and pertinent investigations are dictated by the phenotype and clinical context of an individual patient. The absence of disease progression and atypical clinical features, for instance visual, sensory or sphincter disturbances (Table 1.4) should trigger a search for 'mimic syndromes' (Traynor et al., 2000). The differential diagnosis is broad, particularly early in the course of illness (Kiernan et al., 2011; Traynor et al., 2000; Visser et al., 2008). Table 1.5 outlines the 'MND mimics' and investigations appropriate for the condition.

Table 1.4: Table outlining the clinical findings inconsistent with the diagnosis of motor neurone disease (Taken from Brooks, 1994)

1. Sensory dysfunction.
2. Sphincter abnormalities.
3. Autonomic nervous system dysfunction.
4. Anterior visual pathway abnormalities.
5. Movement abnormalities associated with probable Parkinson's disease.
6. Cognitive abnormalities associated with clinical Alzheimer's disease.

Table 1.5: Table showing the differential diagnosis of motor neurone disease and relevant investigations (Adapted from Kiernan et al., 2011; Traynor et al., 2000; Visser et al., 2008)

Structural Disorders • Syringomyelia or syringobulbia (Magnetic resonance imaging of the spine/brain) • Cervical myelopathy (Magnetic resonance imaging of cervical spine) • Multi-level spinal cord and root compression by disc or tumour (Magnetic resonance imaging of the spine) • Post irradiation myelopathy and/or plexopathy (Magnetic resonance imaging of the spine, nerve conduction studies, EMG) • Tumour of the brain/spinal cord (Magnetic resonance imaging of the brain/spinal cord) • Cerebrovascular disease (Magnetic resonance imaging of the brain) • Foramen magnum lesions (Magnetic resonance imaging of the brain)
Other Motor neurone disorders • Spinal muscular atrophy (Survival motor neurone gene deletion assay) • Post-polio syndrome (History, nerve conduction studies, EMG) • Hirayama disease/ Monomelic spinal muscular atrophy (Magnetic resonance imaging of the cervical spine, nerve conduction studies, EMG)
Hereditary conditions • Spinobulbar muscular atrophy/Kennedy disease (Genetic test) • Hereditary spastic paraparesis (Genetic test) • Facioscapulohumeral muscular dystrophy (Genetic test) • Hexosaminidase deficiency (White-cell enzyme testing) • Acid maltase deficiency (Dried blood spot, muscle biopsy, genetic test) • Adrenomyeloneuropathy (Very long chain fatty acids, serum cortisol)

Dysimmune and/or inflammatory conditions

- Multifocal motor neuropathy (Nerve conduction studies, EMG, ganglioside antibodies)
- Chronic inflammatory demyelinating polyneuropathy (Nerve conduction studies, EMG, lumbar puncture)
- Cramp-fasciculation syndrome/ Neuromyotonia (Nerve conduction studies, EMG, voltage-gated potassium channel antibody)
- Myasthenia gravis (Acetylcholine receptor antibodies, anti-muscle specific kinase antibody, EMG)
- Lambert-Eaton myasthenic syndrome (EMG, voltage-gated calcium channel antibody)
- Inclusion body myositis (Nerve conduction studies, EMG, creatine kinase, muscle biopsy)
- Polymyositis (Nerve conduction studies, EMG, creatine kinase, muscle biopsy)
- Multiple sclerosis (Magnetic resonance imaging of the brain/spinal cord, cerebrospinal fluid analysis, visual evoked potentials)
- Paraneoplastic disorders (Paraneoplastic antibodies, relevant imaging)

Metabolic/Endocrine/Toxic

- Hyperthyroidism (Thyroid function tests)
- Hyperparathyroidism (Calcium, phosphate and parathyroid hormone)
- Heavy metal intoxication (History and relevant analysis)
- Subacute combined degeneration (Vitamin B12 concentrations)

Infections

- Human immunodeficiency virus (Serology)
- Human T-lymphotropic virus-1 (HTLV-1) (Serology)
- Tabes dorsalis (Syphilis serology)
- Lyme disease (Lyme serology)

1.10 Associated conditions

MND has been reported in association with a number of malignancies including lymphomas, breast and lung cancer, possibly as a paraneoplastic manifestation (Corcia et al., 2014). Co-existence of MND with Huntington's disease, a trinucleotide repeat disorder has also been described raising the possibility of a genetic or epigenetic relationship (Chhetri et al., 2014; Tada et al., 2012).

MND has also been reported in association with a spectrum of autoimmune conditions including bronchial asthma, coeliac disease, young onset diabetes mellitus, multiple sclerosis, myasthenia gravis, myxoedema, polymyositis, Sjögren syndrome, systemic lupus erythematosus, voltage gated potassium antibody and ulcerative colitis (Chhetri et al., 2015; Turner et al., 2013). These associations raise the possibility of shared genetic or environmental risk factors between the reported conditions and MND (Turner et al., 2013).

1.11 Investigations

In the absence of a definitive diagnostic test, the diagnosis of MND remains a clinical one (Brooks et al., 2000; Hardiman et al., 2011). Investigations are undertaken to support the clinical diagnosis and exclude other MND 'mimics' (Table 1.5), which may be potentially treatable (Traynor et al., 2000).

EMG and nerve conduction studies are important ancillary tools in the investigation of suspected MND to look for evidence of denervation and reinnervation (de Carvalho et al., 2008; Swash, 2000). These studies will also help to exclude other mimics including multifocal motor neuropathy and a spectrum of axonal and demyelinating neuropathies (Table 1.5).

Transcranial magnetic stimulation and central motor conduction studies are not performed routinely but allows non-invasive identification of subclinical UMN dysfunction (Wijesekera and Leigh, 2009). Neuroimaging studies including magnetic resonance imaging of the brain and cervical spine helps to exclude other differential diagnosis including syringomyelia and structural causes of myeloradiculopathy, for instance spinal cord compression (Table 1.5).

Blood tests including full blood count, erythrocyte sedimentation rate, C-reactive protein, human immunodeficiency virus serology, syphilis serology, serum protein electrophoresis, creatine kinase, antiglycolipid antibodies, renal, liver and thyroid function tests are important in excluding infective, inflammatory, dysimmune, metabolic and endocrine conditions that may potentially mimic MND (Kiernan et al., 2011; Traynor et al., 2000; Visser et al., 2008).

The need for cerebrospinal fluid examination will be dictated by suspicion of an inflammatory pathology, for instance demyelinating neuropathy. Genetic testing for the common mutations may be required, if familial disease is suspected (Hardiman et al., 2011; Kiernan et al., 2011; Wijesekera and Leigh, 2009).

1.12 Diagnostic delays and errors

Diagnostic delays are not uncommon in MND. The median delay from symptom onset to diagnosis is approximately 12 months by which time the disease is halfway through its trajectory (Cellura et al., 2012; Mitchell et al., 2010). This has significant implications in accessing appropriate care and management. Unusual clinical presentations, a broad differential, low index of suspicion, delays in referral to a neurologist, reluctance to give a devastating diagnosis before it is absolutely certain and

misinterpretation of neurophysiological or neuroradiological findings are common causes of diagnostic delays (Chio, 1999; Gelinas, 1999; Mitchell et al., 2010).

One consequence of the need to make an early clinical diagnosis is the risk of misdiagnosis which ranges from 7.3 to 8% and this has far-reaching implications, including missing a potentially curative condition like multifocal motor neuropathy or compressive cervical myelopathy (Davenport et al., 1996; Traynor et al., 2000). A thorough clinical approach combined with rational and assiduous application of tailored investigations may allow a significant reduction in diagnostic delays and errors (Cellura et al., 2012; Traynor et al., 2000).

1.13 Prognosis

The prognosis and rate of deterioration is highly variable (Caroscio et al., 1987). The median survival from onset of symptoms to death varies from 20 to 48 months (Beghi et al., 2011). The 3 and 5 year survival rates are reported to be approximately 48% and 24% respectively and about 4% survive longer than 10 years after symptom onset (Testa et al., 2004; Turner et al., 2003).

Older age at symptom onset is strongly associated with poor survival (del Aguila et al., 2003). Survival is longer and may exceed 10 years in patients with symptom onset before 40 years of age as compared to onset after 80 years of age where the median survival is less than two years (Pradas et al., 2013; Testa et al., 2004).

Other poor prognostic indicators include bulbar onset disease, early respiratory dysfunction, rapid progression of symptoms with decline in the ALSFRS-R scores and short time from symptom onset to diagnosis (Chio et al., 2009a; del Aguila et al., 2003). Malnutrition is an independent prognostic factor for survival in patients with an

approximate eight fold increased risk of death (Desport et al., 1999; Marin et al., 2011). Certain phenotypes for instance flail limb variant and PLS tend to have a better prognosis (Wijesekera et al., 2009).

1.14 Quality of life (QOL) in Motor Neurone Disease

The term 'quality of life' is commonly used in all spheres of life but is conceptually an ill-defined term, because of the lack of a universally accepted definition (Rapley, 2003). QOL is a widely used term, but with little consistency and means different things to different people, depending on the context and area of application (Fayers and Machin, 2007). The World Health Organisation (1995) defines QOL as a subjective, multi-dimensional concept that is embedded in the cultural, social and environmental context and embraces both positive and negative facets of life.

The term 'health related quality of life' is frequently used to differentiate between global QOL in general terms and QOL related to health in clinical medicine and clinical trials (Fayers and Machin, 2007). Health related QOL is also a difficult and multifaceted concept with a number of dimensions which includes physical, social, psychological, cognitive, sexual and spiritual issues (Fayers and Machin, 2007; Haas, 1999). The aim of health related QOL measurement is to quantitatively evaluate the impact of the illness as well as treatment on an individual, as different patients respond differently, both to illness and to treatment (Guyatt et al., 1993).

QOL is remarkably preserved during the course of illness in majority of patients with MND despite decline in strength and function (Robbins et al., 2001). This may be because QOL in MND does not seem to correlate with physical functioning and strength but appears to depend on psychological, spiritual, religious and support factors (Robbins

et al., 2001; Simmons et al., 2000). Increasing hopelessness, fatigue, loss of speech, impaired respiratory function and depression are associated with poor QOL (Bourke et al., 2001; Bromberg, 2007; Lou et al., 2003). Strong social support and spirituality are positively associated with perceived good QOL among MND patients (Bromberg, 2007; Walsh et al., 2003).

The importance of QOL as a major outcome variable has become increasingly obvious in the management of MND (Clarke et al., 2001). In the absence of a cure, management is mainly supportive and palliative, focussed on preserving independence and QOL (Andersen et al., 2012). Measuring and monitoring QOL is therefore important in assessing the effectiveness of any supportive treatment (Brooks, 1997; Neudert et al., 2004). The consensus guidelines for the design and implementation of clinical trials in MND also recommend that a QOL assessment should be developed and incorporated into every clinical trial (Miller et al., 1999).

1.14.1 Instruments for assessment of quality of life

A number of instruments have been used for assessment of QOL in MND. However, there is lack of consensus on which instrument is most appropriate for measuring QOL (Epton et al., 2009; Simmons et al., 2000). An ideal QOL measurement tool should produce the same results on repeated trials (reliability), appear to measure what it is supposed to measure (face validity), accurately measure the intended theoretical construct (construct validity), fully measure the entire scope of the topic being measured (content validity), and the results should correlate well with a previously validated measure (concurrent validity) (Epton et al., 2009). The instrument should aim to address not only the physical but also psychological, spiritual, religious and support factors (Robbins et al., 2001; Simmons et al., 2000).

Most of the instruments used for assessment of QOL are generic and commonly used ones include the sickness impact profile (Bergner et al., 1981), McGill QOL questionnaire (Cohen et al., 1995), the 36 item short form health survey (Ware and Sherbourne, 1992) and its abbreviated version, the 12 item short form health survey (Ware et al., 1996). These scales are health-related and function-based instruments which focus on disease progression and daily functioning. The schedule for the evaluation of individual QOL-Direct Weighting (SEIQoL-DW) (Hickey et al., 1996) and the Schedule for Meaning in Life Evaluation (SMiLE) (Fegg et al., 2008) are two other instruments which capture existential domains of both quality and meaning of life. However, these generic instruments are criticised for not assessing features unique to MND (Palmieri et al., 2010). Moreover there are limited or insufficient data on their validity and reliability (Epton et al., 2009).

Instruments designed specifically for use in MND include the amyotrophic lateral sclerosis assessment questionnaire-40 (ALSAQ-40) (Jenkinson et al., 1999), the sickness impact profile/amyotrophic lateral sclerosis-19 (McGuire et al., 1997) and the amyotrophic lateral sclerosis specific quality of life instrument - revised (Simmons et al., 2006). There are limited data on the reliability and validity of the latter two instruments (Epton et al., 2009; Palmieri et al., 2010) .

The ALSAQ-40 has been demonstrated to show high internal reliability and construct and content validity (Jenkinson et al., 1999; Jenkinson et al., 2000; Jenkinson et al., 2007). However, ALSAQ-40 does not incorporate religious and/or spiritual beliefs which are important to many patients (Bremer et al., 2004; Walsh et al., 2003). Nonetheless, ALASQ-40 is the most commonly used measurement tool in assessment of QOL in MND (Jenkinson et al., 2007; Palmieri et al., 2010).

1.15 Management of motor neurone disease

There is no cure for MND and management strategies are mainly symptomatic and supportive, aimed at preservation of QOL and independence (Andersen et al., 2012; Bede et al., 2011). Pharmacological treatment options are limited and patients will inevitably face major decisions about accepting, deferring or relinquishing life-sustaining therapies (Ng et al., 2009). Management of MND therefore necessitates understanding of the medical, psychosocial and spiritual context of each individual patient and family, as these factors will play a role in influencing their decisions regarding future care (Bede et al., 2011).

Symptomatic treatments remain the cornerstone of management and all efforts should be made to enhance QOL and help maintain the patient's independence for as long as possible (Kiernan et al., 2011; Wijesekera and Leigh, 2009). Patients experience a number of symptoms including weakness, cramps, spasticity, dysarthria, dysphagia, dyspnoea, excessive salivation, emotional liability, insomnia, fatigue, anxiety and depression (Radunovic et al., 2007). Treatment strategies include symptomatic management with drugs for instance antidepressants, non-pharmacological approaches for instance enteral feeding or a combination of both (Radunovic et al., 2007).

There is increasing emphasis on delivery of co-ordinated care within a multidisciplinary environment where neurologists, MND specialist nurses, physiotherapists, occupational therapists, speech and language therapists, dieticians, respiratory physicians, gastroenterologists, social workers and palliative care services work in close collaboration (Chio et al., 2006; Ng et al., 2009; Traynor et al., 2003). The understanding that involvement of multidisciplinary team allows timely institution of individualised supportive care has led to development of MND clinics and care centres

where health care delivery is based on the interdisciplinary care paradigm (Chio et al., 2006; Ng et al., 2009; Traynor et al., 2003). There is some evidence to suggest that multidisciplinary care may improve QOL, possibly due to the delivery of co-ordinated care (Ng et al., 2009; Van den Berg et al., 2005).

In the absence of a cure, supportive care and advance care planning are important management strategies and should be discussed with patients and relatives at the earliest opportunity (Bede et al., 2011; Ray et al., 2014). There is international consensus on ensuring excellence in end of life care as an important focus of management, particularly because disability is relentlessly progressive and death generally occurs in a predictable fashion (Bede et al., 2011; Mitsumoto et al., 2005).

Advance care planning helps to identify and honour care preferences of patients (Bede et al., 2011; Chhetri et al., 2015; Mitsumoto et al., 2005). In addition, advance care planning also empowers patients to gain control over their end of life care and enables them to die at their preferred place of death (Chhetri et al., 2015; Ray et al., 2014). Advance care planning should therefore begin soon after diagnosis and continue throughout the disease trajectory as an integral part of holistic care in MND (Bede et al., 2011; Chhetri et al., 2015; Ray et al., 2014).

1.15.1 Disease modifying therapy

Riluzole, an inhibitor of glutamate release, is the only disease modifying therapy licensed for use in MND. Glutamate is an excitatory neurotransmitter in the central nervous system that accumulates in toxic concentrations at synapses and causes death of motor neurones which are susceptible to excitotoxicity (Bensimon et al., 1994; Rothstein, 2009). Riluzole presynaptically inhibits the release of excitotoxic glutamate and also blocks some of the postsynaptic effects of glutamate (Bensimon et al., 1994).

Two large randomised controlled trials have demonstrated that use of riluzole extends survival by 3 to 6 months (Bensimon et al., 1994; Lacomblez et al., 1996). However, only patients with ALS participated in these trials and the therapeutic benefit of riluzole in other MND phenotypes remains unknown.

1.15.2 Respiratory management

Neuromuscular respiratory insufficiency leading to respiratory failure is a common cause of death (Radunovic et al., 2007). A high index of suspicion is required to identify early respiratory involvement (Gautier et al., 2010). Assessment of respiratory function includes overnight pulse oximetry, early morning arterial blood gas analysis and pulmonary function tests, particularly forced vital capacity (Miller et al., 2009).

Non-invasive ventilation (NIV) has been demonstrated to improve survival and QOL (Bourke et al., 2006; Radunovic et al., 2007). In a randomised trial of NIV in 41 participants, there was an average increase in survival of 48 days among ventilated patients (Bourke et al., 2006). The survival advantage was much greater (205 days) in patients with normal or only moderately impaired bulbar function. No survival benefit was seen in patients with poor bulbar function but NIV significantly improved sleep related symptoms (Bourke et al., 2006).

The randomised controlled trial also demonstrated an improved QOL in addition to survival benefit (Bourke et al., 2006). QOL was measured by using the short form 36 and the symptoms domain of the sleep apnoea quality-of-life index. The QOL in the NIV group was maintained above 75% of baseline during the study period and the QOL benefits exceeded the improvement in survival. The authors concluded that NIV improved survival and QOL rather than prolonging suffering (Bourke et al., 2006).

Practice guidelines recommend that NIV should be considered to treat respiratory insufficiency in MND (Andersen et al., 2012; Miller et al., 2009). There has been a sustained improvement in respiratory management of patients with MND and domiciliary provision of NIV has become an important facet of symptomatic management in MND (Kiernan et al., 2011; Wijesekera et al., 2009).

1.15.3 Nutritional management

Malnutrition is an independent prognostic factor for survival in MND with an eight fold increased risk of death (Desport et al., 1999; Marin et al., 2011). MND is associated with altered nutritional state, energy intake and energy expenditure. Nutritional state has prognostic value for survival at various stages of the illness: at the time of diagnosis (Marin et al., 2011), at the time of gastrostomy placement (Desport et al., 2000) or during the course of the disease (Stambler et al., 1998).

Weight loss from baseline of 5% or more at the time of diagnosis is associated with a twofold increased risk of death (Marin et al., 2011). Body mass index of less than 18.5 kg/m^2 at the time of gastrostomy placement is an unfavourable prognostic factor (Desport et al., 2000). Malnutrition and weight loss is a frequent phenomenon in MND and occurs in approximately 55% of patients with the condition (Mazzini et al., 1995).

Patients may not be able to meet their nutritional needs for a number of reasons including motor weakness interfering with self-feeding and meal preparation, reduced caloric intake, dysphagia, anxiety, depression, respiratory insufficiency and hypermetabolism (Bouteloup et al., 2009; Desport et al., 2000; Greenwood, 2013; Heffernan et al., 2004). Hand weakness slows eating and makes patients dependent on others for preparing meals and in feeding the patients (Radunovic et al., 2007).

Weakness of the tongue and pharyngeal muscles impair swallowing (Simmons, 2005). Anxiety and depression can lead to anorexia (Radunovic et al., 2007).

The energy intakes are below recommended dietary allowances in more than 70% of patients (Genton et al., 2011). Hypermetabolism resulting from a number of factors including include greater effort of breathing, muscle fasciculations and frequent infections, for instance, aspiration pneumonia leads to increased resting energy expenditure (Bouteloup et al., 2009).

Bulbar muscles involved in speech and swallowing are initially involved in 25% of patients with MND, but eventually majority of patients experience bulbar involvement. There is progressive difficulty in swallowing leading to aspiration pneumonia, distressing choking, prolonged effortful meal times, weight loss, malnutrition and/or dehydration (Heffernan et al., 2004; Simmons, 2005). Malnutrition further aggravates muscle weakness and respiratory function (Greenwood, 2013). Nutritional insufficiency may evolve gradually and asymptomatically, and therefore, a proactive approach for early recognition and intervention may delay the attendant complications (Kasarskis et al., 2011).

Nutritional assessment is recommended on a three monthly basis through measurement of body weight (Miller et al., 2009). The various strategies to maintain appropriate caloric intake include use of nutritional supplements for instance high protein and caloric diets, adjustments in diet consistency and the use of feeding techniques, such as chin tuck and taking small meals (Andersen et al., 2012; Hardiman, 2000; Heffernan et al., 2004). With inevitable disease progression, these measures become insufficient and enteral feeding may be needed (Greenwood, 2013; Miller et al., 2009).

1.16 Enteral feeding in motor neurone disease

Enteral feeding refers to delivery of any form of nutrition through a tube which may include nasogastric, gastrostomy or jejunostomy tube placed in the upper gastrointestinal tract (Kirby et al., 1995; Koretz et al., 2007). The American Academy of Neurologists (AAN) and European Federation of Neurological Societies (EFNS) recommend enteral feeding in MND (Andersen et al., 2012; Miller et al., 2009). However, there is a lack of consensus on the appropriate timing of feeding tube insertion (Katzberg and Benatar, 2011).

Practice guidelines state that enteral nutrition should be considered in patients with dysphagia and/or decline in nutritional state (as indicated by weight loss of more than 10% from pre-morbid weight or body mass index of less than 18.5 kg/m^2) and while forced vital capacity is more than 50% of predicted value (Andersen et al., 2012; Desport et al., 2000; Miller et al., 2009). The common methods of delivering enteral nutrition in MND includes use of nasogastric tube, percutaneous endoscopic gastrostomy (PEG) tube (Figure 1.12) or radiologically inserted gastrostomy (RIG) tube (Katzberg and Benatar, 2011; Miller et al., 2009).

Nasogastric tube feeding offers a short term feeding measure, but the evidence for long term nutritional support is not as favourable as gastrostomy tube feeding due to high risk of aspiration pneumonia and inconveniences, particularly in patients with increased oropharyngeal secretions, drooling and choking (Heffernan et al., 2004; Scott and Austin, 1994).

Percutaneous endoscopic gastrostomy tube feeding is the most commonly used method for long term nutritional maintenance in MND (Heffernan et al., 2004; Silani, 1998). PEG tube insertion is a commonly performed procedure by a trained endoscopist under

conscious sedation. Risks of the procedure include pain, aspiration pneumonia, respiratory arrest, laryngeal spasm, localized infection, bowel perforation, gastric haemorrhage and placement failure due to technical difficulties (Mazzini et al., 1995; Thornton et al., 2002).

The morbidity and mortality rates associated with PEG placement increases when a patient has significant respiratory impairment as indicated by a forced vital capacity of less than 50% (Kasarskis et al., 1999; Mazzini et al., 1995). Under these circumstances RIG may be safer than PEG (Blondet et al., 2010; Chio et al., 2004).

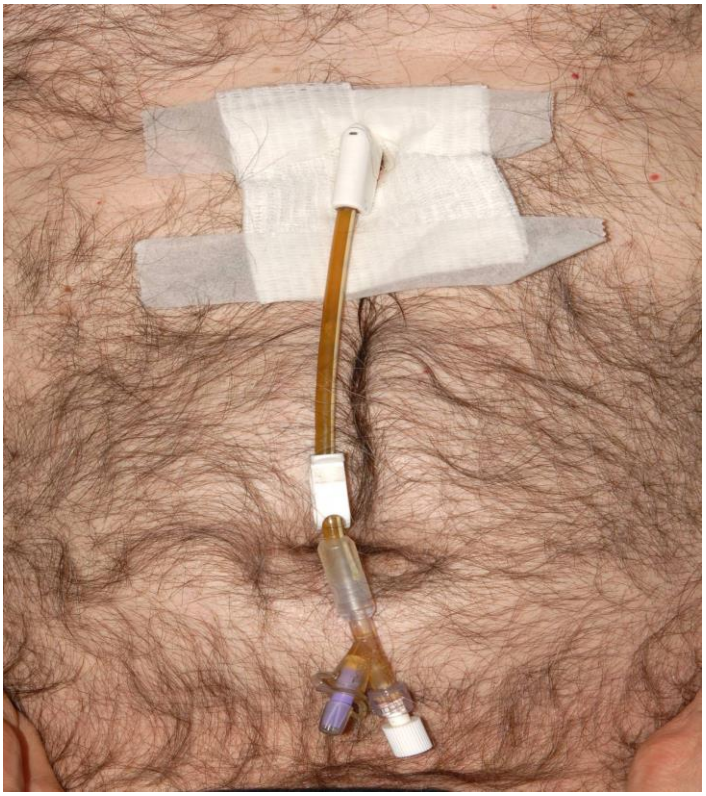

Figure 1.12: Photograph showing percutaneous endoscopic gastrostomy tube in situ (printed with patient's consent)

RIG is performed under fluoroscopic guidance through percutaneous access and does not need endoscopy or conscious sedation, thereby reducing the risks of respiratory

insufficiency (Chio et al., 2004). However, there is increased risk of tube obstruction as the tube is of smaller diameter than the PEG tube (Chio et al., 2004). Only few studies have compared RIG with PEG (Allen et al., 2013; Blondet et al., 2010). RIG therefore needs further validation in the MND cohort through prospective randomized studies (Allen et al., 2013; Blondet et al., 2010).

A relatively new hybrid gastrostomy technique, per-oral image-guided gastrostomy (PIG) has been developed as an effective alternative method of gastrostomy insertion with a higher success and lower re-intervention and complication rates (Laasch et al., 2003). In this procedure, the stomach is punctured under fluoroscopic guidance and the oesophagus is catheterised in a retrograde technique with the aid of a guide wire. The gastrostomy tube is then fed over the guide wire, through the mouth into the oesophagus and finally brought out through the abdominal wall (Laasch et al., 2003).

PIG combines the advantages of both PEG and RIG while minimising their disadvantages (Laasch et al., 2003). It is performed under minimal conscious sedation or local anaesthesia and obviates the need for endoscopic intubation (Chavada et al., 2010; Laasch et al., 2003). A large bore feeding tube can be used and this reduces the risk of tube blockage and migration (Chavada et al., 2010; Stavroulakis et al., 2013). Preliminary evidence suggests that PIG could be a safe, well tolerated and reliable alternative method for gastrostomy insertion in MND (Chavada et al., 2010).

1.17 Working hypothesis

Enteral feeding improves QOL of patients with MND through management of dysphagia and/or malnutrition.

1.18 Main Aim of the study

The main aim of the study was to assess the impact of enteral feeding on survival, nutritional status and QOL of patients with MND.

1.19 Objectives of the study

1. To undertake a systematic literature review regarding the impact of enteral feeding on survival, nutritional status and QOL of patients with MND.
2. To investigate epidemiology, demographics, clinical and survival characteristics of MND in Lancashire and South Cumbria in North West England through an eight year retrospective review of the Preston MND database and patient case notes.
3. To evaluate the impact of enteral feeding on survival through an eight year retrospective review of Preston MND database and patient case notes.
4. To examine change in nutritional status through measurement of body mass index at the time of diagnosis, gastrostomy insertion, and 3, 6 and 12 months following enteral feeding.
5. To explore patients' perspectives about enteral feeding and its impact on their quality of life through a thematic analysis of their experiences with enteral feeding.
6. To analyse the data and write up the MD thesis.

CHAPTER 2

OUTCOMES OF ENTERAL NUTRITION:

A SYSTEMATIC REVIEW

2.1 Introduction

This chapter presents a systematic review undertaken to identify and to analyse results from research studies on the impact of enteral feeding on survival, nutritional status and QOL in patients with MND. A systematic review aims to answer a defined research question by systematically identifying, appraising and synthesising all relevant high quality research evidence that fits the pre-specified eligibility criteria (Akobeng, 2005; Cook et al., 1997).

The use of explicit and reproducible methods in undertaking a systematic review limits bias, generates reliable conclusions and allows comparison of a number of studies to establish consistency and generalisability of findings (Akobeng, 2005; Cook et al., 1997). Systematic reviews may identify areas that lack adequate evidence and/or areas where further research is needed (Cook et al., 1997; Greenhalgh, 1997).

A preliminary, non-systematic literature search did not identify any randomised controlled trials of enteral feeding in MND. However, without a comprehensive and meticulous search, it would be inappropriate to conclude that none have been undertaken. A systematic review has therefore been undertaken in this thesis to ascertain the best available evidence on the impact of enteral feeding on survival, nutritional status and QOL of patients with MND. The systematic review was also intended to identify areas of research that would subsequently become the focus of this thesis.

2.2 Aim of systematic review

The main aim of systematic review was to systematically identify and review research studies on enteral feeding and their outcomes in patients with MND.

2.3 Objectives of systematic review

The three main objectives of the systematic review were to systematically identify and review results of research studies investigating the impact of enteral feeding on:

1. Quality of life
2. Nutritional status
3. Survival

2.4 Methodology

2.4.1 Inclusion criteria

Types of studies

All studies including randomised controlled trials, quasi-randomised trials, prospective and retrospective studies investigating the effectiveness of enteral feeding in MND were reviewed.

Target population

Patients diagnosed with definite, possible, or probable MND according to the El Escorial criteria (Brooks, 1994) or revised El Escorial criteria (Brooks et al., 2000) that had undergone feeding tube insertion were included in the review.

Types of Intervention

The review looked into all studies, both retrospective and prospective, that reported placement of any form of feeding tube including nasogastric, gastrostomy or jejunostomy tubes during the course of the illness.

2.4.2 Exclusion Criteria

Articles published in languages other than English were excluded, as there were no resources for translation of these articles. Studies that were only published as abstracts were excluded because of the limited data that could be extracted.

2.5 Outcome measures

Primary outcome measure

The primary outcome was self-perceived quality of life assessed with or without quality of life scale.

Secondary outcome measures

The secondary outcomes were:

1. Survival time either from symptom onset, time of diagnosis or feeding tube placement.

2. Change in nutritional status measured by body weight or body mass index.

2.6 Search Strategy

A search strategy was developed to search MEDLINE from 1966 to July 2014, and adapted to search EMBASE for all studies reporting enteral feeding in MND using 'amyotrophic lateral sclerosis', 'motor neurone disease', 'motor neuron disease', 'Lou Gehrig', 'gastrostomy', 'percutaneous endoscopic gastrostomy', 'PEG' 'enteral feeding', 'enteral nutrition', 'nasogastric feeding', 'radiologically inserted gastrostomy', 'RIG', and 'feeding tube', as search terms.

Citations were initially screened on title and those retained were screened on abstract. This was carried out independently by the author. If the information was inadequate to decide whether the article should be included in the review, the full paper was obtained. Any published article that appeared to meet the inclusion criteria was read in full. The published articles were also checked to identify any further articles of relevance. The MEDLINE and EMBASE search strategies are outlined in Appendix 1 and 2.

2.7 Data collection and analysis

The data from identified studies were extracted into a word document (Table 2.1). For each article included in the review, summary data were recorded including author, year of publication, type of study, number of patients in each group (enteral feeding versus no enteral feeding), QOL benefit from enteral feeding, nutritional benefit from enteral feeding, survival benefit from enteral feeding and control for potential confounders including onset site and riluzole use. The results are presented narratively because the published studies were heterogeneous in terms of their methodologies, outcome measures and confounders.

2.8 Results

The literature search identified a total of 615 articles and from these, 309 duplicates were removed. Following screening of the title, abstract or complete article, 19 remaining studies met the inclusion criteria. There were no randomized or quasi-randomised controlled trials. 4 studies were prospective and the remaining retrospective in nature. Figure 2.1 outlines the results of the search. The studies meeting the inclusion criteria are summarised in table 2.1.

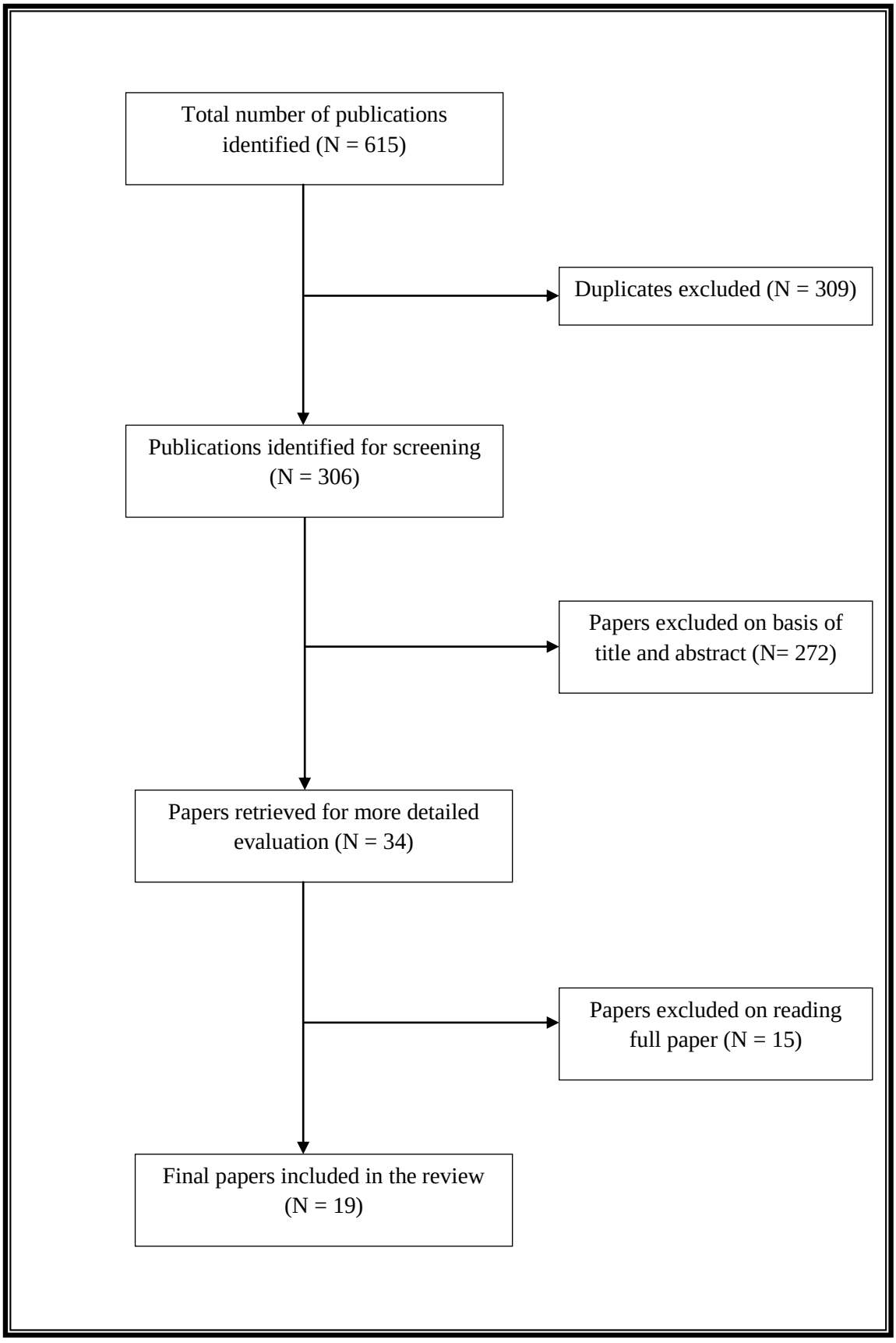

Figure 2.1: Flow diagram showing the summary of methodology for the systematic review of outcomes of enteral feeding in MND.

Table 2.1: Table showing the summary of studies included in the systematic review

Author Year	Study type	No of patients	Quality of life benefit	Nutritional benefit	Survival benefit
Mathus-Vliegen et al. (1994)	Prospective cohort	55 gastrostomy vs 13 oral feeding/ nasogastric feeding	Not reported	Not reported	No
Mazzini et al. (1995)	Prospective cohort	31 gastrostomy vs 35 oral feeding	Anecdotal benefit only	Yes	Yes
Strong et al. (1999)	Case control	73 gastro-jejunostomy vs 293 oral feeding	Not reported	Not reported	No
Chio et al. (1999)	Case control	50 gastrostomy vs 100 oral feeding	Not reported	Yes but observati-onal only	Yes
Kasarskis et al. (1999)	Retrospective cohort	172 gastrostomy	Not reported	Yes but observati-onal only	Not reported
Desport et al. (2000)	Case control	30 gastrostomy vs 30 oral feeding	Not reported	Yes	No
Mitsumoto et al. (2003)	Case control	137 gastrostomy vs 187 oral feeding	17% improved mental wellbeing	Yes but observati-onal only	No
Forbes et al. (2004)	Case control	142 gastrostomy vs 1084 oral feeding	Not reported	Not reported	No

Chio et al. (2006)	Prospective cohort	52 gastrostomy vs 169 oral feeding	Not reported	Not reported	Yes
Czaplinski et al. (2006)	Case control	275 gastrostomy vs 766 oral feeding	Not reported	Not reported	Yes
Mitchell et al. (2006)	Case control	127 gastrostomy versus 348 oral feeding	Not reported	Not reported	No
Sorenson et al. (2007)	Case control	12 gastrostomy vs 28 oral feeding	Not reported	Not reported	No
Murphy et al. (2008)	Prospective cohort	57 gastrostomy vs 187 oral feeding	Not reported	Not reported	No
Lou et al. (2010)	Retrospective cohort	52 gastrostomy	Yes	Not reported	Not reported
Spataro et al. (2011)	Case control	76 gastrostomy vs 74 oral feeding	Not reported	Not reported	Yes
Atassi et al. (2011)	Case control	38 gastrostomy vs 262 oral feeding	Not reported	Not reported	No
Zamietra et al. (2012)	Case control	11 gastrostomy vs 6 ventilation and 5 gastrostomy and ventilation	No	Not reported	Not reported
Zhang et al. (2012)	Case control	31 gastrostomy vs 35 oral feeding	Not reported	Yes, observati-onal only	No
Georgoulopoulou et al. (2013)	Case control	95 gastrostomy vs 98 oral feeding	Not reported	Not reported	No

2.9 Measurement scales used in the identified studies

A number of measurement scales were used for evaluation of QOL. The following scales were used in the identified studies:

Short Form-12 health survey

The Short Form-12 (SF-12) health survey consists of 12 questions designed to rate a number of aspects of a patient's mental and physical functioning (Ware et al., 1996). The questionnaire is self-administered and involves the patient responding, for the most part, on 'Likert'-type response scales although there are some simple 'yes/no' responses on some domains (Ware et al., 1996).

Mini-Sickness Impact Profile

The Mini-Sickness Impact Profile consists of a subset of 19 yes or no questions from the Sickness Impact Profile (SIP), which is a general functional status instrument comprising 136 items (Bergner et al., 1981; McGuire et al., 1997). The questions encompass physical, psychological and social domains of QOL.

Single Item McGill Quality of Life Scale

The Single Item McGill Quality of Life Scale (MQOL-SIS) is an item in the McGill Quality of Life (MQOL) questionnaire asking subjects to rate their overall QOL on a scale from 0 (very bad) to 10 (excellent). The MQOL questionnaire has 16 other questions divided into five domains: physical symptoms, physical well-being, psychological, existential, and support (Cohen et al., 1995; Cohen et al., 1996). Each question is rated from 0 (very bad) to 10 (excellent).

Amyotrophic Lateral Sclerosis Specific Quality of Life Instrument - Revised

The Amyotrophic Lateral Sclerosis Specific Quality of Life Instrument-Revised (ALSSQOL-R) is a 50-item ALS specific QOL instrument that is completed by an individual with MND (Simmons et al., 2006). Each item is rated by the individual using a 0 to 10 point Likert scale, with 0 being the least desirable situation and 10 being the most desirable situation in six different domains: negative emotion; interaction with people and the environment; intimacy; religiosity; physical symptoms and bulbar function.

Amyotrophic Lateral Sclerosis Functional Rating Scale-Revised

The Amyotrophic Lateral Sclerosis Functional Rating Scale-Revised (ALSFRS-R) is a validated 12 item scale that measures bulbar function, upper extremity function, lower extremity function and respiration in patients with MND (Cedarbaum et al., 1999). Each item is scored from 0 (poorest function) to 4 (normal function) and the scores are added to generate a total score from 0 (worst function) to 48 (normal function). The bulbar subscale consists of the domains of swallowing, speech and salivation with each item rated from 0 which indicates marked dysfunction to 4 which implies normal function.

The ALSFRS-R is widely used for evaluation of functional and clinical status of MND patients (Kollewe et al., 2008). The questionnaire is easy to administer, sensitive and clinically meaningful and can be completed by the patient or caregiver or administered by the clinician or a trained evaluator (Gordon et al., 2004; Miano et al., 2004).

The scale is patient rather than clinician centered and measurements are therefore undertaken from a patient's perspective (Kaufmann et al., 2005). It is also a cost

effective way of measuring functional status as it does not require any special equipment unlike other measures like muscle strength testing (Gordon et al., 2004).

The scale is reliable and reproducible with a number of favourable properties including high internal consistency, test-retest reliability and construct validity (Cedarbaum et al., 1999; Gordon et al., 2004). It also has excellent inter-rater and intra-rater reliability (Kaufmann et al., 2007; Miano et al., 2004). There is high consistency and the change in scores over time closely parallels change in other measures, including muscle strength testing and forced vital capacity (Brooks et al., 1996; Cedarbaum and Stambler, 1997).

The scale has been validated for administration over the telephone and internet and highly correlates with in-clinic administration (Kasarskis et al., 2005; Maier et al., 2012). The assessment can also be completed by communicating with the spouse/caregiver over the phone. This provides flexibility as it can be administered to patients who are unable to attend the clinic (Kasarskis et al., 2005; Maier et al., 2012). The instrument has also been validated for self-administration (Montes et al., 2006). The ALSFRS-R scores can also be accurately reproduced from information in clinic notes and therefore, is a useful research tool in retrospective studies (Lechtzin et al., 2009).

The ALSFRS-R also predicts survival outcomes in both clinic and trial settings (Kimura et al., 2006). Baseline ALSFRS-R scores are predictive of survival time in both clinical trial and clinic settings with higher scores indicative of a worse prognosis (Cedarbaum et al., 1999; Kaufmann et al., 2005). The ALSFRS-R scores also predict length of hospital stay and survival of patients on mechanical ventilation (Lo Coco et al., 2007).

The ALSFRS-R, however, has few limitations. The ALSFRS-R may not accurately reflect changes in QOL which may be may be maintained despite deterioration in

physical function (Robbins et al., 2001). Finally, the scale does not include items to assess cognitive function which may occur in more than 40% of patients with MND (Phukan et al., 2012). Despite these limitations, ALSFRS-R has a number of favourable properties and is a widely used tool in both clinical and research settings (Gordon et al., 2004; Kollewe et al., 2008).

The Norris scale

The Norris scale is a 100 point clinical and functional rating scale for assessing disease progression in MND and consists of 22 items in various domains including the bulbar, limb and respiratory functions (Norris Jr et al., 1974).

2.10 Quality of life outcomes of enteral nutrition

The systematic review identified only four studies reporting changes in self-perceived QOL after enteral nutrition, of which only one was prospective (Mazzini et al., 1995) and the remaining retrospective in nature (Lou et al., 2010; Mitsumoto et al., 2003; Zamietra et al., 2012).

In a prospective cohort study of 31 MND patients undergoing gastrostomy insertion, Mazzini et al. (1995) reported anecdotal impressions from patients about their improved QOL following gastrostomy feeding. The patients were interviewed by a Psychologist on a three monthly basis over a two year period to assess their QOL. However, the authors do not convey any concrete data relating to their observations.

Mitsumoto et al. (2003) compared QOL of 137 patients who had received enteral feeding versus 187 patients who continued to feed orally. This was a retrospective study aimed at evaluating clinical characteristics of MND patients with and without

gastrostomy. A cut off score of ≤ 5 on the bulbar subscale of the ALSFRS was used to select the cases and controls. Health status of the patients had been recorded using the generic SF -12 health survey and the mini-sickness impact profile.

Only 17% of the patients reported improved psychological wellbeing and 28% reported less fatigue or less time spent on meals and medications (Mitsumoto et al., 2003). The physical and mental domains of the SF-12 health status scale were similar in both groups. Patients with gastrostomy feeding experienced poorer health status ($p=0.0047$) on the mini-sickness impact profile scale as compared to those who continued to feed orally. However, the bulbar sub scores were significantly lower ($p<0.0001$) in the gastrostomy group indicating that gastrostomy was performed too late to demonstrate a positive impact on QOL (Mitsumoto et al., 2003).

Lou et al. (2010) undertook a retrospective study to investigate the correlates of QOL including enteral feeding in patients who participated in the minocycline trial. This was a double-blinded, placebo-controlled drug trial of 412 subjects aimed at assessing the efficacy of minocycline as a treatment for MND. QOL was evaluated using the MQOL-SIS. A total of 52 patients received PEG feeding during the trial and the authors compared the slopes of MQOL-SIS before and after PEG tube insertion. In each of the study subjects, at least three data points before and after PEG placement was obtained. The authors reported a statistically significant reduction ($p<0.001$) in the rate of decline on the MQOL-SIS, suggesting that PEG feeding improves QOL.

Zamietra et al. (2012) retrospectively reviewed 11 patients who had received PEG feeding. They compared the PEG group to a cohort of 6 patients who had received non-invasive positive pressure ventilation and another cohort of 5 patients who had received both PEG feeding and non-invasive positive pressure ventilation. The overall QOL had

been measured using the ALSSQOL-R. The QOL assessments had been obtained at the last routine clinic visit prior to intervention and for two consecutive visits following gastrostomy insertion, usually on a three monthly basis. ALSSQOL-R was relatively stable over time in all three groups. Although the QOL in the gastrostomy group deteriorated marginally over time, the difference was not statistically significant. However, this is a small observational study lacking a control group and the patients were not specifically asked about the impact of enteral feeding on their QOL.

2.11 Nutritional outcomes of enteral feeding

A total of 6 studies reported nutritional outcomes in association with enteral feeding. In a prospective study, Mazzini et al. (1995) reported statistically significant improvement in nutritional status of 31 patients undergoing enteral feeding as compared to a control group of 35 patients who refused gastrostomy. Gastrostomy placement was proposed to 69 cases with mild or severe dysphagia and weight loss of more than 5% of their normal body weight. The procedure was unsuccessful in three patients who had difficulty in opening their mouth because of spasticity. The average weight gain after a year of enteral feeding was 2.5 kilograms. Following enteral feeding, the BMI increased by 0.5 points over a period of 12 months as compared to a decrease of 4.5 points in the group who continued to feed orally.

In a case control study aimed at investigating the safety and factors related to survival after PEG, Chio et al. (1999) matched 50 MND patients undergoing gastrostomy feeding with 100 historical controls without gastrostomy for age at diagnosis, site of onset and severity of disease as indicated by the forced vital capacity and Norris score at diagnosis. 35 patients with enteral feeding survived more than 90 days, of which 71%

gained weight (from 5.3 to 9.6%) with weight stabilisation in the remainder. However, no comparison was made with the control group in terms of change in nutritional status.

Kasarskis et al. (1999) performed a retrospective analysis of MND patients participating in clinical trials to determine their clinical profile at the time of gastrostomy and define prognostic factors for early mortality following gastrostomy placement. A total of 136 patients in the Brain Derived Neurotrophic Factor (BDNF) study and 36 placebo patients in the Ciliary Neurotrophic Factor (CNTF) study received gastrostomy feeding during the study period. Patients were evaluated on a monthly basis for nine months in both studies. BMI was recorded in each visit. Two pre-gastrostomy and two post-gastrostomy visits were undertaken to assess trends in BMI. A significant stabilization ($p=0.0001$) in BMI was noted following enteral feeding. This was however an observational study, as the clinical trials were not designed to assess the nutritional benefit of enteral feeding.

In a retrospective study comparing 30 patients who underwent enteral feeding with 30 patients who did not receive enteral nutrition, Desport et al. (2000) reported a significant nutritional advantage in the patients undergoing gastrostomy insertion. A significant weight gain of 8% ($p<0.02$) was noted in the cohort receiving enteral feeding. However, the authors do not report the clinical characteristics of the control group. It is also unclear whether the patients in the control group refused gastrostomy or had no indications to necessitate enteral feeding.

Mitsumoto et al. (2003) reported an average weight gain of 2.9 kilograms in 137 patients with enteral feeding. The patients were identified from the American ALS patient care database. This was, however, an observational finding and the change in

nutritional status was not compared with the control group of 187 patients who continued to feed orally.

Zhang et al. (2012) reported weight stabilisation at 3 and 6 months in 31 patients receiving enteral feeding as compared to 35 patients without enteral feeding. The BMI was 22.6 ± 2.2 kg/m^2 at 3 months and 22.5 ± 2.0 kg/m^2 at 6 months following gastrostomy as compared to a BMI of 22.5 ± 3.0 kg/m^2 at the time of gastrostomy placement. However this was not sustained and weight loss recurred in the terminal stages of the illness.

2.12 Survival outcomes of enteral feeding

A number of studies reporting survival outcomes of enteral feeding in MND were identified. Some of these studies were prospective and others retrospective in nature. However, none of these studies were primarily designed to assess the impact of enteral feeding on survival.

Mathus-Vliegen et al. (1994) prospectively investigated the use of PEG in 68 MND patients with impaired pulmonary function. Patients were required to have adequate pulmonary function as indicated by a FVC of 1 litre or more to be considered for PEG. A total of 55 patients received PEG while 13 patients were considered ineligible due to impaired pulmonary function. There was no significant survival advantage with PEG feeding. Median survival from symptom onset in the PEG group was 31.8 months as compared to 29.6 months in the group not eligible for PEG. However, 6 of the 13 ineligible patients underwent nasogastric feeding and this introduces a bias in assessing the survival benefit of enteral feeding. The absence of any survival advantage is therefore questionable because of this methodological bias.

Mazzini et al. (1995) prospectively compared survival of 31 patients undergoing PEG feeding with 35 control patients. PEG was offered to patients with mild or severe dysphagia and weight loss of more than 5% of their usual body weight. The control group had refused PEG. Significant survival advantage was noted with enteral feeding ($p<0.03$). Patients in the PEG cohort had a mean survival of 38 months from symptom onset as compared to 30 months for the control group. There was no significant difference in mortality between the two groups for the first 6 months but a notable difference was observed at 12 months ($p<0.05$) and 24 months ($p<0.001$) post gastrostomy. It is unclear whether the illness was of limb or bulbar onset in both the groups. Patients with limb onset illness have a better prognosis (Chio et al., 2009a; del Aguila et al., 2003), and the lack of matching in this study introduces a potential bias.

Chio et al. (1999) investigated survival in a case control study of 50 patients with and without PEG feeding. The PEG group were matched with 100 historical controls without gastrostomy. The median survival time after PEG feeding was 185 days. The median survival time from diagnosis in the PEG cohort was 915 days as compared to 760 days in the control group. Multivariable analysis demonstrated significant survival advantage both in the whole PEG cohort and bulbar onset patients, but not in spinal onset patients. The cohort without PEG had a hazard ratio of 1.55 (95% CI 1.28-1.88, $p=0.02$). Bulbar onset patients not receiving enteral feeding had a hazard ratio of 1.83 (95% CI 1.39-2.40, $p=0.02$).

Strong et al. (1999) undertook a retrospective review of percutaneous gastro-jejunostomy feeding in MND. Survival of 73 patients with enteral feeding was compared against 293 patients who did not require nutritional support. A negative survival advantage was noted with enteral feeding. The median survival in gastro-jejunostomy group was 22 months for bulbar onset as compared to 30 months in the

control group ($p<0.001$). Similarly, the median survival in the limb onset group was 24 months with gastro-jejunostomy and 35.5 months in the control group. The survival difference in the limb onset group was not statistically significant. The study subjects were, however, not matched with the control group for confounders. Moreover, the control group did not require nutritional support indicating that they had a better nutritional status as compared to patients requiring enteral feeding.

In a retrospective study comparing 30 patients who underwent enteral feeding with 30 patients who did not receive enteral nutrition, Desport et al. (2000) found no survival advantage with enteral feeding. However, the authors do not report the clinical characteristics of the control group. Moreover, it is unclear whether the patients in the control group refused gastrostomy or did not require enteral feeding.

In a retrospective multi-centre study, Mitsumoto et al. (2003) compared survival of 137 patients with PEG feeding against 187 patients with oral feeding. The controls were matched for bulbar dysfunction as indicated by a cut-off point of ≤ 5 in the bulbar subscale of ALSFRS. The majority of those who did not receive enteral nutrition had refused PEG. No survival advantage was noted with enteral feeding ($p=0.33$). The average survival from symptom onset was 47 months in the PEG group as compared to 58 months in the control group. However, there was marked variability in the use of gastrostomy among participating centres raising the possibility of physician bias in recommending enteral feeding. Moreover, the bulbar sub scores were significantly lower in the PEG group ($p<0.0001$) indicating that gastrostomy was performed too late to demonstrate survival benefits.

Forbes et al. (2004) retrospectively analysed 1226 patients in the Scottish MND Register of which 142 had received gastrostomy feeding. The authors found no

evidence of improved survival following enteral feeding. The median survival in the gastrostomy group was 759 days as compared to 752 days in the control group. However, the two groups were not matched for various confounding factors including forced vital capacity and bulbar dysfunction.

In a retrospective cohort study of 1041 patients of which 275 had undergone gastrostomy insertion, Czaplinski et al. (2006) demonstrated significantly improved survival with enteral feeding in a multivariate model (hazard ratio 0.75, CI 0.63 to 0.90, p=0.003). The authors, however, analysed the median survival from symptom onset rather than from the point of gastrostomy. They attributed this limitation to the database not being adequate for identifying the timing of gastrostomy placement. The lack of survival statistics from the point of gastrostomy makes it difficult to ascertain the true impact of enteral feeding on survival.

Chio et al. (2006) prospectively followed 221 patients over a two year period during which 52 patients underwent placement of PEG tube. Patients not receiving gastrostomy feeding had a hazard ratio of 3.38 for death as compared to 52 patients with gastrostomy (p=0.0006). The indication for PEG feeding has not been defined in the paper. It therefore remains unclear whether the clinical characteristics of the PEG cohort were similar or different to the group not receiving PEG.

Mitchell et al. (2006) retrospectively reviewed the records of 625 patients to audit the outcomes of use of riluzole in MND. The demographic and survival characteristics of 475 patients with adequate clinical information were analysed. A total of 127 patients had received PEG and 348 continued to feed orally. No significant survival advantage was noted with PEG feeding (hazard ratio=0.59; 95% CI 0.22 to 1.61, p=0.30). The

indications and timing of PEG placement have not been mentioned in the paper. It also remains unclear what proportion of the patients with missing data had received PEG.

In a retrospective study examining the incidence of aspiration pneumonia in 40 patients with MND, Sorenson et al. (2007) reported no significant survival difference between 12 patients with PEG feeding and 28 patients who continued to feed orally. The two groups were however not matched for possible confounders.

In a 22 year prospective study, Murphy et al. (2008) followed 244 patients with definite or probable MND. 57 patients underwent PEG insertion. The average time from PEG insertion to death was 7.4 months. The median survival from symptom onset for the whole cohort was 27.6 months. There was no survival advantage with enteral feeding when compared to those who continued to feed orally. However, the groups were not matched and the authors have not outlined the indications for gastrostomy.

In a post-hoc analysis of prospectively collected data from clinical trials of celecoxib and coenzyme Q10 in MND, Atassi et al. (2011) reviewed data of 300 subjects of which 38 had received gastrostomy feeding. The authors reported increased mortality hazard of 0.28 ($p=0.02$) in the gastrostomy cohort. The patients were, however, followed up for an average of 3.8 months only. Given the short follow up period, it is difficult to ascertain the true impact of enteral feeding as survival advantage is often not noticed until 6 months after gastrostomy placement (Mazzini et al., 1995).

In a retrospective study of 150 patients, Spataro et al. (2011) evaluated the effect of PEG feeding on survival of patients with dysphagia. Patients were dichotomised into two groups depending on whether they accepted or declined PEG. 76 patients received PEG of which 37 had bulbar and 39 limb onset illness. Survival advantage with enteral feeding was noted in limb onset cases only with a median survival of 44 months as

compared to 36 months without PEG (p=0.046). However, the diagnostic delay in the PEG group was 10.6 ± 8.3 months as compared to 14.8 ± 14 months in the control group (p=0.026). It therefore remains unclear whether the reported survival advantage was due to enteral feeding or active management as earlier diagnosis and timely access to multidisciplinary care is an independent prognostic factor for survival (Chio et al., 2006; Traynor et al., 2003).

Enteral feeding was associated with a trend towards longer survival in 31 patents with dysphagia as compared to 35 dysphagic patients who either refused the procedure, died before PEG placement or were not medically fit for the procedure (Zhang et al., 2012). The results were, however, not statistically significant (p=0.089). The findings have questionable significance because of methodological bias when comparing survival with a group where 9 deaths occurred even before placement of the PEG tube.

Georgoulopoulou et al. (2013) retrospectively investigated the impact of clinical factors and therapeutic interventions on survival of 193 patients with MND. Survival of 95 patients receiving enteral nutrition was compared with 98 patients who continued oral feeding. There was no survival advantage with enteral feeding. However, the indication for enteral feeding and timing of PEG placement has not been described in the paper. It also remains unclear whether gastrostomy was performed too late to demonstrate survival benefits.

2.13 Discussion and Conclusion

The impact of enteral feeding on QOL and survival of patients with MND is an issue of debate (Katzberg and Benatar, 2011; Miller et al., 2009). There are no randomised or quasi-randomised clinical trials assessing the outcomes of enteral feeding. In the

absence of randomised clinical trials, this chapter has attempted to report the outcomes of enteral feeding from observational studies, the majority of which are retrospective.

The evidence for survival advantage with enteral feeding is weakly positive but inconclusive. Although some studies suggest survival advantage with enteral feeding (Chio et al., 1999; Chio et al., 2006; Czaplinski et al., 2006; Mazzini et al., 1995; Spataro et al., 2011), many others have failed to support these findings (Atassi et al., 2011; Desport et al., 2000; Forbes et al., 2004; Mathus-Vliegen et al., 1994; Mitchell et al., 2006; Mitsumoto et al., 2003; Murphy et al., 2008; Sorenson et al., 2007; Strong et al., 1999; Zhang et al., 2012). All studies of enteral feeding in MND have been observational in nature. Therefore, it is difficult to be certain whether the conflicting impact of enteral feeding on survival is due to different study designs, discrepancy in the rate of enteral feeding among various centres, bias or random error.

Malnutrition is a common occurrence in MND and can significantly impact QOL, as patients are often exhausted, tired and spiritless (Greenwood, 2013; Korner et al., 2013). There are some studies which suggest stabilization of body weight and nutritional benefit with enteral feeding (Chio et al., 1999; Mazzini et al., 1995; Kasarskis et al., 1999; Desport et al., 2000; Mitsumoto et al., 2003; Zhang et al., 2012). However, this evidence is weak (Katzberg and Benatar, 2011).

The systematic review identified only four studies reporting changes in self-perceived QOL after enteral nutrition, of which only one was prospective (Mazzini et al., 1995) and the remaining retrospective in nature (Lou et al., 2010; Mitsumoto et al., 2003; Zamietra et al., 2012). However, none of these studies were principally designed to investigate the association between enteral feeding and QOL. There is a distinct lack of literature to support or refute enteral feeding for improving QOL in patients with MND.

It is interesting to note that despite the obvious burden of malnutrition in MND, most studies assessing the outcomes of enteral feeding were primarily not intended to determine the efficacy of enteral feeding as a therapeutic intervention. A careful dissection of the available literature has thus identified the need for a study to address the critical issue of impact of enteral feeding on quality of life of MND patients.

CHAPTER 3

EPIDEMIOLOGY AND CLINICAL CHARACTERISTICS OF MOTOR NEURONE DISEASE IN LANCASHIRE AND SOUTH CUMBRIA

3.1 Introduction

Motor Neurone Disease (MND) is a neurodegenerative disorder that predominantly affects middle-aged and elderly individuals with the mean age of onset varying from 55 to 65 years (Wijesekera and Leigh, 2009). The median survival from symptom onset to death varies from 20 to 48 months (Beghi et al., 2011). For reasons that are not clear, there is a male preponderance with the male to female ratio of 1.5 (Beghi et al., 2006; McCombe and Henderson, 2010; Wijesekera and Leigh, 2009). The incidence ranges from 1.5 to 2.5 cases per 100,000 per year, although it varies between different studies and countries (Hoppitt et al., 2011; Logroscino et al., 2010; Mehal et al., 2013).

The importance of descriptive epidemiology and detailed clinical characterisation of MND has emerged following the increasing recognition of clinical, pathological, prognostic and genetic heterogeneity of the illness (Logroscino et al., 2008; Ravits et al., 2013). It is also becoming obvious that such comprehensive clinical characterisation and epidemiological variations will form the basis of future genetic association studies designed to ascertain both risk and protective factors for MND (Logroscino et al., 2008; Renton et al., 2014).

The range of studies on MND using population based registries can shed light on demographic characteristics, disease phenotype, geographical and temporal variations of the illness (Logroscino et al., 2008). There is lack of up to date population based data on MND in Lancashire and South Cumbria in North West England. It is also unclear whether the epidemiology and clinical characteristics of MND in this region are similar to our MND cohorts.

The availability of the Preston MND database maintained by the Preston MND Care and Research Centre provided a unique opportunity to study the epidemiology,

demographic and clinical characteristics of MND in Lancashire and South Cumbria. This chapter presents the findings of a retrospective study that was undertaken to evaluate the demographic and clinical characteristics of MND in Lancashire and South Cumbria in North West England.

3.2 Aim of the retrospective study

The aim of this retrospective study was to evaluate the demographic and clinical characteristics of MND in Lancashire and South Cumbria in North West England.

3.3 Objectives of the retrospective study

The following were the objectives of the retrospective study:

1. To determine the incidence of MND in Lancashire and South Cumbria.
2. To review the demographic and clinical characteristics of MND in a large cohort of patients in Lancashire and South Cumbria.
3. To evaluate the impact of enteral feeding on survival of patients with MND.

3.4 Setting/Methods

The study was conducted at the Preston MND care and research centre. The centre located at Royal Preston Hospital was inaugurated in 1993 and serves an approximate population of 1.6 million in Lancashire and South Cumbria (Mitchell et al., 2010). The fast-track diagnostic service was introduced in January 2005 in order to reduce diagnostic delays (Callagher et al., 2009; Mitchell et al., 2010). Patients are referred from seven different hospitals including Royal Preston Hospital, Furness General

Hospital, Royal Lancaster Infirmary, Burnley General Hospital, Blackburn Royal Infirmary, Blackpool Victoria Hospital, and Chorley District General Hospital.

3.5 Ethics

The study was approved by the National Research Ethics Service (NRES) Committee East Midlands - Nottingham 1 Research Ethics Committee, Nottingham (Appendix 3). As a host organisation, ethical approval was also obtained from Lancashire Teaching Hospitals NHS Foundation Trust (Appendix 4). Ethical approval was also obtained from the Science, Technology, Engineering and Medicine (STEM) research degrees sub-committee, University of Central Lancashire (Appendix 5).

3.6 Study area and study Population

Patients diagnosed with MND by a Consultant Neurologist in Lancashire and South Cumbria district during the period January 2005 to December 2012 were recruited into the study. The study province had an approximate population of 1.6 million.

3.7 Inclusion criteria

Patients with a diagnosis of definite, probable, laboratory supported or possible MND as defined by the revised El Escorial criteria for diagnosis of Motor Neurone Disease/Amyotrophic Lateral Sclerosis (Brooks et al., 2000) were recruited.

3.8 Exclusion criteria

Patients, where the diagnosis of MND, were revised either due to atypical presentation or failure of symptom progression were excluded from the study.

3.8 Data Collection

Patients were identified through the Preston MND database which is a computerised password protected resource. Case notes of study subjects were scrutinized where available, for the following details: demographics, age of symptom onset, site of onset, date of diagnosis, date of feeding tube insertion (if applicable), situation at last follow up (dead or alive) and date of death (if applicable). The date of diagnosis was taken as the date when the diagnosis of MND was disclosed to the patient. The extracted data were entered on a excel sheet.

3.9 Statistical analysis

All statistical analyses of association between clinical manifestation, survival and feeding tube insertion were analysed using Statistical Package for the Social Sciences (SPSS) version 22. Kaplan-Meier survival curves were used for survival analysis and a log-rank test was applied to compare the survival curves. A multivariate Cox regression model was used to assess the effectiveness of enteral nutrition in relation to survival. Patient characteristics were recorded as mean ± standard deviation and counts (percentages) and p values < 0.05 were considered statistically significant.

3.10 Results

The data source identified 407 patients. 67 cases with insufficient clinical information were excluded and the final cohort included 340 patients.

3.10.1 Incidence

The overall crude incidence rate was 3.15 per 100,000 population (95% CI 2.99-3.31).

3.10.2 Demographic characteristics

Demographic profile

Among the 340 patients, 181 (53.2%) were males and 159 (46.8%) females. A total of 6 cases (1.8%) were under 40 years of age, 85 cases (25%) between 40 to 60 years of age, 216 cases (63.5%) between 60 to 80 years of age and 33 cases (9.7%) over 80 years of age at symptom onset. These data suggest that MND is an age related disease. Table 3.1 summarizes the age categories and distribution for sex and site of symptom onset.

Table 3.1: Table showing the age, sex and site of symptom onset among 340 patients

Age of onset (years)	**Bulbar**			**Limb**		
	Male	Female	Total (%)	Male	Female	Total (%)
< 40	1	0	1 (0.3)	4	1	5 (1.5)
40 - 60	12	14	26 (7.6)	32	27	59 (17.4)
60 - 80	34	47	81 (23.8)	86	49	135 (39.7)
>80	7	14	21 (6.2)	5	7	12 (3.5)
Total	54	75	129 (37.9)	127	84	211 (62.1)

Age at symptom onset

The overall mean age of onset was 67.28 years (S.D. 11.06; range 22.78-93.06). It was 66.74 years (S.D. 11.50; range 22.78-89.46) for males and 67.89 years (S.D. 10.53; range 39.48-93.06) for females. The mean age of symptom onset was 69.22 years (S.D. 11.13; range 45.97-93.06) for bulbar onset illness and 66.10 years (S.D. 10.88; range 22.78-89.46) for limb onset illness.

Symptom onset was rare before the age of 40 years occurring in only 6 patients, of which 5 were males. There was a dramatic increase after 60 years of age. The onset increased with increasing age in both sex groups and declined rapidly after the age of 80 years. Figure 3.1 illustrates the illness onset in various age groups.

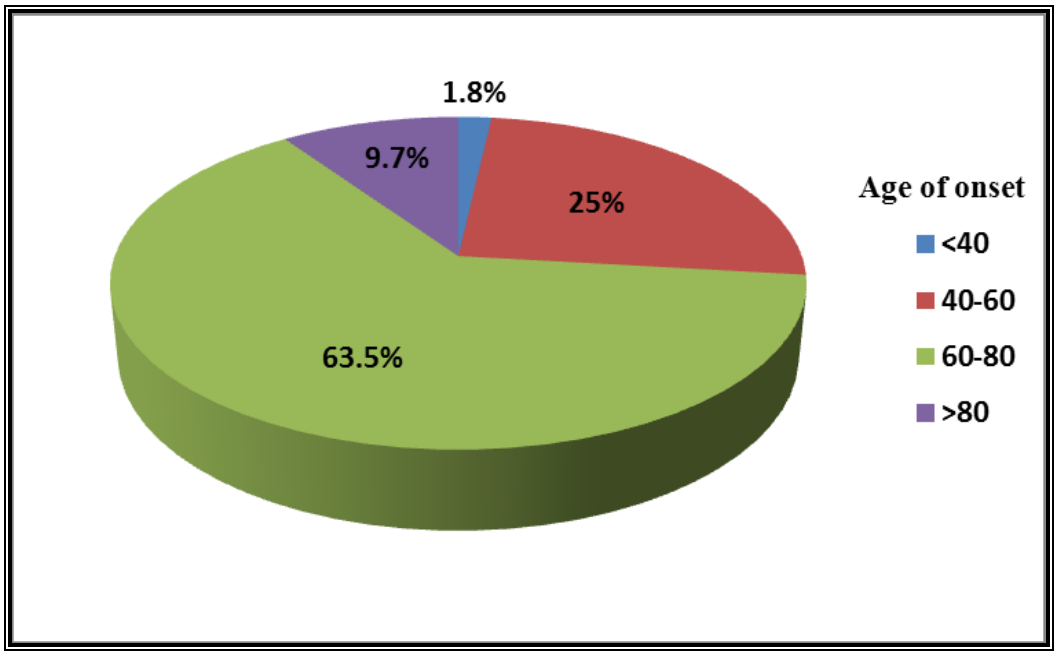

Figure 3.1: Pie chart depicting age groups at symptom onset

Age at diagnosis and diagnostic delay

The mean age at diagnosis was 68.51 years (S.D 10.93; range 23.85-93.58); 68.07 years (S.D. 11.35; range 23.85-89.84) for males and 68.85 years (S.D 10.41; range 40.99-93.58) for females. Median delay between symptom onset and diagnosis was 0.86 years (range 0.50-1.24).

Duration of illness

Median overall illness duration was 1.98 years (range 1.18-3.05); 2.06 years (range 1.20-3.10) for males and 1.97 years (range 1.15-2.99) for females.

3.10.3 Clinical characteristics

Limb onset motor neurone disease

A total of 211 (62.1%) cases had limb onset of the illness and presenting features included limb clumsiness and muscle weakness of gradual onset, starting either proximally or distally. Limb onset MND was more common in males. 127 cases were males and 84 cases were females. The vast majority of limb onset cases (135 cases; 63.9%) were in the 60 - 80 year age group.

The presenting symptoms in the upper limb included impaired hand dexterity, poor grip, cramps, muscle weakness and wasting. Symptoms in the lower limbs included difficulty in walking, heaviness in the legs, cramps, tendency to trip, foot drop, muscle weakness and wasting. Figure 3.2 illustrates the distribution by age of symptom onset and gender in limb onset MND. The data show that significantly ($p<0.05$) more patients within the age group 60 – 80 years had limb onset of the illness as compared to other age groups.

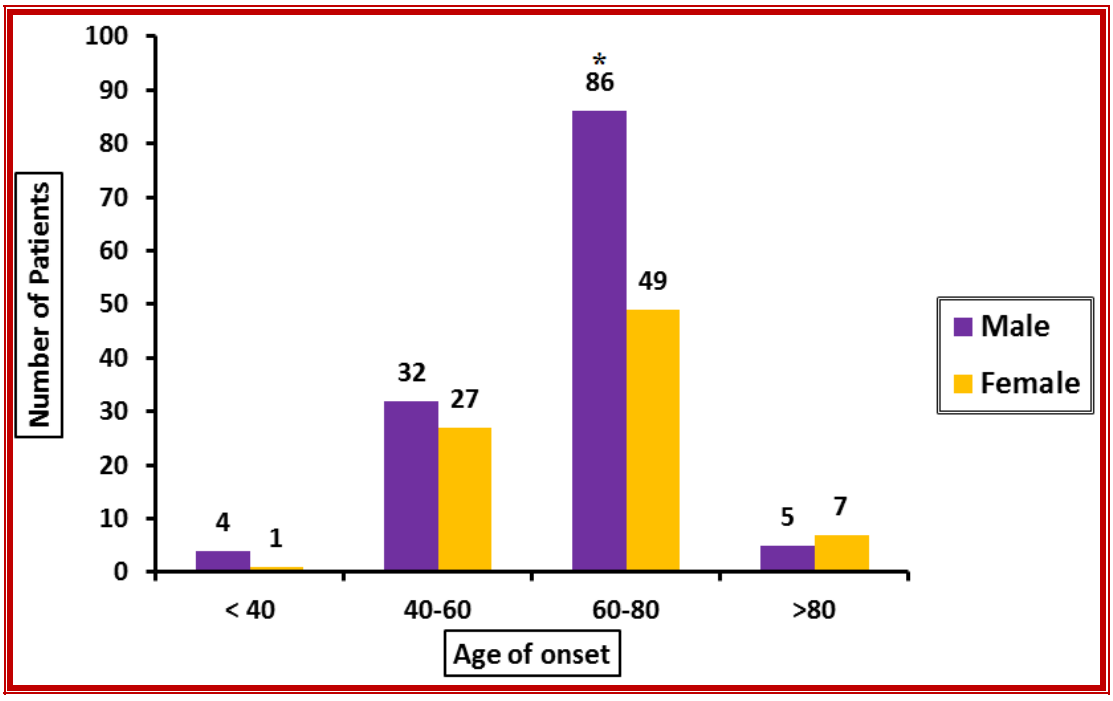

Figure 3.2: Bar charts showing gender and age distribution of limb onset MND (n=211), *p <0.05 for males as compared to females.

Bulbar onset motor neurone disease

A total of 129 (37.9%) cases had bulbar onset of the illness and presenting features included dysarthria and/or difficulty swallowing. Bulbar onset illness was more common in females. A total of 75 cases were females and 54 cases were males.

The number of patients with bulbar onset illness increased significantly ($p<0.05$) with increasing age and 102 (79.1%) of cases were more than 60 years of age. Onset of bulbar onset illness was very rare before the age of 40 years and declined after the age of 80 years. Figure 3.3 illustrates the distribution by age of symptom onset and gender in bulbar onset MND. The data further reveal that significantly ($p<0.05$) more cases within the age group 60 – 80 years had bulbar onset of the illness compared to other age groups.

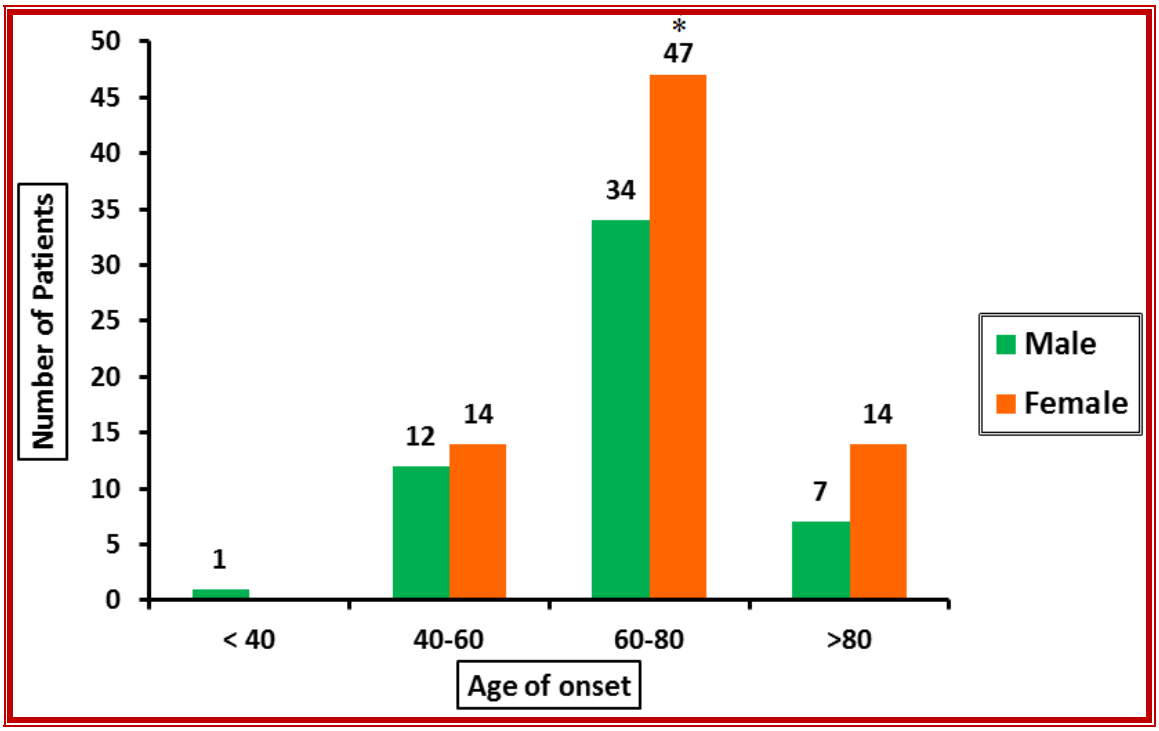

Figure 3.3: Bar charts showing gender and age distribution of bulbar onset MND (n=129), *p <0.05 for females as compared to males.

3.10.4 Overall Survival characteristics

The median survival from symptom onset was 721 days (95% CI 637.98-804.02) for limb onset and 731 days (95% CI 611.99-850.00) for bulbar onset illness. Log-Rank analysis revealed no significant difference in survival between bulbar and limb onset MND (Log-Rank $\chi 2$ (1) = 0.15, p=0.70).

The overall one year survival rate was 82.2% (SE 0.034) for limb and 82.5% (SE 0.026) for bulbar onset MND. The overall five year survival rate was 5.2% (SE 0.02) for limb and 7.8% (SE 0.02) for bulbar onset illness.

3.10.5 Enteral Feeding and survival

A total of 91 (26.8%) patients received enteral feeding, of which 61 (67.0%) had bulbar onset of the illness. The remaining had limb onset MND. The main indication for enteral feeding was dysphagia and/or progressive weight loss.

Cox regression analysis was used to assess the effect of various covariates on survival following enteral feeding. Enteral nutrition was not associated with a statistically significant survival advantage, (Log-Rank $\chi 2$ (1) = 1.73, p=0.19) after adjusting for effects of gender, onset age, onset site, time from onset to diagnosis and riluzole treatment (Figure 3.4).

The regression coefficients, degrees of freedom, p-values and odds ratios for each covariables are included in Appendix 6. Three of the covariates reliably predicted survival time at $p<0.001$: onset age, delay from symptom onset to diagnosis and riluzole. Younger patients treated with riluzole at an early stage were more likely to survive longer. Survival at one year with enteral nutrition was 82% (SE 0.04) and without enteral nutrition 83% (SE 0.02).

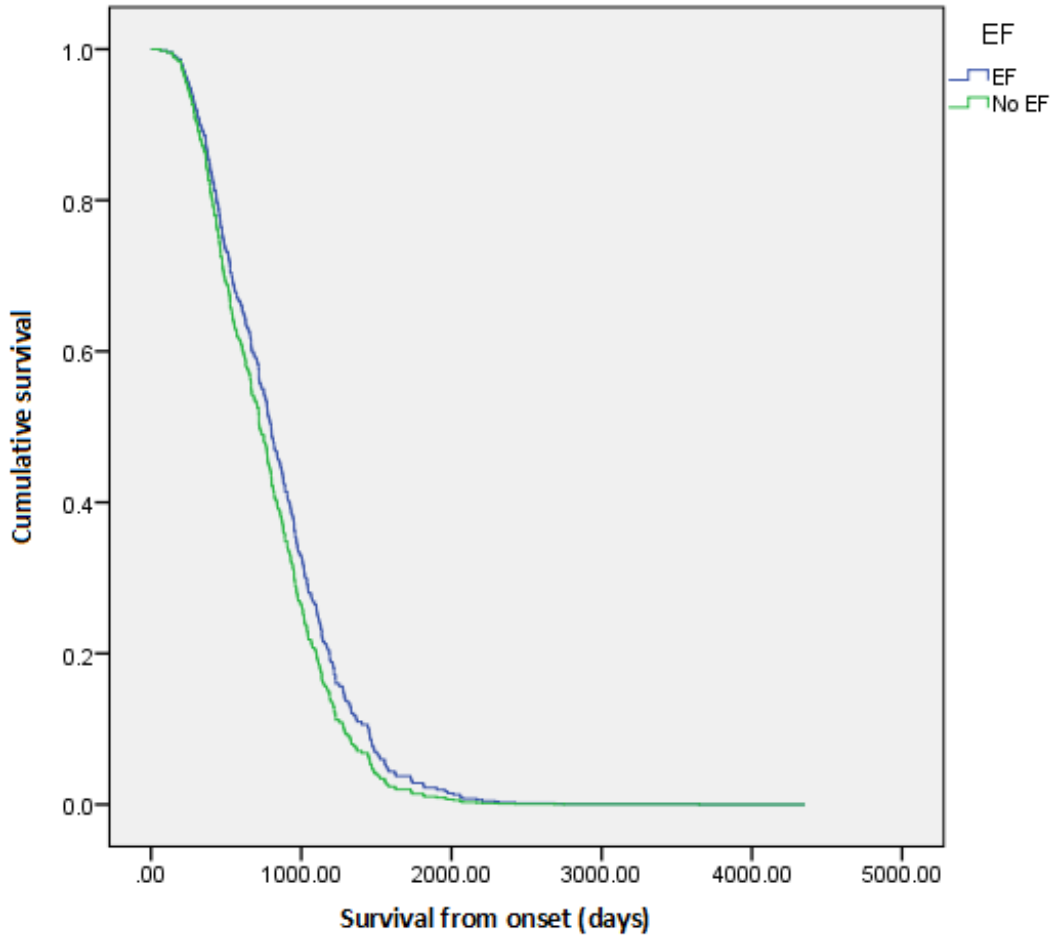

Figure 3.4: Kaplan-Meier cumulative survival curve from symptom onset in patients with enteral feeding (EF) versus no EF (n= 340; EF = 91; No EF = 249).

A further Log-Rank analysis revealed no significant difference in survival time between bulbar onset and limb onset (Log-Rank $\chi 2$ (1) = 0.57, p = 0.45), irrespective of whether patients received enteral nutrition or not (Log-Rank $\chi 2$ (1) = 0.05, p = 0.82). Median (95% CI limits) survival times for limb onset illness with and without enteral nutrition were 777 (498.67-1055.13) days and 718 (625.02-810.98) days, respectively. Median survival times for bulbar onset with and without enteral nutrition were 799 (677.64-920.36) days and 645 (427.82-862.19) days respectively.

3.11 Discussion

The clinical features of the study cohort are largely similar to those described in previous population based studies (Bandettini di Poggio et al., 2013; Fang et al., 2009; Imam et al., 2010; Logroscino et al., 2010; Mehal et al., 2013; Murphy et al., 2008; O'Toole et al., 2008; Pradas et al., 2013; Traynor et al., 2000; Zoccolella et al., 2006). There was a slight male preponderance. The data show that bulbar onset was identified in about one third of patients, being more common among females. Median overall illness duration was 1.98 years (range 1.18-3.05 years).

The mean age of symptom onset was 67.28 years (S.D. 11.06; range 22.78-93.06). Onset was rare before the age of 40 years with a significant ($p<0.05$) and dramatic increase after 60 years of age. The onset increased with increasing age and declined rapidly after the age of 80 years, a finding that has been reported in other studies (Alonso et al., 2009; Logroscino et al., 2008; Pradas et al., 2013). This may be due to the fact that the patients die by the age of 80 years. In addition, the decline in trend in elderly has been attributed to a number of factors including difficulty in case ascertainment due to competing comorbidities, difficult access to specialised care and loss of follow up or to a more aggressive illness ending in death before the diagnosis of MND is secured (Beghi et al., 2006).

The incidence rate of 3.15/100,000 is similar to other population based studies (Bandettini di Poggio et al., 2013; Imam et al., 2010; Logroscino et al., 2008; Logroscino et al., 2010; Murphy et al., 2008; Pradas et al., 2013; Traynor et al., 1999). The incidence in the study area in early nineties was 1.76/100 000 population (Mitchell et al., 1998). Some studies have also shown an increase in incidence rate over the past several decades and this may be due to improvements in case ascertainment and better

diagnostic methods (Fang et al., 2009; Murphy et al., 2008; Seljeseth et al., 2000). MND care in the study region is centralized in one hospital and the majority of cases were prospectively recorded which may have improved case ascertainment.

The median diagnostic delay from symptom onset was 0.86 years (range 0.50-1.24 years). The diagnostic delay is similar to other studies which report a median diagnostic delay ranging from 0.75 to 1.2 years (Cellura et al., 2012; Chio, 1999; Kraemer et al., 2010; Mitchell et al., 2010). Delays in diagnosis has significant implications in accessing appropriate care, formulating individualized supportive management plan and difficulty in planning future care (Chio, 1999).

Bulbar onset illness was more common in elderly females, a finding that has been described in other studies (Chio et al., 2009b; Traynor et al., 1999). Bulbar onset illness is usually associated with a worse prognosis (Chio et al., 2002; Norris et al., 1993; Traynor et al., 2000). However, this study did not find a significant survival difference between bulbar onset and limb onset illness, irrespective of whether or not they received enteral feeding. The retrospective nature of this study does not provide any clues to explain this finding and needs to be evaluated in a prospective study. However, bulbar onset patients were more likely to require enteral feeding than limb onset cases, a finding reported in many other studies (Atassi et al., 2011; Forbes et al. 2004; Georgoulopoulou et al., 2013).

Enteral feeding was not associated with a survival advantage, a finding that is in keeping with the results of many other studies (Atassi et al., 2011; Desport et al., 2000; Forbes et al., 2004; Mathus-Vliegen et al., 1994; Mitchell et al., 2006; Mitsumoto et al., 2003; Murphy et al., 2008; Sorenson et al., 2007; Strong et al., 1999; Zhang et al., 2012). However, the present results also are in disagreement with the findings of few

other studies that report a survival advantage with enteral feeding (Chio et al., 1999; Chio et al., 2006; Czaplinski et al., 2006; Mazzini et al., 1995; Spataro et al., 2011).

Previous studies that have demonstrated survival advantage with enteral feeding have their own limitations. Mazzini et al. (1995) reported survival of 38 months versus 30 months ($p<0.03$) in a prospective study comparing 31 patients undergoing gastrostomy with 35 control patients. The control group had refused the procedure. However, multivariable regression analysis to assess possible confounders was not undertaken in this study.

Chio et al. (1999) demonstrated a survival advantage with enteral feeding in a case control study of 50 patients undergoing gastrostomy who were matched with 100 historical controls. Survival advantage was noted only in bulbar onset but not spinal onset illness.

In a retrospective cohort study of 1041 patients of which 275 received gastrostomy, Czaplinski et al. (2006) demonstrated significantly improved survival rate with enteral feeding. However, the median survival was analysed from symptom onset rather than from the point of gastrostomy. The lack of survival statistics from the point of gastrostomy makes it difficult to ascertain the true impact of enteral feeding on survival.

Chio et al. (2006) prospectively followed 221 patients with MND over a two year period. Patients not receiving gastrostomy had a hazard ratio of 3.38 ($p=0.0006$) for death compared to 52 patients with gastrostomy. However, it is unclear whether the clinical characteristics of the gastrostomy cohort were similar or different to the group not receiving gastrostomy.

In a prospective study by Spataro et al. (2011), it was uncertain whether the reported survival advantage in 76 patients who underwent gastrostomy was due to either enteral feeding or early active management as earlier diagnosis and timely access to multidisciplinary care is an independent prognostic factor for survival (Chio et al., 2006; Traynor et al., 2003).

For methodological and ethical reasons, it is difficult to demonstrate a survival advantage with enteral feeding. A true comparison can only be made with cases that require enteral feeding, but do not receive it. However, for obvious ethical reasons, a randomized controlled study cannot be undertaken as it would be immoral to deny enteral feeding to those who need it. Comparison can therefore only be made with patients who refuse the procedure but such patients are uncommon.

3.12 Conclusion

The present results show that the overall crude incidence of MND was 3.15 per 100,000 population. The mean age of onset was 67.28 years (S.D. 11.06; range 22.78-93.06). The number of new cases increased with increasing age and declined rapidly after the age of 80 years. There was a slight male preponderance. The presentation was limb onset in 62.1% and bulbar onset in 37.9% cases. Bulbar onset was more frequent among females. Median survival was 1.98 years (range 1.18-3.05 years).

A total of 91 (26.8%) patients received enteral feeding of which 67% were bulbar onset. Enteral feeding was not associated with a statistically significant survival advantage ($\chi 2$ (1) = 1.73, p = 0.19). Median (95% CI limits) survival times for limb onset illness with and without enteral feeding were 777 (498.67-1055.13) days and 718 (625.02-810.98) days respectively. Median survival times for bulbar onset with and without enteral

feeding were 799 (677.64-920.36) days and 645 (427.82-862.19) days respectively. In conclusion, the present results show that enteral feeding is not associated with survival advantage.

CHAPTER 4

ENTERAL NUTRITION:

IMPACT ON

QUALITY OF LIFE

4.1 Introduction

'Quality of life' is a ubiquitous and multifaceted concept with a wide range of definitions and interpretations (Brotherton and Judd, 2007; Rapley, 2003). It is an ambiguous and ill-defined term due to its holistic and subjective dimension and means differently to different individuals, depending on the context and subject of application (Fayers and Machin, 2007).

Motor Neurone Disease (MND) is a fatal neurodegenerative illness and management is mainly supportive, focussed on preserving independence and maintaining and/or enhancing QOL of patients (Andersen et al., 2012). The significance of QOL as a major outcome variable has therefore become increasingly evident in the management of MND (Clarke et al., 2001). The perspectives and wishes of patients are of paramount importance and treatment efforts should be directed towards improving quality rather than just quantity of life (Bozzetti, 2008). Measuring and monitoring QOL is therefore essential in appraising the efficacy of any supportive treatment (Brooks, 1997; Neudert et al., 2004).

Placement of a gastrostomy feeding tube has important ethical concerns and the decision to offer gastrostomy should depend on whether a patient will derive any actual benefit from it (Good et al., 2014). Enteral feeding through a gastrostomy tube is associated with number of complications and psychosocial inconveniences (Blomberg et al., 2012; Potack and Chokhavatia, 2008; Rogers et al., 2007). Assessing QOL is therefore important to optimize the adequacy of enteral feeding to the needs and expectations of every individual patient.

Enteral feeding is routinely offered to patients with MND but the there is no evidence to support or refute enteral feeding for maintaining or improving QOL. This chapter will

present the findings of a prospective study that was undertaken over a three year period from February 2012 to September 2014 to explore the experiences of MND patients with enteral feeding and its impact on their quality of life.

4.2 Aim of the prospective study

The aim of the study was to investigate the impact of enteral feeding delivered via gastrostomy tube on QOL of patients with MND in Lancashire and South Cumbria in North West England.

4.3 Objectives of the prospective study

The objectives of the prospective study are:

1. To explore patients' experiences with enteral nutrition.
2. To explore the impact of enteral nutrition on quality of life.
3. To examine change in nutritional status through measurement of body mass index at the time of diagnosis, pre and post enteral feeding.

4.4 Setting/Methods

The study was conducted at the Preston MND Care and Research Centre. The Centre located at Royal Preston Hospital, United Kingdom, serves an approximate population of 1.6 million in Lancashire and South Cumbria in North West England.

Patients were reviewed by the MND team on a three monthly basis and assessed for nutritional and respiratory impairment. The facility also operated a unique service delivery model which provided outreach nurse-led clinics in hospice settings and home visits, if patients were unable to travel because of their disability. During the follow up

visits, weight and forced vital capacity were recorded. However, it was not possible to record weight in all cases, particularly if patients were bedbound and/or there was no access to a hoist weighing scale. Functional and QOL assessment were also undertaken during the follow up visits by completing the ALSFRS-R and ALSAQ-40 questionnaires.

4.5 Ethics

The study was approved by the National Research Ethics Service (NRES) committee East Midlands - Nottingham 1 Research Ethics Committee (Appendix 3). As a host organisation for the study, ethical approval was also obtained from the research directorate and clinical studies centre of the Lancashire Teaching Hospitals NHS Foundation Trust (Appendix 4).

Ethical approval was also obtained from the Ethics Committee for Science, Technology, Engineering and Medicine (STEM) ethics committee, University of Central Lancashire (Appendix 5).

Lancashire Teaching Hospitals NHS Foundation Trust provided public liability insurance cover for the work.

4.6 Study subjects

Patients with MND referred for gastrostomy were considered for the study. Patients were identified through the Preston MND and Research Centre by the researcher or a member of the MND team.

4.6.1 Purposive sampling

All participants were selected through a non-probability purposive sampling technique where patients with MND referred for gastrostomy were assessed for eligibility. Purposive sampling is a non-probability sampling method which involves the deliberate selection of certain subjects who represent the desired population to be included in the study (Teddlie and Yu, 2007). A purposive sample is constructed to serve a very specific need or purpose and targets a specific group of individuals, particularly when the desired population for recruitment in the study of interest is rare (Teddlie and Yu, 2007).

MND is an uncommon condition and only a proportion of patients with the condition receive enteral nutrition. A purposive sampling method was therefore employed to address the specific question of whether enteral feeding improves quality of life in this rare study population.

4.7 Inclusion Criteria

Patients diagnosed with definite, probable, laboratory supported or possible MND as defined by the revised El-Escorial diagnostic criteria (Brooks et al., 2000) and referred for gastrostomy.

4.8 Exclusion Criteria

The exclusion criteria for the study were as follows:

a. Patient declined gastrostomy.

b. Contraindications to gastrostomy.

4.9 Recruitment and study design

Patients with MND referred for gastrostomy were informed about the study by the researcher or a staff member of the MND team. Interested patients were assessed for eligibility by the researcher based on the inclusion and exclusion criteria as outlined above.

Eligible patients were given a letter of invitation (Appendix 7) and a comprehensive patient information sheet (Appendix 8) explaining the details of the study and requesting them to contact the researcher, if they were interested in participating in the study. In order to ensure that the perspectives of participants were accurately represented, the patient information sheet and letter of introduction clearly outlined the intent and purpose of the study.

Interested patients were also given the opportunity to speak to the researcher if they had any questions. The study also had the option of sending one reminder to those patients who did not contact the researcher within four weeks of the original invitation (Appendix 9). Patients were also informed about the voluntary nature of their participation and that they may decline to participate in the study without the risk of compromising clinical care. They were also made aware of their right to withdraw from the study at any time, including during follow up, without having to provide any explanations.

A signed consent was obtained from the participants to confirm their willingness to participate in the study (Appendix 10). Participants who were unable to communicate due to dysarthria or loss of ability to speak coherently were given the opportunity to communicate by writing or with the aid of an iPad or other assistive communication

devices. Participants who were unable to sign the consent form due to hand weakness permitted their next of kin to sign the form in their presence.

Patients who consented to participate in the study had their age, gender, height, weight and forced vital capacity recorded, where possible. Functional and QOL assessment was undertaken using the ALSFRS-R (Appendix 11) and the ALSAQ-40 (Appendix 12). With the patient's consent, a letter was sent to their general practitioner informing them about the patient's participation in the study (Appendix 13).

The study participants were followed up at 3, 6 and 12 months following the procedure. The letter of invitation (Appendix 7) was posted along with the Liverpool PEG questionnaire (Appendix 14) four weeks before the scheduled follow up appointments. The letter was intended to serve as a reminder to the patient that they were invited to complete the PEG questionnaire in order to understand their experiences with enteral feeding and its impact on their QOL at different timeframes. Participants were requested to bring the completed questionnaire to the follow up visits.

Participants who were not able to bring the completed PEG questionnaire to the follow up appointments were given the opportunity to complete it during the appointment. If patients were unable to travel to the clinics because of their disability, the assessments were undertaken during the scheduled home visits by a member of the MND team.

Participants who were unable to complete the PEG questionnaire due to limb weakness permitted their next of kin or a staff member of the MND team to transcribe their responses. In addition to the PEG Questionnaire, the ALSFRS-R and ALSAQ-40 forms were also completed during the scheduled follow up visits. The weight was also recorded, where possible, during the follow up visits. The recruitment strategy and study flow chart is outlined in figure 4.1.

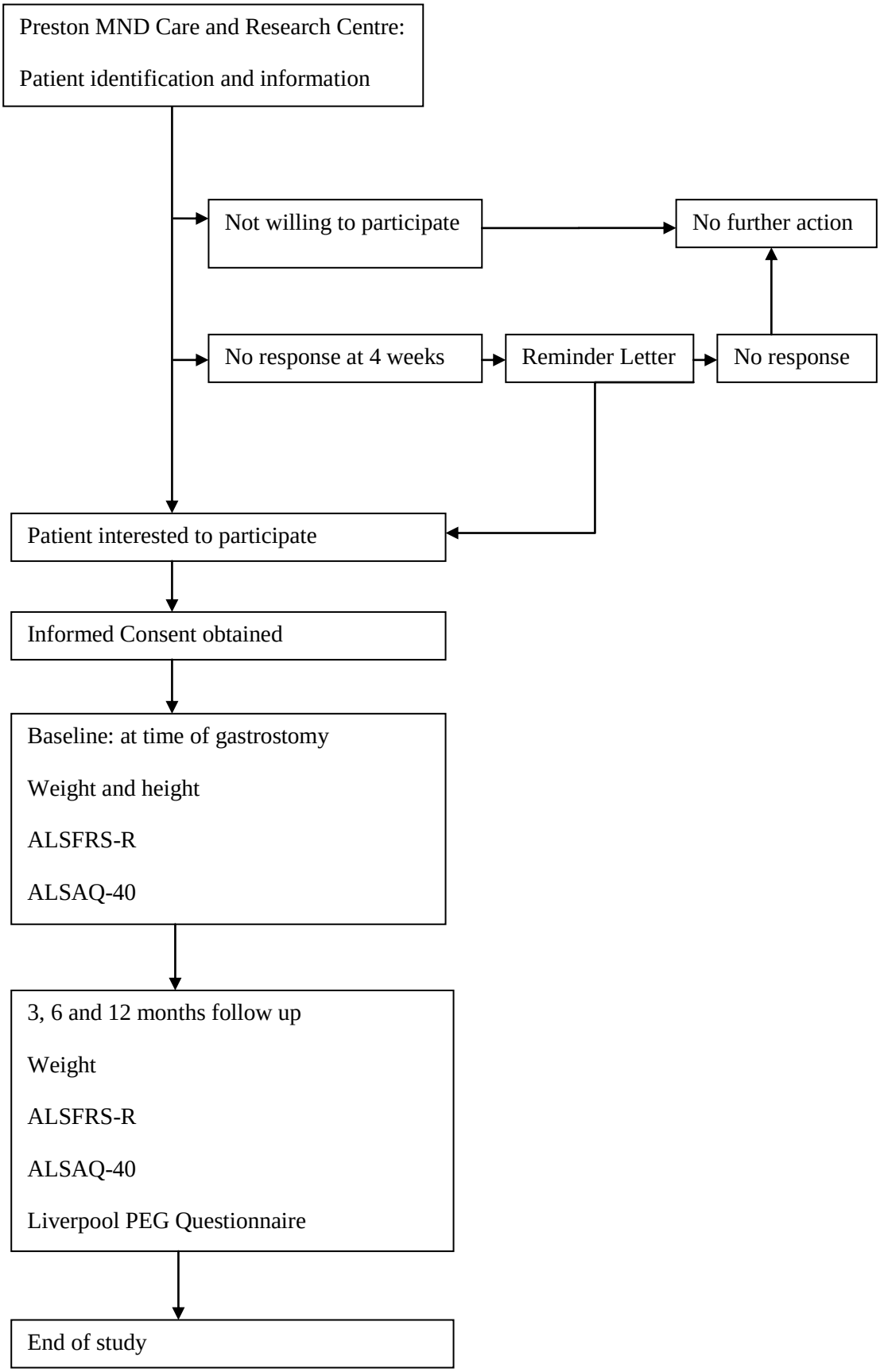

Figure 4.1: Flow chart showing patient recruitment

4.10 Instruments used in the study

Measuring change in a patient's health status is central to the management of any condition as well as designing research studies (Munsat, 1996). The measurement tools should be reliable, valid, sensitive to change, convenient, safe, cost and time efficient (Brooks, 1997; Munsat, 1996). The following section provides an overview of the instruments used in this study.

4.10.1 Amyotrophic Lateral Sclerosis Functional Rating Scale – Revised (ALSFRS -R)

The ALSFRS-R, a validated, questionnaire-based, 12 item scale was used for evaluating the functional status and functional change in patients with MND (Cedarbaum et al., 1999). Each item in the ALSFRS-R was scored from 0 (worst function) to 4 (normal function). The scores were added to generate a total score ranging from 0, indicating worst function, to 48, which implied normal function. The bulbar subscale consisted of the domains of swallowing, speech and salivation. Handwriting, cutting food, dressing and hygiene were included under the fine motor domain. Questions relating to turning in bed, walking and climbing stairs measured gross motor function. Dyspnoea, orthopnoea and the need for ventilatory support were integrated under the respiratory domain (Cedarbaum et al., 1999).

4.10.2 Amyotrophic Lateral Sclerosis Assessment Questionnaire-40 (ALSAQ - 40)

The ALSAQ-40, a validated, disease specific measure of QOL was used in this study to measure the subjective well-being of patients with MND. The scale had also been validated for use in other languages (Maessen et al., 2007). It was the only self-reported

QOL instrument designed specifically for use in MND. The questionnaire had 40 items incorporated in five distinct areas of health: physical mobility (10 items), activities of daily living (10 items), eating and drinking (3 items), communication (7 items) and emotional functioning (10 items). Patients were asked to respond on a five point Likert type scale how true each item statement had been in the past two weeks (Jenkinson et al., 1999; Jenkinson et al., 2007). The answers from each of the five scales were then collated into a summary scale.

The scale had been demonstrated to show high internal reliability and construct and content validity (Jenkinson et al., 1999; Jenkinson et al., 2000; Jenkinson et al., 2007). ALSAQ-40 scores were also sensitive to changes that have an impact on the overall health status of patients over time (Jenkinson et al., 1999; Jenkinson et al., 2003; Norquist et al., 2004). However, ALSAQ-40 did not incorporate areas of religious/spiritual beliefs which are important to many patients with MND (Bremer et al., 2004; Walsh et al., 2003). Nonetheless, ALSAQ-40 was more widely used than many other QOL measurement tools in MND (Jenkinson et al., 2007; Palmieri et al., 2010). The ALSAQ-40 was the instrument of choice for assessment of QOL at the Preston MND Care and Research Centre.

4.10.3 Liverpool Percutaneous Endoscopic Gastrostomy (PEG) Questionnaire

The Liverpool PEG Questionnaire had been designed to look at experiences of patients with PEG feeding (Rogers et al., 2007). The questionnaire involved multiple close ended questions aimed at identifying the problems of gastrostomy feeding and its impact on QOL. Patients were asked to respond on a four point Likert type scale for majority of the questions.

The questionnaire also had an open question to capture any other problems or concerns with PEG. The questionnaire was originally designed for use in patients with PEG in head and neck cancers and needs further validation (Rogers et al., 2007). There were no other relevant gastrostomy specific questionnaires to explore patients' experiences with gastrostomy feeding.

The commonly used QOL instruments did not provide specific information regarding the impact of nutritional problems and intervention on an individual's QOL. This study had therefore incorporated an open question that reads *"How would you describe your quality of life since the insertion of your feeding tube?"* aimed at capturing in-depth data about patients' perspectives about tube feeding and its implications on their QOL. It was hoped that this single open question would encourage the expression of subjective perception and self-appreciation of QOL following enteral feeding. This open question was added to the end of the Liverpool PEG questionnaire.

4.11 Data Collection

Case notes of participants were scrutinized, for the following details: demographics, age of symptom onset, site of onset, weight at diagnosis and date of diagnosis. The results of ALSFRS-R, ALSAQ-40 and PEG questionnaires were entered on a excel sheet. When possible, weight was recorded. However, some participants could not be weighed as they were either bedbound and/or there was no access to a hoist weighing scale.

4.12 Statistical analysis

Data were managed with the aid of SPSS version 22. Patient characteristics were recorded as mean ± standard deviation and counts (percentages). The total score was

computed for ALSFRS-R. Scores were computed for the ALSAQ-40 scale and its emotional functioning domain. The mean scores at diagnosis, gastrostomy and 12 months were compared using the unpaired student's t test. Data from the PEG questionnaire were computed to determine the percentage of participants encountering the itemized inconveniences. The qualitative data relating to patients' perceptions about the impact of enteral feeding on their QOL were subjected to thematic analysis.

4.13 Results

A total of 23 patients were approached to take part in the study. However, 2 patients declined to participate and 21 patients were recruited. One participant withdrew before the 3 month assessment and a second participant withdrew after completion of 6 month assessment. One patient was lost to follow up after completion of 6 month assessment. A total of 8 participants died during the study period. Another 17 patients completed 6 months of the study and 10 patients completed the entire 12 months of study.

4.13.1 Participant characteristics

Among the 21 participants, 8 (38.1%) were males and 13 (61.9%) were females. The overall mean age of symptom onset was 64.23 years (S.D. 12.27; range 39.60-79.00). It was 62.69 years (S.D. 14.09; range 39.60-76.44) for males and 65.18 years (S.D. 11.51; range 43.84-79.00.) for females. The mean age of symptom onset was 66.95 years (S.D. 8.56; range 48.00-77.52) for bulbar onset illness and 60.61 years (S.D. 15.58; range 39.60-79.00) for limb onset illness.

The illness was of limb onset in 9 (42.9%) cases and bulbar onset in 12 (57.1%) cases. Among the limb onset cases, 5 (55.6%) were males and 4 (44.4%) were females.

Among the bulbar onset cases, 3 (25%) were males and 9 (75%) were females. Median duration between symptom onset and gastrostomy was 490 days (95% CI 252.33-1303.68 days).

The indications for gastrostomy were: dysphagia for 4 patients, weight loss for 1 patient and combined dysphagia and weight loss for the remaining 16 patients. 4 patients had received RIG and 17 had received PEG. All patients with RIG had significantly impaired respiratory function as indicated by low FVC, the highest recorded in this group being 41% of the predicted value.

4.13.2 Survival characteristics

There were no deaths within 30 days of gastrostomy, 2 deaths within 90 days, 1 further death within 180 days and 5 additional deaths within 365 days of gastrostomy. Among the 8 participants who died during the study period, median illness duration was 652 days (95% CI 385.71-1557.04). Median survival from gastrostomy to death was 210 days (95% CI 109.14 - 277.61).

4.13.3 Nutritional characteristics

The mean BMI at diagnosis was 25.2 kg/m^2 (S.D. 3.10; range 23.8-26.7 kg/m^2). It was 22.4 kg/m^2 (S.D. 3.25; range 20.9-23.9 kg/m^2) at gastrostomy, indicating a significant weight loss from diagnosis (p=0.007). The BMI stabilised following gastrostomy and the decline in BMI at 12 months following gastrostomy was not statistically significant (p=0.310) (Figure 4.2).

The mean BMI at 3, 6 and 12 months post gastrostomy were 21.5 kg/m^2 (S.D. 3.01; range 19.9-23.2 kg/m^2), 21.1 kg/m^2 (S.D. 2.52; range 19.7-22.6 kg/m^2) and 20.89 kg/m^2

(S.D. 2.99; range 17.5-24.2 kg/m^2) respectively. These data clearly demonstrates that the disease is leading to malnutrition over time.

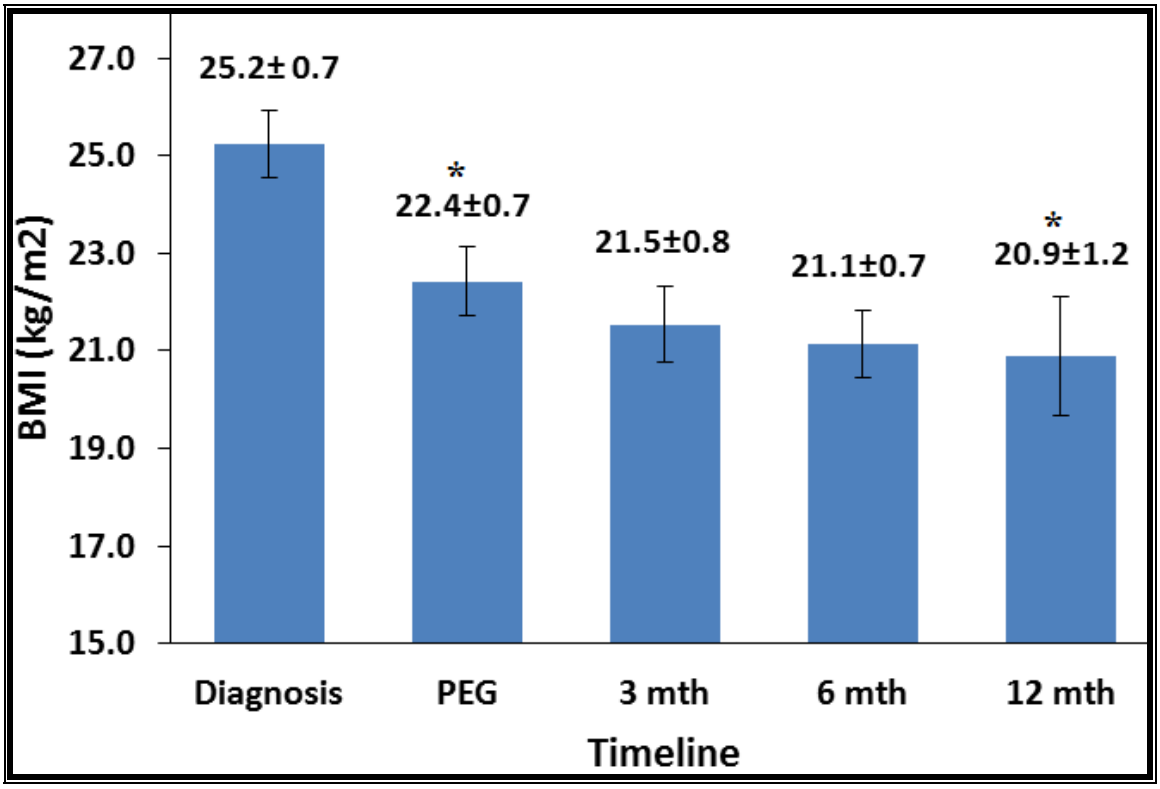

Figure 4.2: Bar charts showing the mean BMI (± SE) at diagnosis (n=20), gastrostomy (n=21) and 3 (n=15), 6 (n=14) and 12 (n=6) months following gastrostomy. Note the BMI stabilised following gastrostomy. *p<0.007 at PEG compared to p=0.310 at 12 months following PEG.

4.13.4 ALSFRS -R scores

The mean ALSFRS-R scores declined over time (Figure 4.3). The mean score at diagnosis was 39.39 (SD 6.34; range 36.23-42.54); 31.05 (SD 6.99; range 27.87-34.23) at gastrostomy and 18 (SD 5.25; range 14.25-21.75) at 12 months post gastrostomy.

The decline in mean score from diagnosis to gastrostomy was statistically significant (p<0.001). There was also a significant difference in the scores between gastrostomy

and 12 months post gastrostomy (p=0.043), indicating a substantial decline in functional and clinical status over time.

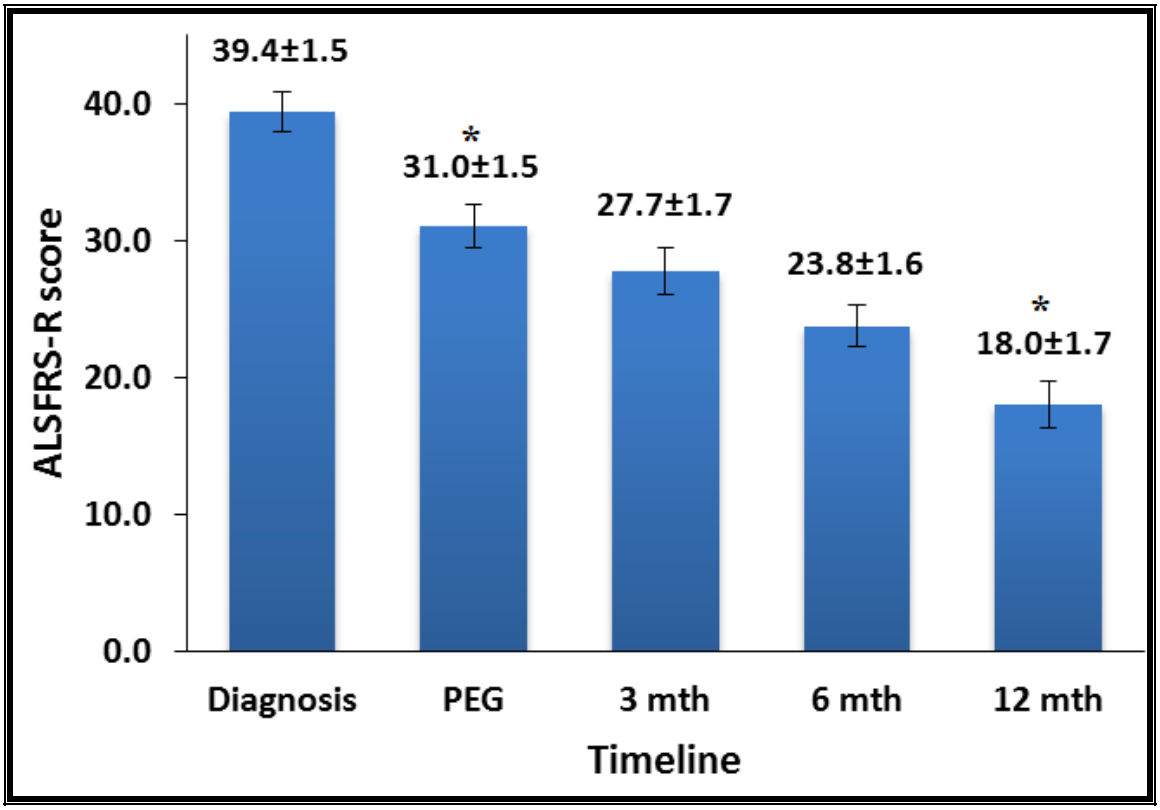

Figure 4.3: Bar charts showing the mean ALSFRS-R scores (± SE) at diagnosis (n=18), gastrostomy (n=21) and 3 (n=18), 6 (n=17) and 12 (n=10) months following gastrostomy. Note the gradual and signficant decline in scores with time. *p<0.001 at PEG compared to p<0.05 at 12 months following PEG.

4.13.5 ALSAQ - 40 scores

The ALSAQ-40 scores increased with illness progression indicating deterioration of subjective well-being (Figure 4.4). The mean ALSAQ-40 score at diagnosis was 61.94 (SD 24.78; range 48.81-75.07) and 79.70 (SD 29.08; range 66.09-93.31) at gastrostomy. The difference in these mean scores was significant (p<0.05). The mean score at 12 months post gastrostomy was 102.90 (SD 20.17; range 88.49-117.11) and the difference

was significant when compared to the mean score at gastrostomy (p=0.03), indicating a progressive decline in subjective functioning and well-being of patients.

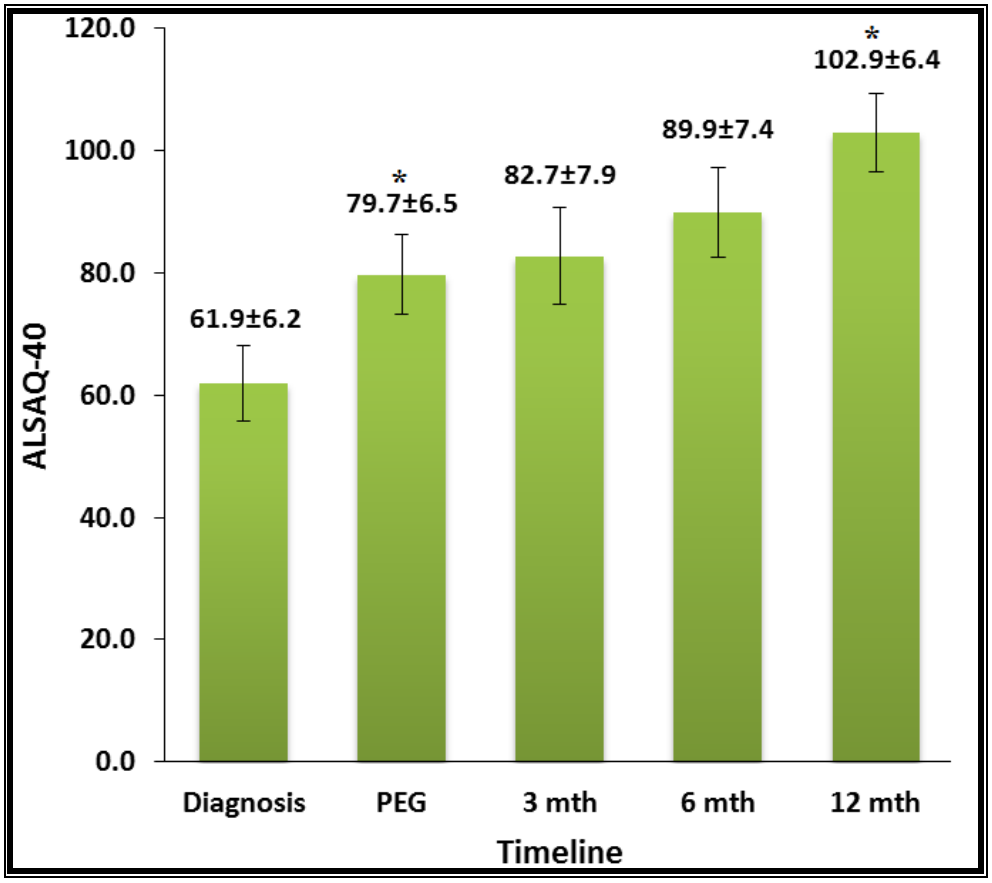

Figure 4.4: Bar charts showing the mean ALSAQ-40 scores (±SE) at diagnosis (n=16), gastrostomy (n=20) and 3 (n=18), 6 (n=17) and 12 (n=10) months following gastrostomy. Note the gradual and significant increase in scores with time. *p<0.05 for PEG as compared to p=0.03 at 12 months post PEG.

The mean emotional functioning sub-score of ALSAQ-40 at diagnosis was 13.00 (SD 7.62; range 8.94-17.06). The sub-scores at gastrostomy insertion and 3, 6 and 12 months post gastrostomy were 15.45 (SD 9.60; range 10.96-19.94), 11.67 (SD 9.46; range 6.96-16.37), 11.35 (SD 6.86; range 7.82-14.88) and 10.70 (SD 7.36; range 5.44-15.96), respectively.

Despite a significant increase in the overall mean ALSAQ-40 scores following gastrostomy ($p<0.05$), the mean emotional functioning sub-scores remained fairly stable during the study period (Figure 4.5). The difference in mean scores between gastrostomy and 12 months was not significant ($p=0.181$). This indicates that enteral feeding ameliorates the decline in emotional functioning.

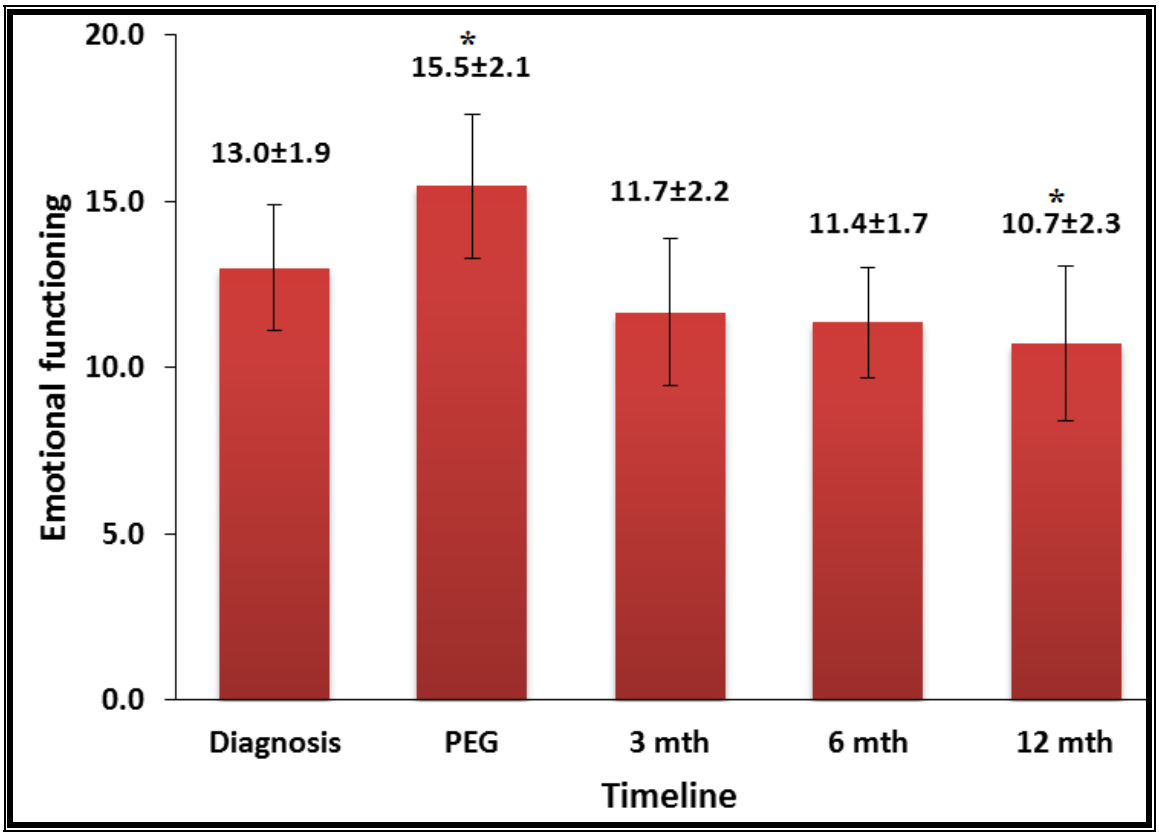

Figure 4.5: Bar charts showing the mean emotional functioning subscores (±SE) at diagnosis (n=16), gastrostomy (n=20) and 3 (n=18), 6 (n=17) and 12 (n=10) months post gastrostomy. Note there is no signficant decline in emotional functioning subscores from gastrostomy . *p=0.181 for difference in scores from PEG to 12 months post PEG.

4.13.6 Liverpool PEG Questionnaire results

Gastrostomy feeding tube was used regularly by 10 (55.6%) participants at 3 months, 11 (64.7%) at 6 months and 6 (60%) at 12 months. The tube was not used 'at all' by 3

participants each at 3 and 6 months. At 12 months follow up, 1 participant was still not using the feeding tube. The rest of the patients were using the tube very occasionally (2 participant each at 3 and 12 months) or frequently (3 each at 3 and 6 months; 1 at 12 months).

The majority reported 'little' or no problem 'at all' with the tube. The problems were generally more common in the first 3 months following gastrostomy. Only a small minority felt that the problems were significant ('very much'). Clinical complications including leakage, pain, redness/irritation, bleeding and infection were common, occurring in up to 70% of the study participants. However, majority of the participants perceived this to be a 'little' problem. Table 4.1 details the problems encountered by participants.

More than 70% reported no interference with their family life, intimate relationships, social activities and hobbies. Up to 40% of the participants had difficulty in keeping the gastrostomy site clean. Approximately 30% reported altered appearance and up to a quarter felt that the tube had an impact on the type of clothes they wore. More than 70% of participants had no difficulties 'at all' in using the gastrostomy tube. At 12 months, only 10% perceived the gastrostomy tube to be a 'little' difficulty.

A total of 4 participants required one change of gastrostomy tube and 1 participant required 4 changes due to problems with the tube. Despite the problems associated with gastrostomy, a vast majority did not wish for the gastrostomy tube to be removed. Only 11.1% (n=2) and 17.7% (n=3) wished for the tube to be removed at 3 and 6 months respectively. No one wished for the tube to be removed at 12 months. It is of note that none wished 'very much' for the tube to be removed at any point.

Table 4.1: Table showing the Liverpool (PEG) Questionnaire: Problems encountered by participants at 3, 6 and 12 months post gastrostomy (% of responders)

	How much of a problem was the PEG to you (% of responders)											
	3 months (n= 18)				6 months (n=17)				12 months (n=10)			
	Not at all	A Little	Quite a bit	Very much	Not at all	A Little	Quite a bit	Very much	Not at all	A Little	Quite a bit	Very much
Pain / Discomfort	50	38.8	5.6	5.6	52.9	41.2	5.9	0	60	30	10	0
Leakage	38.9	44.4	11.1	5.6	41.2	52.9	0	5.9	40	50	10	0
Dirtying of your clothes by leakage	72.2	22.2	0	5.6	64.7	29.4	5.9	0	70	30	0	0
Redness / irritation	50.0	38.9	0	11.1	35.3	47.1	17.6	0	30	50	20	0
Blockage	100	0	0	0	94.1	5.9	0	0	90	0	10	0
Bleeding	61.1	33.3	5.6	0	58.8	35.3	5.9	0	50	50	0	0
Infection	77.8	16.6	0	5.6	76.5	23.5	0	0	100	0	0	0
Tube splitting	94.4	0	0	5.6	94.1	5.9	0	0	100	0	0	0
Falling out	100	0	0	0	88.2	11.8	0	0	90	0	0	10
Keeping the PEG and PEG site clean	72.2	11.1	5.6	11.1	76.5	0	11.8	11.8	60	20	0	20
Appearance	83.3	11.1	0	5.6	76.5	17.6	0	5.9	70	20	10	0
Types of clothes worn	77.8	22.2	0	0	52.9	23.5	17.6	5.9	80	10	0	10
Difficulties using the PEG tube	77.8	5.6	5.6	11.1	70.6	17.6	5.9	5.9	90	10	0	0
Interference with family life	77.8	22.2	0	0	76.5	17.6	5.9	0	80	20	0	0
Interference with intimate relationships	94.4	5.6	0	0	94.1	0	5.9	0	100	0	0	0
Interference with social activities	72.2	27.8	0	11.1	76.5	11.8	5.9	5.9	90	0	10	0
Interference with hobbies or leisure time	88.9	11.1	0	0	88.2	0	11.8	0	90	10	0	0
How much has the PEG affected QOL	50.0	27.8	0	22.2	58.8	17.6	11.8	11.8	50	20	0	30
How much do you think about your PEG	44.4	33.3	16.7	5.6	52.9	23.5	23.5	0	50	50	0	0
Do you wish the PEG could be removed	88.9	11.1	0	0	82.3	11.8	5.9	0	100	0	0	0

This study also identified a major shortcoming of the Liverpool PEG questionnaire. The question *"How much has the PEG affected QOL"* is crucial to capture patients' perception of enteral feeding. However, the question is ambiguously worded as it is not explicit whether it implies a positive or negative effect on QOL. For instance, one participant (P20) reported that QOL was "m*uch better"* but recorded 1 *('not at all')* on the questionnaire. The score of 1 may have been considered by P20 to imply that PEG has *'not at all'* worsened the QOL. Another participant (P13) reported that the PEG tube was a *"god send"* and recorded 4 *('very much')* on the questionnaire. Similarly P2 at 3 months reported "worse" QOL but recorded 4 *('very much')* on the Likert scale. It is therefore unclear whether high scores imply significant improvement or deterioration in QOL. Given the vagueness on the relevance of scores, this domain was not analysed in this study.

4.14 Quality of life results: A thematic analysis of participants' perspectives

The written comments from participants in response to the two open questions *"What other comments you wish to make about your PEG?"* and "*How would you describe your quality of life since the insertion of your feeding tube?"* were subjected to thematic analysis, a qualitative mode of methodical inquiry that systematically investigates textual data, to identify relevant themes (Braun and Clarke, 2006).

Due to the distinct lack of literature on the impact of enteral feeding on QOL, it appeared essential to identify, analyse and report patterns within the data set to provide a set of themes which could inform clinical practice. These themes could also form a basis, from which future research can build upon and develop further. Moreover, it was essential to employ a flexible, replicable and transparent analytic method. It was

therefore felt that thematic analysis would be the most appropriate methodology for data analysis.

Thematic analysis is a highly flexible approach that provides a rich thematic description of the entire data set and is therefore a useful methodology when exploring new or under researched areas (Braun and Clarke, 2006). Finally, thematic analysis does not necessitate the detailed theoretical and technological knowledge of other qualitative approaches and can therefore, offer a more accessible and transparent form of analysis, particularly for those with no previous experience of qualitative research (Braun and Clarke, 2006).

An inductive, semantic and realist approach to thematic analysis was followed in accordance with the step-by-step guidelines recommended by Braun and Clarke (2006). As the study intended to explore patients' perspectives about the impact of enteral feeding on their QOL, the analysis was data-driven. In this sense, the analysis was inductive as the data was coded without any analytic preconceptions. The analysis took a semantic approach and themes were identified from the obvious meanings of data rather than looking for underlying presumptions (Braun and Clarke, 2006). A realist approach allowed identification and reporting of patients' perspectives of enteral feeding on their QOL.

During the analysis, the written views of participants were read repeatedly to ensure familiarity with the data set. The focus was on what content the narratives communicated. Coding was then undertaken, ascribing each sentence or account a code that described the main essence of the narrative. The codes were then assembled into more and more abstract codes, incorporating those that were similar in meaning and content until they represented a theme.

The analysis was an iterative and cyclical process, initially looking for shared themes between the sentences and searching for patterns in semantic content. Any substantial themes were noted and the data reread in the context of these themes. By immersing deeper in the generated themes and the underlying key perceptions, themes deemed similar were merged and those encompassing conceptually distinct themes were divided. The themes were finally refined and grouped into clusters to form overarching themes and subthemes. Meticulous care was undertaken during the analytical process to ensure that the original context of the data was not eroded.

The thematic analysis resulted in identification of four main themes: No change in QOL, worse QOL, improved QOL and problems with enteral feeding. A number of subthemes were identified which will be discussed further. The identified themes and subthemes are displayed in Figure 4.6. The subthemes are not exclusively distinct but remain interrelated to one another.

There were accounts from 17 participants at 3 months post gastrostomy; 13 participants indicated improvement in QOL, 3 reported no change in QOL and 1 reported worse QOL. At 6 months post gastrostomy, there were comments from 17 participants; 13 participants reported improved QOL despite inconveniences associated with enteral feeding. No participant reported worsening of QOL. At 12 months post gastrostomy, there were comments from 8 participants of which 1 participant (P1) reported no change in QOL, although did note that the gastrostomy tube was an *"inconvenience".* No participants reported worsening of QOL. For one participant, enteral feeding was "*a God send"* (P13). A number of selected verbatim quotations to illustrate the views and perspectives of the participants will be included in the section that follows. Table 4.2 shows detail individual patient accounts regarding the impact of enteral feeding on their QOL at 3, 6 and 12 months following gastrostomy insertion.

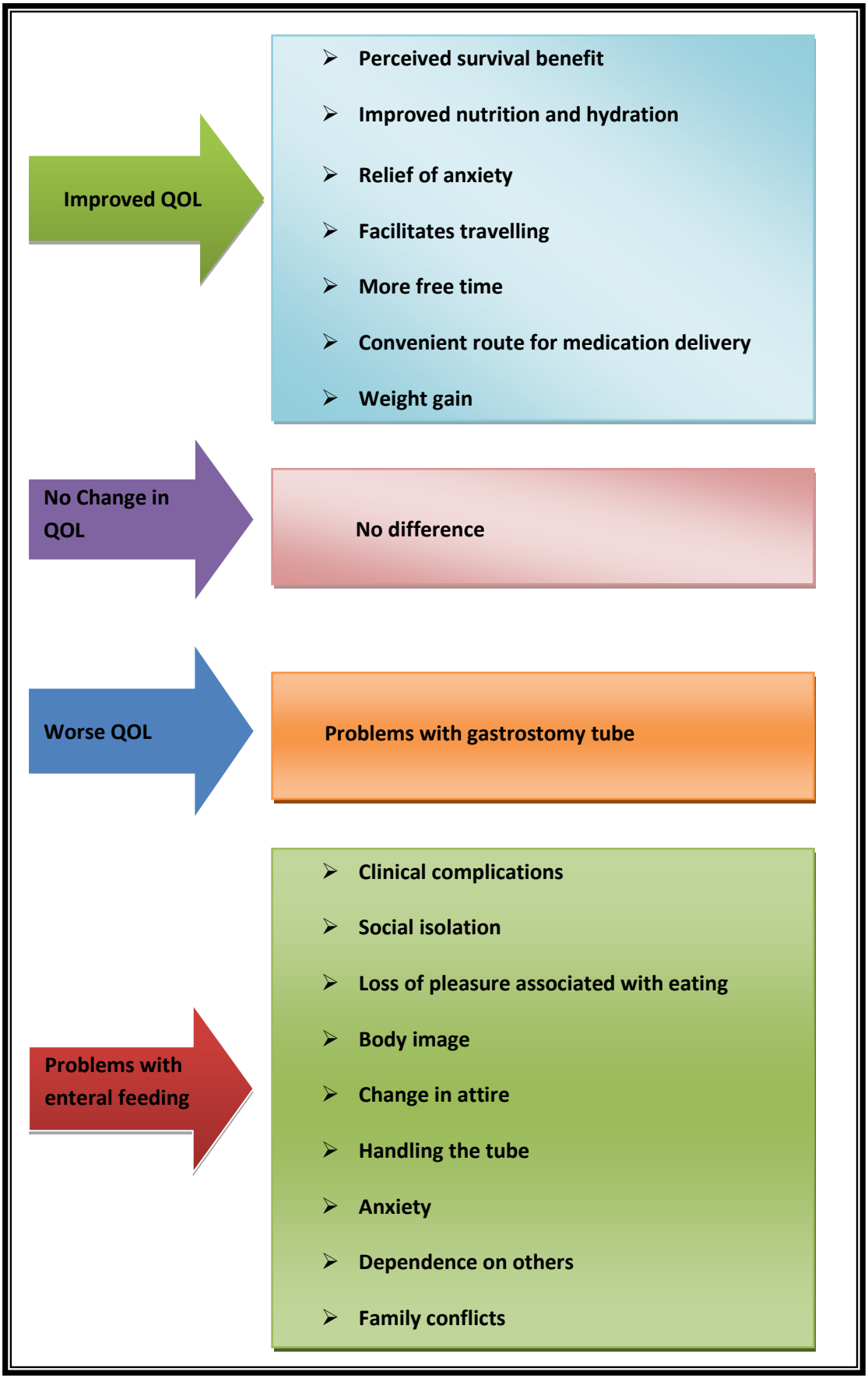

Figure 4.6: Diagram depicting the main themes and subthemes

4.14.1 Improved QOL

The vast majority of participants reported improved QOL. Data analysis identified the following themes which were associated with improved QOL.

Perceived survival benefit

Enteral feeding was perceived as being essential to survival and some participants expressed the view that enteral feeding had kept them alive. Enteral feeding was felt to have a positive impact not only on quantity but also QOL. These are exemplified in the following statements:

> *"It has been a great help. I couldn't manage without it."* (P3)
>
> *"I'm just so grateful it's helping me to live, and live more comfortably."* (P9)
>
> *"Without it – it would be (RIP)."* (P14)

Some participants had disinclination towards gastrostomy tube, but they acknowledged the positive impact of enteral feeding on survival and QOL.

> *"Would rather not have it, but for the purpose it was fitted think it has kept me alive for longer and made my quality of life much better."* (P6)

Improved nutrition and hydration

Participants felt that their nutritional and hydration needs were met with enteral feeding. Their views about improved nutrition were maintained throughout the study period:

> *"On the whole better with PEG than without it. I was not able to get enough food or fluid into me by mouth anymore so now feel better."* (P5)

"My quality of life has changed for the better. Improved, I am not hungry or thirsty and don't have to struggle to swallow." (P8)

"Quality of life has improved greatly. Without it I could not get any nutrition!." (P11)

Some participants were glad that they considered enteral feeding at an early stage as they no longer had to struggle at meal times with choking or coughing:

"I'm glad I had it inserted early, it's been so useful in ensuring that I could have sufficient fluids and medication daily and recently I have used it to take fortisips as my ability to swallow has weakened also, I do not have to cough or choke any more when using the PEG instead of oral intake." (P9)

Relief of anxiety

A number of participants reported that enteral feeding had helped to alleviate their anxieties about the inability to eat or drink. Participants did not have to *"worry"* about nutrition (P2, P5, P11, P13, P17 and P6) and hydration (P9, P17 and P20).

"The PEG has not stopped me from doing anything. It is not difficult to use and is easy to maintain. It has taken the stress out of eating and drinking." (P5)

"Much improved as I can now have sufficient fluid without worrying about dehydration." (P9)

"It means I don't have to worry about getting nutrients and calories into my system. It gives me more energy. Thanks." (P11)

"Much better, such a relief to be able to take liquid which because of my swallowing difficulties I can't manage otherwise…… No trouble at all using it and thankful for it." (P20)

Some participants felt that enteral feeding was brilliant. It helped to removing the 'stress' of eating and they would recommend it to other patients needing it:

"I think they are brilliant.... Took stress off me eating. It has made my quality of life so much better I would recommend it." (P10)

Participants felt that enteral feeding was a source of relief not only for themselves but also for their family members:

*"Quality of life is much better for me and my family since PEG fitted, I know I am getting all my dietary needs and my family know I am which is relief for all." (*P6)

A change in QOL may not be noticed in the first few postprocedural months. P16 had reported no change in QOL at 3 months but this view changed at 6 months:

"Glad that I had it done, swallowing is becoming more and more difficult and I am choking more." (P16)

Similarly P2 noticed improved QOL at 12 months despite reporting worse QOL at 3 months:

"My quality of life is better. I do not worry about food." (P2 at 12 months)

Facilitates travelling

Enteral feeding can give patients the freedom to travel without fear of prolonged meal times. Patients also adjust to the notion of administering feeds through the gastrostomy tube, even in presence of other people:

> *"My quality of life has improved it has made travelling better as I can take my own supplies. Putting a feed in by tube is much quicker than the speed I was eating before. I am no longer shy of people seeing me put a feed in so I can go anywhere I want to go.*" (P5)

More free time

Dysphagia is associated with prolonged meal times and can be tiring for patients. Enteral feeding can help to reduce the cumbersome meal times:

> *"Since having my PEG tube fitted I have found my life has become a lot easier. At first it took a lot of getting used to. Having a PEG has freed up a lot of my time."* (P19)

Enteral feeding also helped to save "*time and energy"*.

> *"It has removed the pressure. Although I have only used it for bolus feeds once a day. That has helped enormously saving time and energy."* (P13)

Convenient route for medication delivery

Gastrostomy tube can be a helpful alternative route for delivery of medicines. Patients do not have to struggle to swallow tablets and it can also help delivery of medications, if hospital admission is required. Delivery of medicines through the gastrostomy tube

enabled one participant to avoid the unpleasant taste of some of the medicines. All these factors may have a positive impact on QOL:

> *"Better, I can take medication via the tube, saves swallowing."* (P21)

> *"I am currently in hospital so the nurses are giving me feeds. It has made it easier for me to take medication."* (P16)

> *"A lot more pleasant now, bad tasting medication goes down the tube."* (P19)

Although patients may find the need for gastrostomy tube upsetting, they appreciate the benefits associated with gastrostomy tube feeding:

> *"Better for taking meds poorer for needing it."* (P21)

Weight Gain

One participant reported improvement in QOL and attributed this to weight gain.

> *"Much better, weight gained."* (P6)

4.14.2 No change in QOL

Some participants (P1, P7 and P16) reported no changes in their QOL at 3 months:

> *"I don't really think about it. It hasn't really changed my quality of life"* (P16)

Despite no perceived change in QOL, one participant found the presence of gastrostomy tube reassuring:

> *"Just as same as before; been a good thing, a reassurance"* (P1)

At 6 months, three patients (P1, P2, and P7) reported no change in QOL. P1 however, felt that it provided *"assurance as backup".* At 12 months, only P1 reported no change in QOL. Despite the inconveniences, it was still a reassurance:

> *"To be honest, irritating to have to flush it daily but realise it is there as a vital back up to be used if and when required."* (P1)

P7 was not using the gastrostomy tube at 3 and 6 months and therefore may not have noted any difference in QOL. P7 did not provide any comments at 12 months follow up but indicated in the Liverpool PEG questionnaire that it had not affected the overall QOL. Participants P2 and P16 however, reported improved QOL at subsequent follow up evaluation, as described in the foregoing section on improved QOL.

4.14.3 Worse QOL

Percutaneous gastrostomy tube can be associated with complications including wound infection and pain. These complications can negatively affect patient's QOL. One participant (P2) reported worse QOL at 3 months post gastrostomy due to problems with the gastrostomy tube. However improved QOL was reported in subsequent visits following successful management of infection and pain. Despite the complications, gastrostomy tube can be a source of hope for the future:

> *"Quality of life worse due to infection + pain. However, I do not regret having it done as I know I will need it in the future."* (P2)

4.14.4 Problems with enteral feeding

Enteral nutrition via a gastrostomy tube can be associated with a number of problems including tube leakage, pain and bleeding. Some patients are fully reliant on their

families/relatives for help with delivery of feeds. The following problems were identified from the comments provided by the study participants.

Clinical complications

Participants had an uneventful recovery following gastrostomy insertion and did not experience any major complications. However, minor complications including pain, infection and tube leakage were experienced, mainly in the first 3 months following gastrostomy insertion. These complications could potentially have a negative impact on the QOL of patients:

> *"Quality of life worse due to infection + pain."* (P2 at 3 months)

> *"It's the irritation from the disk digging into my skin - It pushes the skin off and its constantly sore."* (P11 at 3 months)

> *"Sore for 1st 2 weeks."* (P17 at 3 months)

> *"It bleeds and leaks quite a bit."* (P21 at 3 months)

One participant reported upper gastrointestinal bleeding:

> *"… a duodenal ulcer bleed. Possible cause me producing too much stomach acid for the change in food type – rushed into hospital – had drips for a few days and a couple of bags of blood – (still 8 in credit)."* (P14)

Social isolation

Enteral feeding can prevent patients from socialising with friends and/or families. Despite this drawback, enteral feeding can still have a positive impact on QOL:

"....it prevents me from eating out with friends or going out for a whole day. But I get round that as my friends understand and as the PEG so is so discreet when not in use I'm just so grateful its helping me to live and live more comfortably." (P9)

"To begin with had to organise the social life around the PEG feeds or take a big bag with me. Now only needs one top up during day. Life has greatly improved before I was always choking when eating food even mashed up food." (P19)

Altering the feeding times with the majority of feeds being delivered at night can reduce the negative impact on social life. One participant came up with a solution to reduce the impact of enteral feeding on social life:

"Since going to all night feeding + top up, the feeding has become less of a trial. Before needed to feed every 4 hours it affected our social life and general life." (P19)

Loss of pleasure associated with eating

Eating is associated with a number of pleasurable themes including taste and smell. Enteral feeding can lead to loss of pleasure associated with eating:

"At first longed for food (Real food, I dream of roast beef and fish and chips). Not really missing eating food. As I know there is no chance of being hospitalised due to choking. Only downside is getting used to feeling full and not taking anything in my mouth or down my throat." (P19)

Body image

The location of the gastrostomy tube can lead to perception of uneasiness about the body image:

> *"It dangles where other things dangle. The problems seem to be associated with its location, just under my prominent breastbone."* (P21)

Change in attire

Participants also had to adjust their attire to accommodate for the gastrostomy tube:

> *"Need to wear clothes with large elastic waist." (*P17)

Handling the tube

Maintaining the tube hygiene and preventing it from blockage, when not in use, can be a source of irritation to patients:

> *"To be honest, irritating to have to flush it daily but realise that it is there as a vital back up to be used if and when required."* (P1)

Patients may also struggle using the syringes to aid delivery of nutrition through the gastrostomy tube:

> *"Of course, using the PEG takes longer sometimes than normal feeding + taking medication as I have to use syringes, and other preparations. Most tiresome is having to take Fibre Fortisip which requires a plunger, and is difficult with weakening fingers and wrists."* (P9)

Anxiety

Living with a feeding tube can be a source of anxiety for patients. One participant was anxious about potential tube blockage:

> *"I worry about it getting blocked. I wonder if someone will invent a 'brush' to ensure that it can be cleaned so that it will not block."* (P2)

Dependence on others

Some participants (P2, P8, P14 and P21) were dependent on their family or carers for help with enteral feeding or maintenance of tube hygiene.

> *"My husband helps me with my feeds and cleaning and turning the tube. I definitely needed to have it."* (P8)

> *"My carer dresses the PEG site every day because of leakage."* (P21)

Participants also indicated dependence on things they expressed as being out of their control:

> *"I feel I have to use gauze around the tube after showering as carers do not dry the area properly."* (P2)

The role of family members in helping with enteral feeding and thereby enhancing QOL of patients cannot however be understated:

> *"If I had not got a loving and caring wife I would be in difficulties. She sorts out all medications, feeds, and with her ability to get on with everybody (despite having bad knees) we get on great."* (P14)

Family Conflicts

Dependence on others for instance, family members, can be a source of potential conflict:

> *"...my children have to give medication + feeds via the tube which causes anxiety + arguments."* (P2)

Despite all the inconveniences, patients have a positive attitude towards enteral feeding:

> *"I am grateful that the PEG offers an alternative way of nourishing myself, and whatever inconveniences I may have are greatly outweighed by the advantages"* (P9)

Table 4.2: Table showing individual patient accounts regarding the impact of enteral feeding on their QOL at 3, 6 and 12 months following gastrostomy insertion

Patient Number	3 months	6 months	12 months
1	Just the same as before; been a good thing, a reassurance.	No difference but provides assurance as back up.	To be honest, irritating to have to flush it daily but realise it is there as a vital backup to be used if and when required. No inconvenience.
2	Quality of life worse due to infection + pain. However, I do not regret having it done as I know I will need it in the future.	Not really any different though my children have to give medication + feeds via the tube which causes anxiety + arguments. I feel I have to use gauze around the tube after showering as carers do not dry the area properly	My quality of life is better. I do not worry about food. I worry about it getting blocked. I wonder if someone will invent a 'brush' to ensure it can be cleared so it will not block.
3	It has been a great help. I couldn't manage without it	RIP	RIP
4	RIP	RIP	RIP

5	The PEG has not stopped me from doing anything. It is not difficult to use and is easy to maintain. It has taken the stress out of eating and drinking.”	On the whole better with PEG than without it. I was not able to get enough food or fluid into me by mouth anymore so now feel better. My quality of life has improved it has made travelling better as I can take my own supplies. Putting a feed in by tube is much quicker than the speed I was eating before. I am no longer shy of people seeing me put a feed in so I can go anywhere I want to go.	Moved out of area
6	Much better, weight gained	Would rather not have it, but for the purpose it was fitted think it has kept me alive for longer and made my quality of life much better. Quality of life is much better for me and my family since PEG fitted, I know I am getting all my dietary needs and my family know I am which is relief for all.	RIP

7	No change	No difference	No comments
8	My quality of life has changed for the better	Improved, I am not hungry or thirsty and don't have to struggle to swallow. My husband helps me with my feeds and cleaning and turning the tube. I definitely needed to have it.	RIP
9	Much improved as I can now have sufficient fluid without worrying about dehydration.	I'm glad I had it inserted early, it's been so useful in ensuring that I could have sufficient fluids and medication daily and recently I have used it to take fortisips as my ability to swallow has weakened also, I do not have to cough or choke any more when using the PEG instead of oral intake. Swings + roundabouts. On the upside are the comments above, on the downside it prevents me from eating out with friends or going out for a whole day. But I get	I am grateful that the PEG offers an alternative way of nourishing myself, and whatever inconveniences I may have are greatly outweighed by the advantages. Of course, using the PEG takes longer sometimes than normal feeding + taking medication as I have to use syringes, and other preparations. Most tiresome is having to take Fibre Fortisip which requires a plunger, and is difficult with weakening fingers and wrists.

		round that as my friends understand and as the PEG so is so discreet when not in use I'm just so grateful it's helping me to live, and live more comfortably."	
10	Better made me get an appetite.	I think they are brilliant	Took stress off me eating. It has made my quality of life so much better I would recommend it
11	It means I don't have to worry about getting nutrients and calories into my system. It gives me more energy. Thanks. It's the irritation from the disk digging into my skin - It pushes the skin off and its constantly sore	Quality of life has improved greatly. Without it I could not get any nutrition!	No comments
12	Withdrew from the study	Withdrew from the study	Withdrew from the study
13	It has removed the pressure. Although I have only used it for bolus feeds once a day. That has helped enormously saving time and energy.	Mainly beneficial	It's a godsend. Didn't think about after a few months, aware of it at the beginning.

14	Apart from a duodenal ulcer bleed. Possible cause me producing too much stomach acid for the change in food type – rushed into hospital – had drips for a few days and a couple of bags so blood – (still 8 in credit).	Without it – it would be (RIP). If I had not got a loving and caring wife I would be in difficulties. She sorts out all medications, feeds, and with her ability to get on with everybody (despite having bad knees) we get on great.	Wouldn't be here if I had not got it. A well thought of idea.
15	RIP	RIP	RIP
16	I don't really think about it. It hasn't really changed my quality of life.	Glad that I had it done, swallowing is becoming more and more difficult and I am choking more. I am currently in hospital so the nurses are giving me feeds. It has made it easier for me to take medication.	RIP
17	Much better – eating food/drinking liquid was making me choke and cough. Sore for 1st 2 weeks	Need to wear clothes with large elastic waist.	Withdrew from the study
18	No comments	Good	RIP

19	Forget PEG is even there. Quality of life easier with PEG. No fear of choking not like trying to swallow real food. A lot more pleasant now, bad tasting medication goes down the tube. Only downside is, could be lazy, easier to get nutrition from PEG feeding rather than struggling to swallow.	To begin with had to organise the social life around the PEG feeds or take a big bag with me. Now only needs one top up during day. Life has greatly improved before I was always choking when eating food even mashed up food. Since going to all night feeding + top up, the feeding has become less of a trial. Before needed to feed every 4 hours it affected our social life and general life. At first longed for food (Real food, I dream of roast beef and fish and chips). Not really missing eating food. As I know there is no chance of being hospitalised due to choking. Only downside is getting used to feeling full and not taking anything in my mouth or down my throat.	Since having my PEG tube fitted I have found my life has become a lot easier. At first it took a lot of getting used to. Having a PEG has freed up a lot of my time. I found all night feeding was much better than feeding every four hours which I found took up a lot of my time.

20	Much better, such a relief to be able to take liquid which because of my swallowing difficulties I can't manage otherwise. Also being able to take Fortisip as a back up. No trouble at all using it and thankful for it	Much better	RIP
21	Better, I can take medication via the tube, saves swallowing. The problems seem to be associated with its location, just under my prominent breastbone. But I'm not looking forward to when it's the only method of feeding that I have. It dangles where other things dangle. The cap at the end is difficult to remove. Its location leads to problems, it's very prominent. It bleeds and leaks quite a bit.	Better for taking meds poorer for needing it. My carer dresses the PEG site every day because of leakage	Beneficial for taking pills which I was struggling to take.

4.14 Discussion

Quality of life (QOL) is conceptually an ill-defined term due to its holistic and subjective dimension and means different things to different people (Fayers and Machin, 2007; Rapley, 2003). Despite its subjective nature, the views and perspectives of patients about the impact of any treatment on their QOL adds another dimension to the evaluation of treatment (Good et al., 2014).

Although enteral feeding is routinely offered to patients with MND, there is no evidence to support or refute enteral feeding for maintaining or improving QOL. This prospective study is the first of its kind in the literature to demonstrate that enteral feeding helps to maintain or enhance QOL of patients.

Placement of a gastrostomy feeding tube has fundamental ethical issues and the decision to offer gastrostomy should depend on whether a patient will derive any actual benefit from it (Good et al., 2014). The needs, expectations, views and wishes of patients are of paramount importance and treatment efforts should be focussed at improving quality rather than just quantity of life (Bozzetti, 2008).

Eating is associated with a number of non-nutritional but pleasurable themes including taste, smell and socialization (Bozzetti, 2008; Brotherton and Judd, 2007; Roberge et al., 2000). Eating food with others helps to foster social and familial relationships and is related to a feeling of general wellbeing (Spataro et al., 2011). Enteral feeding, however, removes all these themes, thereby depriving the patient of the social role of a meal (Bozzetti, 2008; Brotherton and Judd, 2007; Roberge et al., 2000). Moreover, enteral feeding is not without complications. It can, thus, be speculated that the psychosocial inconveniences and difficulties with enteral feeding has a significant

impact on QOL of patients. Assessing QOL is, therefore, important to optimize the adequacy of enteral feeding to the needs and expectations of every individual patient.

This study was designed mainly to evaluate the effect of enteral feeding on QOL of patients with MND. The progressive deterioration in the ALSFRS-R and ALSAQ-40 scores are in keeping with the natural history of the condition (Cedarbaum et al., 1999; Jenkinson et al., 2003; Kaufmann et al., 2005; Norquist et al., 2004). Interestingly, the mean emotional functioning sub scores of ALSAQ-40 remained relatively constant following enteral feeding, as opposed to all other domains which increased with time. This interesting finding indicates that enteral feeding ameliorates emotional problems, for instance, feeling lonely, bored, and depressed or worry about how the disease will affect them in the future. The thematic analysis has given valuable insights into patients' perspectives of enteral feeding and its impact on their QOL.

The vast majority of participants had a positive attitude towards enteral feeding. Enteral feeding was perceived as being essential to survival by some patients while others felt that it helped to facilitate travelling, gain weight and save time and energy. Participants also reported a sense of relief and security that their nutritional needs were met. The BMI stabilised following gastrostomy and some participants felt that this had a positive impact on their QOL. Malnutrition and weight loss can significantly impact QOL, as patients are often exhausted, tired and spiritless (Greenwood, 2013; Korner et al., 2013). The findings of this study strongly indicate that management of malnutrition can play an important role in either maintaining or enhancing QOL.

Gastrostomy tube was associated with a number of complications including pain, leakage and infection. Despite the complications, participants had no regrets with gastrostomy as they see it as a "vital back up to be used if and when required". Enteral

feeding caused conflicts among family members and also led to loss of ability to share a meal and socialise with friends/families. These experiences can potentially lead to social isolation and anxiety/depression. Moreover, placement of feeding tube is associated with a multitude of emotions and adaptations. It is, therefore, important for health care professionals to understand these consequences of enteral feeding, monitor for signs of anxiety/depression, educate family members involved in the patient's care, and help patients and families to develop effective coping strategies.

Despite the inconveniences associated with enteral feeding, the reported positive benefits outweigh the negative aspects of enteral feeding. Only one participant reported worse QOL at 3 months post gastrostomy. However, this view changed at 12 months post gastrostomy and there was a perception of improved QOL. Finally, at 12 months follow up, none wished for the feeding tube to be removed, indicating a positive attitude towards enteral feeding.

Only 11.1% (n=2) and 17.7% (n=3) wished for the gastrostomy tube to be removed at 3 and 6 months, respectively. It is noteworthy that none wished 'very much' for the tube to be removed at any point. This is in contrast to a study involving 39 patients with head and neck cancers where 69% of the patients wished to have the feeding tube removed (Roberge et al., 2000). However, 80% of the patients were fed through nasogastric tube and the evaluation was undertaken at 7 days following discharge. Nasogastric tube feeding is often poorly tolerated (Heffernan et al., 2004; Scott and Austin, 1994) and this coupled with early evaluation may explain the high percentage of patients longing to have the tube removed.

The first few months following gastrostomy can be very challenging for patients who may encounter clinical and non-clinical problems associated with enteral feeding.

However, with passage of time, patients appear to cope well with the inconveniences and appreciate the positive impact of enteral feeding on their QOL. The positive impact may therefore not be noticed within the first few months after gastrostomy. A similar observation has been made by Bannerman et al. (2000) in a study evaluating the impact of enteral feeding on patients with dysphagia due to a range of causes. The authors reported an overall positive impact of gastrostomy on QOL among 55% patients at 1 month, 71% at 6 months and 75% at 12 months (Bannerman et al., 2000).

Percutaneous gastrostomy is a safe procedure associated with low risk of complications. The 30 day mortality following gastrostomy in MND ranges from 2 – 25% (Chio et al., 1999; Desport et al., 2000; Forbes et al., 2004; Mathus-Vliegen et al., 1994; Mazzini et al., 1995). This is similar to the 30 day mortality of 8 – 28% following gastrostomy insertion in an unselected patient population including a range of neurological disorders and tumours of the head, neck and gastrointestinal system (Blomberg et al., 2012). In the current study, there were no deaths within 30 days of gastrostomy insertion.

The two most common complications in this study were redness/irritation and tube leakage occurring in up to 70% and 60% of the cases, respectively. The clinical complications were similar to those observed in unselected patient population receiving gastrostomy for a number of tumours and neurological conditions, where tube leakage and peristomal infection occurred in 78% and 53% of the patients, respectively (Blomberg et al., 2012; Potack and Chokhavatia, 2008; Rogers et al., 2007). Infection was less common in the current study and was reported by only a quarter of the participants, which may reflect improvement in standards of infection prevention.

There is little in the published literature on the impact of enteral feeding on QOL of MND patients. The literature review identified only 4 studies on the topic. Three of

these (Lou et al., 2010; Mitsumoto et al., 2003; Zamietra et al., 2012) provide retrospective data from studies that were not primarily intended to investigate the association between enteral feeding and QOL. The only prospective study by Mazzini et al. (1995) provides anecdotal impressions from patients about their improved QOL but the authors do not present any concrete data relating to their observations.

Lou et al. (2010) reported a statistically significant reduction ($P < 0.001$) in the rate of decline on the MQOL-SIS, suggesting that enteral feeding improves QOL. The authors compared the slopes of MQOL-SIS, before and after gastrostomy insertion of 52 patients receiving PEG tube. Zamietra et al. (2012), retrospectively, reviewed the QOL scores, measured by using the ALSSQOL-R scale of 11 patients who had received PEG tube. Although the QOL scores deteriorated marginally over time, the difference was not statistically significant.

In a retrospective study, 28% listed less fatigue or less time spent on meals and 17% listed improved psychological wellbeing as positive effects of enteral feeding (Mitsumoto et al., 2003). Patients with enteral feeding experienced a significant ($p=0.0047$) poorer health status on the mini-sickness impact profile scale as compared to patients without enteral feeding. However, the bulbar sub scores were significantly lower in the gastrostomy group ($p<0.0001$) indicating that gastrostomy was performed too late to demonstrate a positive impact on QOL.

It is interesting to note that even outside the field of MND, the impact of enteral feeding on QOL remains a topic of debate (Good et al., 2014). A recent systematic review aimed at assessing the impact of medically assisted nutrition on the QOL of palliative care patients including cancer, dementia and neurodegenerative conditions did not

identify any randomised controlled trials or prospective non-controlled studies on the topic (Good et al., 2014).

Prospective studies of enteral feeding delivered through gastrostomy tube in patients with cancer (mainly head and neck) and neurological disorders (mainly stroke) has demonstrated maintenance or even improvement in QOL of patients, particularly in those without cancer (Klose et al., 2003; Schneider et al., 2000; Senft et al., 1993). Enteral feeding was associated with personal independence and improved physical and mental wellbeing (Schneider et al., 2000; Verhoef and Van Rosendaal, 2001).

Other studies in head and neck cancer, on the contrary, report negative psychosocial implications of enteral feeding including interference with family life, intimate relationship and social activities (Roberge et al., 2000; Rogers et al., 2007). About 50% of patients feel socially excluded due to the loss of social function of eating (Bannerman et al., 2000). In another study involving 20 patients with a wide range of neurological conditions and cancer, patients felt that tube feeding finally came to dominate their lives and was associated with an appreciable burden of treatment (Jordan et al., 2006). However, 17 out of 20 participants had experienced serious technical problems with their gastrostomy tubes which could have contributed to the 'burden of treatment'.

These studies, therefore, report a variable impact of enteral feeding on QOL. The conflicting results may be due to a number of variable factors including the heterogeneous population in terms of underlying primary diagnoses. Moreover, the studies have used different measuring instruments that generate results which cannot be meaningfully compared. However, these studies clearly paint a common picture – enteral feeding has an impact on QOL of patients. The expected benefits, risks and burden to the QOL should therefore be carefully considered and discussed with the

patient and the family to help ensure that all decisions about enteral feeding are informed and appropriate.

Although 17 patients completed the study, the sample size is felt to be appropriate as no additional themes were emerging and data saturation was therefore achieved. The data can also be deemed as robust and complete as almost all surviving participants completed the study. Strengths of this study include the prospective design and the completeness of inclusion and follow-up. Despite being a single site study, the subjects in this investigation are representative of the MND population requiring enteral feeding and the findings may therefore be transferable to other MND patient cohorts.

4.16 Conclusion

This work is the first study of its kind in the United Kingdom to demonstrate the positive impact of enteral feeding on QOL of patients with MND. The study offers support for the use of enteral feeding in improving or maintaining QOL of MND patients. A major theme that has surfaced from the study is that the available QOL instruments do not provide specific information regarding the impact of enteral feeding on an individual patient's QOL. There is a need to develop measurement tools that will mirror the QOL of MND patients receiving enteral feeding. Such tools should also take into account the emotional impact of the disease itself, which has a fatal prognosis.

Placement of a gastrostomy tube for enteral feeding requires careful individualisation based on the needs, expectations, views and wishes of the patient and its impact on their QOL. This study provides rich narratives from MND patients regarding their perceptions of enteral feeding. A key finding relevant for clinical practice is that most

study subjects acknowledged the importance of feeding tube and hence, the positive perception of enteral feeding.

In conclusion, the positive impact of enteral feeding on QOL and the themes that have surfaced from this research assuredly require further studies. The described themes provide important descriptions of the emotional, psychological and social impact of enteral feeding and can serve as a starting point for other prospective studies on the topic. This understanding is crucial for providing patients with evidence-based counselling on nutritional management and identifying areas for interventions aimed at maximizing the QOL benefit of enteral feeding.

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CHAPTER 5

GENERAL DISCUSSION

5.1 Preview to the Discussion

This thesis consisted of a programme of work which investigated the outcomes of enteral feeding and clinico-demographic characteristics of MND in Lancashire and South Cumbria in North West England. This final chapter presents a synopsis of the thesis and describes the key findings of the work. Conclusions are drawn within the context of limitations and recommendations for future research and practice proposed.

5.2 Overview of the thesis

Motor neurone disease is a fatal neurodegenerative disease of unknown aetiology, associated with the degeneration of upper and lower motor neurones (Hardiman, 2000; Miller et al., 2009). The clinical course is characterised by relentlessly progressive wasting and weakness of skeletal muscles leading to respiratory failure and death. The median survival from symptom onset to death varies from 20 to 48 months (Beghi et al., 2011). In the absence of a cure, supportive and palliative treatments remain the mainstay of management (Bede et al., 2011). Palliative and supportive management should start early as disability is unremittingly progressive and death generally occurs in a predictable fashion (Bede et al., 2011; Mitsumoto et al., 2005).

The main goal of treatment in MND is either to maintain or enhance QOL of patients through understanding and identification of their physical, psychological and social needs (Simmons, 2005). Health care professionals should therefore have a good understanding of the concept of QOL and how it is measured. The clinician caring for MND patients therefore encounters not only extraordinary challenges, but also extraordinary opportunities in providing expert care throughout the trajectory of this cruel and devastating illness.

Malnutrition is an independent prognostic factor for survival in MND (Desport et al., 1999; Marin et al., 2011). Malnutrition and weight loss negatively impacts QOL and patients feel exhausted, tired and spiritless, irrespective of the stage of illness (Greenwood, 2013; Korner et al., 2013). The requirement for enteral feeding eventually becomes a common occurrence in a significant proportion of patients with MND (Strong et al., 1999). Although enteral nutrition is offered to patients with dysphagia and/or weight loss, its effect on various outcomes including survival and QOL remains an issue of debate (Katzberg and Benatar, 2011; Miller et al., 2009).

This thesis was originally designed to assess the impact of enteral feeding on survival, nutritional status and QOL of patients with MND. The thesis also intended to describe the demographic and clinical characteristics of MND in Lancashire and South Cumbria in North West England.

Chapter 1 provided a background to the thesis. The chapter began with a discussion on the history and nomenclature of MND. Key concepts including epidemiology, aetio-pathogenesis, clinical characteristics, diagnosis and management of MND were reviewed, highlighting the phenotypic, genetic and prognostic heterogeneity. The concept of malnutrition as an independent prognostic factor for worsened survival was then introduced, thereby setting the scene for use of enteral feeding in MND.

Chapter 2 presented a systematic review assessing the impact of enteral feeding on survival, nutritional status and QOL of patients with MND. The majority of identified studies were retrospective and there were no randomised or quasi-randomised controlled trials. The systematic review demonstrated that the evidence for survival advantage with enteral feeding is inconclusive and a subject of debate. Although some studies suggested survival advantage, many others have failed to support these findings. There

is weak evidence to suggest stabilization of body weight with enteral feeding. There is a distinct lack of literature to support or refute enteral feeding for improving QOL.

Chapter 3 reported the demographic and clinical characteristics of MND in Lancashire and South Cumbria in North West England. The crude incidence rate of MND in the study population was 3.15/100,000. There was a slight male preponderance. The overall mean age of onset was 67.28 years (S.D. 11.06; range 22.78-93.06 years). The presentation was limb/spinal in 62.1% and bulbar in 37.9% cases. Median overall illness duration was 1.98 years (range 1.18-3.05 years). 91 patients received enteral feeding of which 67.0% were bulbar onset. Enteral feeding was not associated with survival advantage.

Chapter 4 investigated the impact of enteral feeding on QOL by exploring the perspectives of patients with MND regarding enteral feeding. The chapter provides rich data describing the views and experiences of patients with enteral feeding and its impact on their QOL. The results are also discussed in the broader context of extant literature on QOL.

5.3 Impact of enteral feeding on survival

The retrospective study investigating the demographic and clinical characteristics of MND in Lancashire and South Cumbria did not demonstrate any survival advantage from enteral feeding. This finding is consistent with a majority of other population based studies (Atassi et al., 2011; Desport et al., 2000; Forbes et al., 2004; Mathus-Vliegen et al., 1994; Mitchell et al., 2006; Mitsumoto et al., 2003; Murphy et al., 2008; Sorenson et al., 2007; Strong et al., 1999; Zhang et al., 2012). However, the finding contradicts with the outcomes of few other studies that suggest survival advantage with

enteral feeding (Chio et al., 1999; Chio et al., 2006; Czaplinski et al., 2006; Mazzini et al., 1995; Spataro et al., 2011).

All studies of enteral nutrition in MND have been observational in nature. Therefore, it is difficult to be certain whether the discordant impact on survival is due to different study designs, discrepancy in the rate of enteral feeding among various centres, bias or random error.

Most studies evaluating the survival outcomes of enteral nutrition were principally not designed to determine the effectiveness of enteral feeding as a therapeutic intervention. Some studies reported positive survival outcomes from retrospective database analysis of patients who had participated in MND drug trials (Kasarskis et al., 1999). However, patients enrolled in clinical trials are demographically and clinically different from the epidemiologic cohorts as they are usually younger and have spinal onset of the illness (Chio et al., 2011b). The findings from these studies therefore lack external validity (Chio et al., 2011b).

There is marked heterogeneity in the rate of enteral feeding among various centres caring for patients with MND. In a multicentre study in the United States, only 41% of MND patients with dysphagia underwent feeding tube insertion (Mitsumoto et al., 2003). There was a striking variation in the use of enteral feeding among the nine MND centres that participated in this study. The rates of enteral feeding ranged from 0% to 63% in the various participating clinics (Mitsumoto et al., 2003). In another study in northern Italy, 75% of dysphagic patients underwent gastrostomy for enteral feeding (Chio et al., 1999).

A number of factors may explain the variability in the rate of gastrostomy tube insertion including criteria for gastrostomy, acceptance rate of gastrostomy by patients, cultural

issues and physician bias. In the multicentre study by Mitsumoto et al. (2003), the criteria for gastrostomy insertion was stringent. Dysphagic patients were offered gastrostomy only when their ALSFRS-R bulbar sub score was less than 5, out of a possible total of 12 (Mitsumoto et al., 2003). Other studies have used less stringent criteria and feeding tube insertion was performed at higher bulbar subscores (Chio et al., 1999; Spataro et al., 2011). This may partly explain why the study by Mitsumoto et al. (2003) did not demonstrate survival advantage as compared to the studies by Chio et al. (1999) and Spataro et al. (2011).

Although some evidence can be assembled from these studies, the introduction of bias from self-selection of patients for gastrostomy may also influence survival outcomes. Some patients opt for gastrostomy whilst others either defer or refuse the procedure (Mitsumoto et al., 2003). There is often a tendency by patients to defer gastrostomy until they lose a significant amount of bulbar function and severe impairment of swallowing becomes a major issue (Mitsumoto et al., 2003).

The acceptance rate of gastrostomy is also variable across studies reporting survival outcomes. In a study carried out in Northern Italy, 75% of MND with dysphagia accepted gastrostomy (Chio et al., 1999). However, in another study from Southern Italy, only 50.6% accepted the procedure (Spataro et al., 2011). The reasons for these incongruities are unclear and it has been suggested that cultural factors may influence the rate of gastrostomy acceptance (Spataro et al., 2011). The variability in timing of gastrostomy insertion and self-selection bias may offer another explanation for the conflicting impact of enteral nutrition on survival.

Physician bias and availability of resources are other reasons for variability in gastrostomy use (Mitsumoto et al., 2003; Stavroulakis et al., 2013). In a survey of

Neurologists from MND Centres in United Kingdom, no Neurologist had the view that gastrostomy should be offered soon after diagnosis (Stavroulakis et al., 2013). Objective measures such as declining BMI and weight loss were the least used indicators in making decisions about enteral feeding. Only 73.7% of the Neurologists indicated offering gastrostomy when the BMI drops to less than 18.5 Kg/m^2. Patient reported factors including prolonged and difficult mealtimes were considered more important in the decision making process (Stavroulakis et al., 2013). This is surprising, given the robust evidence that malnutrition is an independent risk factor for prognosis. However, in the absence of convincing evidence on the impact of enteral feeding on survival, it is no surprise that there is variation regarding the timing of gastrostomy.

For methodological and ethical reasons, it is difficult to demonstrate a survival advantage with enteral feeding. An accurate comparison can only be made with cases that require enteral nutrition but do not receive it. All studies evaluating the impact of enteral nutrition in MND are limited by absence of randomization. However, for obvious ethical reasons, a randomized controlled study cannot be undertaken in MND as it would be immoral to deny enteral feeding to those whom it is a necessity. Comparison can, therefore, only be made with patients who refuse the procedure but such patients are uncommon.

5.4 Impact of enteral feeding on nutritional status

The BMI stabilised following gastrostomy and this study adds to the limited literature on the positive impact of enteral feeding on nutritional status of MND patients. An important observation relevant to clinical practice was that participants reported a sense of relief and security that their nutritional needs were met. It is well recognised that malnutrition and weight loss can significantly impact QOL, as patients are often

exhausted, tired and spiritless (Greenwood, 2013; Korner et al., 2013). The findings of this study strongly indicate that management of malnutrition can play an important role not only in stabilising BMI/weight but also maintaining or enhancing QOL.

5.5 Impact of enteral feeding on quality of life

The major objective of enteral feeding as a supportive measure in MND is to optimise QOL rather than prolong survival (Chio et al., 1999; Mitsumoto and Del Bene, 2000). However, there is distinct lack of literature to support or refute enteral feeding for maintaining or improving QOL of MND patients. The perspectives of patients and their relatives are important in formulating nutritional management plans (Heffernan et al., 2004). There is however, paucity of qualitative research in this area which would be useful in exploring subjective viewpoints of patients with MND in relation to enteral feeding.

The commonly used QOL instruments do not provide explicit information regarding how nutritional issues are experienced, addressed and related to an individual patient's QOL. Moreover, QOL in MND depends on a number of psychological and existential factors including the meaning that patients attach to their life, and therefore, an ideal QOL should encompass all these domains (Connolly et al., 2005; Robbins et al., 2001). However, the currently available QOL instruments do not address the impact of enteral feeding on all these domains of QOL in patients with MND.

All three studies that have evaluated QOL in relation to enteral feeding provide retrospective data from studies that were not primarily intended to investigate the association between enteral feeding and QOL (Lou et al., 2010; Mitsumoto et al., 2003; Zamietra et al., 2012). The only prospective study by Mazzini et al. (1995) did not

provide any concrete data relating to QOL. None of the studies have directly investigated the effect of enteral feeding on QOL.

Apart from anecdotal impressions of enhanced QOL (Mazzini et al., 1995), the only available quantitative information relating to QOL is from the study by Mitsumoto et al (2003). 28% patient listed less fatigue or less time spent on meals and 17% listed improved psychological wellbeing as positive effects of enteral feeding (Mitsumoto et al., 2003). This may suggest that other factors such as reduction of the tiresome and prolonged meal teams may be important for patients.

The prospective study described in chapter 4 provides rich qualitative data to support the view that enteral feeding improves QOL, a major goal of supportive management in MND. This is the first ever prospective study that has attempted to qualitatively investigate the impact of enteral feeding on QOL. A key finding relevant for clinical practice is that most study subjects acknowledged the importance of feeding tube and hence, the positive perception of enteral feeding.

Despite the inconveniences including clinical complications, anxiety, dependence on others, social isolation and altered body image, the vast majority of patients reported improved QOL with enteral feeding. Enteral feeding was perceived as being essential to survival by some patients while others reported that it helped to facilitate travelling and save time and energy. Participants also reported a sense of relief and security that their nutritional needs were met. Finally, participants had no regrets with gastrostomy insertion and no participant at 12 month follow up wished for the gastrostomy tube to be removed, indicating a positive attitude towards enteral feeding. The positive impact may however, not be noticed within the first few months following gastrostomy insertion and enteral feeding.

5.6 Limitations

This section will discuss the limitations of both the retrospective and prospective studies. These limitations will be exercised to draw recommendations for future work on enteral feeding in MND.

A major limitation of the study exploring the characteristics of MND in Lancashire and South Cumbria is its retrospective nature. The Preston MND database was not initially constructed with the aim of investigating the association between enteral feeding and survival. Therefore, there is no mechanism for controlling the impact of potential confounders on survival. Information about vital capacity, timing of gastrostomy and percentage of weight loss at gastrostomy tube insertion could not be ascertained from the case notes. It therefore remains unclear whether gastrostomy was offered in line with the clinical guidelines on the topic.

The retrospective study was also unable to ascertain the number of patients who were offered gastrostomy insertion and either refused or delayed the procedure. This would obviously have implications as gastrostomy placement late in the disease process, particularly when the forced vital capacity drops to less than 50% of the predicted, is associated with increased mortality.

The prospective study investigating the impact of enteral feeding on QOL is also not without limitations. The sample size was small but reflective of an overall cohort of patients requiring enteral feeding and sufficient enough to generate meaningful results. It would be difficult to obtain a larger study sample given the low prevalence of MND patients requiring enteral feeding. A multicentre study would be ideally placed to address this shortcoming and build on the findings of this preliminary work.

It is of note that no specific criterion was used by the referring neurologists in making decisions about enteral feeding. In most cases, it was triggered by dysphagia but objective measures such as declining BMI and weight loss were used very infrequently. Although there was a significant ($p<0.05$) weight loss in the study cohort at the time of gastrostomy as compared to diagnosis, enteral feeding was recommended to only one patient on the basis of weight loss alone. This echoes the findings of a survey conducted among neurologists from MND Centres in United Kingdom where measures of weight loss were the least used indicators in making decisions about enteral feeding (Stavroulakis et al., 2013).

The ALSAQ-40 and Liverpool PEG questionnaires are also limited in their ability to explore the QOL of individual patients. The Liverpool PEG questionnaire has not undergone rigorous validation but it encapsulates a number of themes associated with the impact of enteral feeding on QOL. This study also identified a major shortcoming of the PEG questionnaire. The crucial question "*How much has the PEG affected QOL"* is ambiguously worded as it is not explicit whether it implies a positive or negative effect on QOL. Moreover, these questionnaires do not explore all facets of enteral feeding that may be important to an individual patient. In order to address this inadequacy, this study incorporated an open question to the Liverpool PEG questionnaire. This open question has generated rich data about the views and perspectives of patients regarding the impact of enteral feeding on their QOL.

The participants were recruited from one care centre only and their views regarding the impact of enteral feeding on QOL may not necessarily reflect the experiences of MND patients from other centres. There is also the possibility of positively biased responses, given the unique service delivery model in the study centre where patients are supported at every stage of the disease process through provision of outreach and hospice clinics.

However, the service delivery model should not significantly influence the outcome as the questionnaire was specifically designed to address the impact of enteral feeding rather than the model of service delivery on QOL. Moreover, the clinical and demographic characteristics of MND in the study centre are highly consistent with data from other population based studies. It can therefore be convincingly argued that the study cohort is representative of the overall MND population.

The lack of control group in the prospective study is an unavoidable limitation, as it would be unethical to deny enteral feeding to patients who require it, for the sole purpose of undertaking a study. A proportion of patients with MND defer or refuse gastrostomy insertion and it would be interesting to study the QOL outcomes of early enteral feeding as compared to late or no enteral feeding in patients who defer or refuse gastrostomy. Despite the limitations, this is the first study of its kind to explore the impact of enteral feeding on QOL of patients with MND.

5.7 Conclusion

Symptomatic and palliative treatment remains the mainstay of management in MND (Bede et al., 2011; Radunovic et al., 2007). In the absence of a cure, advance care planning is important to develop individualised care plans, particularly addressing decisions regarding nutritional support including enteral feeding (Chio et al., 2006; Ng et al., 2009). Achieving the best QOL for patients, their families and carers should be the primary goal of management (Radunovic et al., 2007).

Enteral feeding may not improve survival, but this work demonstrates that it helps to maintain or even enhance QOL of MND patients. Although clinicians cannot cure or halt the inexorable disease progression, they are distinctively placed to identify and

offer symptomatic treatments including nutritional support throughout the disease trajectory. The topic of enteral feeding should be raised early in the disease process through a multidisciplinary approach to raise awareness about malnutrition, its consequences and management. Patients and their caregivers should be educated about the risks and benefits of enteral feeding and the optimal timing for insertion of feeding tube. The autonomy of the patient should, however, be respected throughout the care planning and delivery process (Radunovic et al., 2007).

Nutritional management approaches including nutritional surveillance through measurement of BMI on a 3 monthly basis, dietary counselling and consideration of enteral feeding should therefore become an integral part of ongoing care (Andersen et al., 2012; Greenwood, 2013; Miller et al., 2009). Early involvement of dietician is imperative in nutritional assessment and management. Patients should be encouraged to record their decisions regarding enteral feeding as part of their care plan. These advance decisions will help to reduce the risk of gastrostomy placement, late in the illness, when invasive interventions can be potentially hazardous.

Evidence-based information is of paramount importance in formulating treatment decisions regarding enteral feeding. However, given the wide clinical heterogeneity of the disease, self-selection bias and ethical issues in randomising patients, the feasibility of randomised controlled trials on assessing the impact of enteral feeding on QOL is extremely limited. Furthermore, the rarity of the condition implies that it can take a single centre a number of years to accrue significant patient numbers into any study evaluating the efficacy of enteral feeding. The difficulty of undertaking randomised controlled trials in such a rare disease is a challenge to the international MND community to organise multicentre observational studies to address this contentious but fundamental issue.

The subject of enteral feeding in MND and its impact on survival and QOL has remained as much supposition as science. Multicentre studies will almost certainly be required to obtain a level of evidence sufficient to recommend enteral feeding for improving QOL. In conclusion, until such evidence is forthcoming, the results from this work can help to inform nutritional management of patients with MND.

5.8 Scope and recommendations for future research

The thesis has identified the following topics for future research:

1. Investigate the impact of deferring or refusing enteral feeding on QOL and survival of patients with MND in a prospective study. The study should be adequately powered and therefore, multicentre in nature. Undertaking a randomized controlled study may be difficult as it would be unethical to deny enteral feeding to those who need it. However, it is well recognized that a proportion of patients with MND defer or refuse enteral feeding and identifying these patients early would allow an ethically acceptable control group. This would also allow comparison between QOL outcomes of early enteral feeding and late or no enteral feeding in patients who defer or refuse gastrostomy.

2. Investigate the impact of enteral feeding on QOL of relatives and carers of patients with MND. It is becoming increasingly recognized that relatives and carers of patients with MND experience caregiver burden due to the rapid and progressive nature of the illness. The physical and psychological demands of caring for a patient with MND and subsequent bereavement can lead to significant caregiver strain with implications for QOL of relatives and carers. Providing assistance with enteral feeding can further add to the challenges of

caring for a patient with MND. Understanding these challenges and implications on QOL will be crucial in formulating appropriately tailored interventions including bereavement support that may help to improve the well-being and QOL of relatives and carers.

3. Investigate the impact of enteral feeding on survival through prospective population based observational data. The systematic review has shown that none of the studies reporting the impact of enteral feeding on survival were primarily designed to determine the efficacy of enteral feeding as a therapeutic intervention. Moreover, there is marked heterogeneity in the rate of enteral feeding among various study centres with discernible variation in the criteria for recommending enteral feeding. For methodological and ethical reasons, it is difficult to demonstrate a survival benefit as factual comparison can only be made with patients that require enteral feeding but do not receive it. Comparison can however be made with patients who refuse the procedure but such patients are uncommon. This clearly highlights the need for multicentre studies specifically designed to evaluate the impact of enteral feeding on survival. Such studies should follow a uniformly agreed criterion for recommending enteral feeding.

4. Explore the reasoning behind why some patients accept and others defer or reject enteral feeding. Unfortunately, some patients defer enteral feeding until late in the illness, when invasive interventions like gastrostomy can be potentially hazardous. Adult competent patients are entitled to refuse enteral feeding, but the reasons for this are unclear and may comprise social, cultural, support and personal factors including concerns about potential disadvantages of gastrostomy tube. Understanding these factors will be important to tailor

discussions around enteral feeding with patients to ensure that decisions around enteral feeding are timely and well informed.

5. Incorporate health related QOL as an important end-point in studies involving enteral feeding in MND. Health related QOL is a multifaceted concept that aims to quantitatively evaluate the impact of illness as well as treatment on an individual, as different patients respond differently, both to illness and treatment. Management of MND is mainly supportive and palliative focussed on preserving and/or improving QOL. It is therefore important that QOL should be incorporated as a major outcome variable in studies involving enteral feeding in MND.

6. Develop measurement tools to assess the impact of enteral feeding on QOL of patients with MND that encompasses not only the physical but also the emotional and social implications of enteral feeding. The measurement tool should also take into account the emotional impact of the disease itself, which has a fatal prognosis. Most of the commonly used QOL instruments are generic and not MND specific. Moreover, the currently available QOL instruments do not provide explicit information about how nutritional issues are experienced, addressed and related to an individual patient's QOL. There is increasing evidence that QOL in MND does not seem to correlate with physical functioning but appears to depend on psychological, social support, spiritual and religious factors. A MND specific QOL instrument should therefore not only address the domains included in ALSAQ – 40, but also incorporate the existential facet that will capture the meaning that patients attach to their life. Finally, such an instrument should also encapsulate the impact of nutritional issues including enteral feeding, where applicable, on the QOL of patients with MND.

5.9 Outputs from the research

Some of the findings from the retrospective study were presented as a poster at the 25th International Symposium on ALS/MND held at Brussels in December 2014 (Appendix 15). During the course of the study, three papers on MND, not directly related to the research were published (Appendix 16).

The retrospective study presented in chapter 3 was submitted as a research paper entitled "Motor neurone disease in Lancashire and South Cumbria in North West England and an 8 year experience with enteral nutrition" to the Journal of Clinical Neuroscience for consideration for publication. This paper has been accepted and is currently with the production team of the Journal of Clinical Neuroscience.

The prospective study presented in chapter 4 is being prepared as a paper entitled "Impact of enteral feeding on quality of life of patients with motor neurone disease" for submission to the Palliative Medicine journal for consideration for publication.

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APPENDICES

Appendix 1: Ovid MEDLINE search strategy

Database: Ovid MEDLINE(R) <1946 to July Week 1 2014>

Search Strategy:

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1 exp Motor Neuron Disease/ (19962)

2 motor neurone disease.mp. (709)

3 motor$ neuron$ disease$.mp. or Motor Neuron Disease/ (6259)

4 exp Amyotrophic Lateral Sclerosis/ (13109)

5 lou gehrig.mp. (25)

6 lou gehrig$.mp. (119)

7 1 or 2 or 3 or 4 or 5 or 6 (21416)

8 exp Enteral Nutrition/ (15730)

9 enteral feeding.mp. or Enteral Nutrition/ (16792)

10 feeding tube.mp. or Enteral Nutrition/ (16535)

11 nasogastric feeding.mp. (430)

12 exp Gastrostomy/ (6504)

13 percutaneous endoscopic gastrostomy.mp. (2180)

14 radiologically inserted gastrostomy.mp. (22)

15 PEG.mp. (22852)

16 RIG.mp. (2163)

17 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 (45517)

18 7 and 17 (228)

19 limit 18 to english language (196)

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Appendix 2: Ovid EMBASE search strategy

Database: Embase <1980 to 2014 Week 28>

Search Strategy:

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1 exp Motor Neuron Disease/ (27510)

2 motor neurone disease.mp. (950)

3 motor$ neuron$ disease$.mp. or Motor Neuron Disease/ (9277)

4 exp Amyotrophic Lateral Sclerosis/ (22342)

5 lou gehrig.mp. (35)

6 lou gehrig$.mp. (165)

7 1 or 2 or 3 or 4 or 5 or 6 (28624)

8 exp Enteral Nutrition/ (20274)

9 enteral feeding.mp. or Enteral Nutrition/ (21308)

10 feeding tube.mp. or Enteral Nutrition/ (21947)

11 nasogastric feeding.mp. (596)

12 exp Gastrostomy/ (7459)

13 percutaneous endoscopic gastrostomy.mp. (4693)

14 radiologically inserted gastrostomy.mp. (52)

15 PEG.mp. (35589)

16 RIG.mp. (3131)

17 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 (67639)

18 7 and 17 (484)

19 limit 18 to english language (419)

****

Appendix 3: National Research Ethics Service (NRES) approval

NHS
Health Research Authority

NRES Committee East Midlands - Nottingham 1
The Old Chapel
Royal Standard Place
Nottingham
NG1 6FS

Telephone: 0115 8839390 (Direct Line)
Facsimile: 0115 9123300

14 December 2011

Dr Suresh Kumar Chhetri
Department of Neurology
Royal Preston Hospital
Sharoe Green Lane
Preston
PR2 9HT

Dear Dr Chhetri

Study title: **Enteral tube feeding for Motor Neuron Disease (MND): Effect on quality of life and nutritional status**

REC reference: **11/EM/0468**

The Proportionate Review Sub-committee of the NRES Committee East Midlands - Nottingham 1 Research Ethics Committee reviewed the above application on 13 December 2011.

Ethical opinion

Prior to the meeting, a reviewer requested further information via email regarding the application. You responded to the queries and details and clarification are detailed below:-

- You were asked if there is any reason for using the term 'neuron' in the title rather than the more commonly used term motor neurone disease. It is suspected that patients will be more familiar with 'neurone' than 'neuron' and this might avoid any confusion. You confirmed that the term will be changed to 'neurone' in documentation.
- On the Consent Forms, the recommendation is that participants should initial (not tick) each of the boxes to indicate they have read and understand each statement they are consenting to. You had included both options, and the reviewer questioned if there is a reason for this. You responded that there is no particular reason for giving the option of 'tick/initial'. You are prepared to amend this to read 'Please sign in the boxes next to the statements that you agree with'.
- You were informed that questions 10 to 12 of the ALSFRS questionnaire are not provided in the copy submitted with the application. You were asked if you were going to include these questions. You confirmed that question 10 – 12 of the ALSFRS questionnaire will be included and you enclosed a copy of the complete ALSFRS for review.
- The Reviewer informed you that the ALSAQ-40 has the fifth option "Always or cannot do at all" for questions 6 & 7. The version of the questionnaire submitted

has a different fifth option for these same questions. The ALSAQ-40 fifth option for questions 24 to 30 is also at variance with your fifth option. You were asked if the changes are validated or are they a mistake. You confirmed that the fifth option for questions 6 and 7 should read 'always or cannot do at all' and the correct form will be used. This will also apply for the fifth option for questions 24 - 30 ('always or cannot do at all') to ensure that the validated questionnaire is used.

- You were asked at which stage and for what reason the patient letter is sent. You confirmed that the patient letter will be sent as a covering letter along with the PEG questionnaire four weeks before the scheduled follow up appointments (3, 6 and 12 months after gastrostomy). The patient letter will serve as a reminder to the patient that they are invited to complete the PEG questionnaire in order to understand their experiences with tube feeding and its impact on their quality of life at different timeframes (3,6 and 12 months). The participants would be informed about this both verbally, during the initial stage of consent and through the Patient Information Sheet. They will also be requested to bring the completed questionnaire during the follow up visit. If they fail to bring the completed questionnaire to the follow up appointment, they will be given the opportunity to complete this during the follow up visit.

- You were asked to provide a copy of the Patient Reminder Letter mentioned in the flow chart. This was subsequently submitted and reviewed at the meeting.

- You were informed that it is usually suggested that the Participant Information Sheet includes the hospital's PALS contact details should a participant wish to complain. You confirmed that you will incorporate this into the Participant Information Sheet to read "If you still remain unhappy, then please contact the Patient Advice and Liaison Services (PALS), Lancashire Teaching Hospitals, Sharoe Green Lane, Preston, PR2 9HT. Telephone: 01772 522972 or 01257 247280)"

At the meeting, the Committee also agreed that the statement 'I consent to the processing of my personal information for the purposes explained to me' stated in the Consent Form is superfluous to the study, and is not required. Therefore, it should be removed.

The Committee noted that in the ALSF Rating Scale under the section 'handwriting', the word 'right' against the number 1 should be changed to 'write'.

On behalf of the Committee, the sub-committee gave a favourable ethical opinion of the above research on the basis described in the application form, protocol and supporting documentation, subject to the conditions specified below.

Ethical review of research sites

The favourable opinion applies to all NHS sites taking part in the study, subject to management permission being obtained from the NHS/HSC R&D office prior to the start of the study (see "Conditions of the favourable opinion" below).

Conditions of the favourable opinion

The favourable opinion is subject to the following conditions being met prior to the start of the study.

Management permission or approval must be obtained from each host organisation prior to

the start of the study at the site concerned.

Management permission ("R&D approval") should be sought from all NHS organisations involved in the study in accordance with NHS research governance arrangements.

Guidance on applying for NHS permission for research is available in the Integrated Research Application System or at http://www.rdforum.nhs.uk.

Where a NHS organisation's role in the study is limited to identifying and referring potential participants to research sites ("participant identification centre"), guidance should be sought from the R&D office on the information it requires to give permission for this activity.

For non-NHS sites, site management permission should be obtained in accordance with the procedures of the relevant host organisation.

Sponsors are not required to notify the Committee of approvals from host organisations.

Additional Conditions:-

1. The reference to 'neuron' should be changed in documents to 'neurone'. Revised documents should be submitted to the Committee.

2. In the Consent Form above the boxes, the header should be reworded to state 'Please sign in the boxes next to the statements that you agree with'.

3. The Committee agreed that the statement 'I consent to the processing of my personal information for the purposes explained to me' in the Consent Form is superfluous to the study, and is not required. Therefore, it should be removed.

4. The Participant Information Sheet should include the hospital's PALS contact details should a participant wish to complain.

5. In the ALSF Rating Scale under the section 'handwriting', the word 'right' against the number 1 should be changed to 'write'.

It is the responsibility of the sponsor to ensure that all the conditions are complied with before the start of the study or its initiation at a particular site (as applicable).

You should notify the REC in writing once all conditions have been met (except for site approvals from host organisations) and provide copies of any revised documentation with updated version numbers. Confirmation should also be provided to host organisations together with relevant documentation.

Approved documents

The documents reviewed and approved were:

Document	*Version*	*Date*
Covering Letter		
GP/Consultant Information Sheets	1.0	05 December 2011
Investigator CV		
Letter from Statistician	1.0	
Letter of invitation to participant	1.0	05 December 2011
Other: Referee Letter		

Other: CV for Robert Lea		
Other: Cv for Suresh Chhetri		
Participant Consent Form	1.0	05 December 2011
Participant Information Sheet	1.0	05 December 2011
Protocol	1.0	05 December 2011
Reminder letter to participants	1.0	05 December 2011
Questionnaire: Amyotrophic Lateral Sclerosis Functional Rating Scale		
Questionnaire: Liverpool PEG Questionnaire	1.0	05 December 2011
Questionnaire: Quality of Life Questionnaire		12 March 2008
REC application		07 December 2011
Summary/Synopsis	1.0	05 December 2011

Membership of the Proportionate Review Sub-Committee

The members of the Sub-Committee who took part in the review are listed on the attached sheet.

Statement of compliance

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

After ethical review

Reporting requirements

The attached document "After ethical review – guidance for researchers" gives detailed guidance on reporting requirements for studies with a favourable opinion, including:

- Notifying substantial amendments
- Adding new sites and investigators
- Notification of serious breaches of the protocol
- Progress and safety reports
- Notifying the end of the study

The NRES website also provides guidance on these topics, which is updated in the light of changes in reporting requirements or procedures.

Feedback

You are invited to give your view of the service that you have received from the National Research Ethics Service and the application procedure. If you wish to make your views known please use the feedback form available on the website.

Further information is available at National Research Ethics Service website > After Review

11/EM/0468 **Please quote this number on all correspondence**

With the Committee's best wishes for the success of this project

Yours sincerely

pp **Reverend Keith Lackenby**
Vice-Chair

Email: trish.wheat@nottspct.nhs.uk

Enclosures: *List of names and professions of members who took part in the review*

"After ethical review – guidance for researchers"

Copy to: *Dr Tahir Majeed – Chief Investigator/Academic Supervisor*

Mrs Lin Nelson, Lancashire Teaching Hospitals NHS Foundation Trust

Appendix 4: Lancashire Teaching Hospitals NHS Foundation Trust approval

Lancashire Teaching Hospitals NHS
NHS Foundation Trust

Research Directorate
Royal Preston Hospital
Sharoe Green Lane, Fulwood
Preston, PR2 9HT

Tel: 01772 524956
Fax: 01772 523184
Email: Kina.Bennett@lthtr.nhs.uk
Reply to: Royal Preston Hospital

RESEARCH AND DEVELOPMENT DIRECTORATE

Our Ref: LN/KB

12th January 2012

Dr. Suresh Chhetri
Specialist Registar in Neurology,
Royal Preston Hospital,
Sharoe Green Lane,
Preston, PR2 9HT

Dear Dr Chhetri,

R&D Ref:1571 **REC Ref: 11/EM/0468**

Enteral tube feeding for Motor Neurone Disease (MND): Effect on quality of life and nutritional status

The above study was reviewed on behalf of Lancashire Teaching Hospitals NHS Foundation Trust by the Research Committee on 21st December 2011.

I am pleased to inform you that the study was approved and the Trust is happy for this study to go ahead, subject to the conditions listed in the attached document.

This letter acts as proof of NHS Permission to conduct the research project described in the Protocol submitted for review. Any variations to the protocol must be re-submitted to this Committee and new approval sought. The research project must not start until:

- Ethical approval, from the National Research Ethics Service
- The declaration attached to this letter has been signed, dated and returned to the Research Directorate.
- Funding arrangements in place

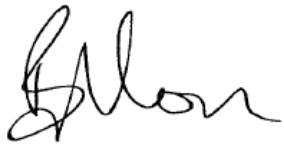
Any failure to comply with these requirements will result in action being taken under the Lancashire Teaching Hospitals NHS Foundation Trust Policy for Fraud and Misconduct in Research.

List of documents reviewed and approved

- **REC_Form**
- **RandD Form**
- **NHS_SSI Form**
- **Quality of life questionnaire**
- **Letter to the patient**
- **Patient Information leaflet_v2**
- **GP Letter_v2**
- **Reminder letter to participants**
- **Liverpool PEG questionnaire**
- **Amyotrophic Lateral Sclerosis Functional Scale**

Attached to this letter is a summary of the general terms and conditions for the conduct of all research in this Trust. Please read this and return a signed copy to the Research Directorate at the above address to indicate your acceptance of these terms and conditions within one month of the date of this letter.

Yours sincerely



Mrs Lin Nelson
Research and Development Manager

Appendix 5: University of Central Lancashire approval

Date: 22ND November 2012

Suresh Chhetri
Block I, Staff Village
Royal Preston Hospital
Preston
PR2 9HT

University of Central Lancashire

Graduate Research School
University of Central Lancashire
Preston PR1 2HE
United Kingdom
Telephone 01772 895085
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Email researchdegrees@uclan.ac.uk
www.uclan.ac.uk

Dear Suresh

REGISTRATION FOR THE AWARD OF RESEARCH DEGREE OF THE UNIVERSITY OF CENTRAL LANCASHIRE

I am pleased to inform you that the STEM Research Degrees Sub-Committee has approved your registration on a PART time basis for the degree of MD (Res)

Title of Programme of Research

Enteral tube feeding for Motor Neurone Disease (MND): Effect on quality of life and nutritional status.
Abbreviated title: ENFED

Supervisors

Director of Studies: Professor Robert Lea – School of Pharmacy & Biomedical Sciences

Second Supervisor 1: Dr Anthony Ashton - School of Pharmacy & Biomedical Sciences

Date of Registration and Duration of Programme

The expected period of registration is 36 months with effect from 1st April 2012, subject to conditions specified in the University Regulations.

The expected date for submission of your final thesis is **31st March 2015**.

Examination Arrangements

a) The arrangements for examining you on your programme of work.
b) The external and internal examiners to be appointed.

These arrangements should be submitted no later than 4 months before you propose to submit your thesis for examination. Please note that you will not be able to submit your thesis until examination arrangements have been approved.

Please feel free to contact me about any aspect of the registration procedures or with any other queries you may have.

Yours sincerely

Clare Altham
On behalf of the STEM Research Degrees Sub-Committee

Copies: Bob Lea
Anthony Ashton
Jai Singh

Appendix 6: Cox Regression analysis of non-enteral nutrition variables on survival time

Covariate	Regression coefficient (β)	Degrees of freedom (df)	p-value	Odds Ratio
Sex	-0.086	1	0.44	0.92
Onset age	0.03	1	0.001	1.03
Onset site	0.17	1	0.15	1.19
Riluzole	-0.61	1	0.001	0.60
Diagnostic Delay	-0.002	1	0.001	0.998

Appendix 7: Letter of invitation to Participant

Lancashire Teaching Hospitals NHS
NHS Foundation Trust

Preston MND Care and Research Centre,
Department of Neurology,
Royal Preston Hospital
Sharoe Green Lane,
Preston,
PR2 9HT
Tel: 0177 252 2545

To,

Patient details and address

Re : "Enteral tube feeding for Motor Neurone Disease (MND): Effect on quality of life and nutritional status"

Dear ……..,

Thank you for participating in the above study. We are studying the experience of patients with gastrostomy and its impact on their quality of life and nutritional status. We would be grateful if you could complete the enclosed questionnaire entitled "Liverpool PEG questionnaire". Please bring the completed questionnaire to your next appointment.

Completing this questionnaire is entirely voluntary and will not alter your care in any way.

All information will be strictly confidential and stored securely in a locked filing cabinet in the Preston MND care and research centre office. Further information about the study can be found on the participant information sheet enclosed with this letter.

If you have any questions or would like further information regarding this study, please free to contact the researcher (Dr. Suresh Chhetri) or a staff member of the Preston MND Care and research centre team.

Thank you.

Yours sincerely,

Dr. Suresh Chhetri,
Specialist Registar in Neurology,
Royal Preston Hospital,
Sharoe Green Lane,
Preston, PR2 9HT
Contact : 0177 252 2317

Appendix 8: Participant information sheet

Lancashire Teaching Hospitals NHS
NHS Foundation Trust

PARTICIPANT INFORMATION SHEET

Research study title: Enteral tube feeding for Motor Neurone Disease (MND) - Effect on quality of life and nutritional status.

You are being invited to participate in a study that aims to get a better understanding of the effect of feeding/gastrostomy tube on quality of life and nutritional status of patients diagnosed with Motor Neurone Disease. Before you decide, it is important for you to understand why the research is being done and what it will involve. You should only participate if you want to; choosing not to take part will not affect your medical care or disadvantage you in any way. Please take time to read this information carefully and discuss it with others if you wish. If after reading this leaflet, you have any questions, then please discuss them either with the study doctor (Dr. Suresh Chhetri) or a member of the MND team (contact details appear below).

What is the purpose of the study?
MND can affect the muscles involved in chewing and swallowing leading to malnutrition, dehydration and weight loss. Placement of feeding tube called gastrostomy tube into the stomach can be a suitable means of long-term nutritional maintenance. The study aims to get a better understanding of patient's experience with tube feeding and its impact on their quality of life. The study will also examine change in nutritional state through measurement of bodyweight at the time of diagnosis, before and after gastrostomy.

Why have I been chosen to take part?
You have been invited to take part in this research because you have taken the decision to have a feeding/gastrostomy tube inserted.

Do I have to take part and what will happen if I want to stop taking part?
You do not have to volunteer to take part. If you decide not to participate, or to withdraw at any time during the study, you may do so without having to give a reason. Leaving the research will not compromise your standard of care or treatment. If you decide to withdraw from the study, we will ask for your permission to use any data you have already given us.

What will happen to me if I take part?
If you decide to take part, you will be given this information sheet to keep and be asked to sign a consent form. Taking part in the project will involve completing one short questionnaire at 3 months, 6 months and 12 months following the gastrostomy placement and answering one question about the impact of the gastrostomy on your quality of life. This questionnaire will be posted to you four weeks before the scheduled follow up appointment. We would request you to bring the completed questionnaire to the appointment. This would be in addition to other two questionnaires which you would complete as part of your routine care and we will collect the relevant information relating to these two questionnaires from your medical records. With your consent, we will notify your own GP of your participation in the study.

Will there be any benefits to taking part?
There may be no personal benefit in your participation in this study. The benefits of your participation lie mainly in helping advance understanding of the impact of gastrostomy on the quality of life and nutritional status of MND patients. We hope that the findings will help to inform clinical decisions in care of patients with MND and benefit other patients in the future.

Are there any risks involved in taking part?
We do not anticipate any physical risks. It is possible that you may become upset when expressing your experiences about the gastrostomy. Please be assured that you do not have to answer any questions that you are uncomfortable with, and you can withdraw from the study at any time. If you continue to feel distressed about these, please feel free to speak to the MND team who will organise counselling.

Will I be paid for taking part in the Study?
We do not expect that participation in this research study would result any specific expenses on your side. Your participation is on a voluntary basis. We are unable to offer financial compensation for participation in this study.

What happens when the study ends?
The results of the study will be used in the MD (Doctor of Medicine) dissertation of Dr. Suresh Chhetri and may be presented at medical meetings or published in medical journals. The findings will contain no information as to your identity. A summary of our findings can be sent to you at the end of the study if you wish. The results of this study may be used as a basis for further research projects.

Will my taking part in this study be kept confidential?
Yes, all information obtained during the course of a study will be kept strictly confidential. Access to data will be restricted to the researcher and MND care team. To help protect your confidentiality, arbitrary identification code numbers will be used in place of names or other identifying features. All records will be kept in a locked filing cabinet, in a secure access restricted office. Electronic records will be held on password-protected NHS computer. Any data included in the final report will remain anonymous. However, disclosure may be required if you were to say something that potentially indicated that you or someone else was at risk of harm.

Who is organising the research?
Dr. Suresh Chhetri, neurology registrar at Royal Preston Hospital, is undertaking this study as an educational project at University of Central Lancashire. The motivation for undertaking this study comes from the very limited research in relation to the experiences of MND patients with tube feeding and its impact on their quality of life. The study is organised through the Lancashire University Teaching Hospital NHS Foundation Trust and University of Central Lancashire.

Who has reviewed the study?
This study has been reviewed by the Nottingham 1 Research Ethics Committee and the Research Directorate and Clinical Studies Centre of the Lancashire Teaching Hospitals NHS Foundation Trust.

Appendix 9: Reminder Letter to Participants

Lancashire Teaching Hospitals NHS
NHS Foundation Trust

Preston MND Care and Research Centre
Department of Neurology
Royal Preston Hospital
Sharoe Green Lane
Preston
PR2 9HT
Tel: 0177 252 2545

To,

Patient details and address

Re : "Enteral tube feeding for Motor Neurone Disease (MND): Effect on quality of life and nutritional status" study.

Dear ……..,

Further to our discussion during your visit at the Preston MND care and research centre on _____, you kindly indicated your willingness to participate in the above study. However, we have not received confirmation to indicate that you have formally accepted to participate in this study.

I am therefore writing this reminder letter to invite you to participate in this study. In order to help you make an informed decision, I have attached a participant information sheet which details why the study is being done and what it will involve.

Please be informed that your participation is voluntary and choosing not to participate will not affect your medical/other rights in any way. After reading the information sheet if you decide to participate or would like further information regarding this study, please feel free to contact the study doctor (Dr Suresh Chhetri) or a staff member of the Preston MND Care and research centre team within the next four weeks.

Many thanks once again.

Sincerely,

Dr Suresh Kumar Chhetri
Specialist Registrar in Neurology
Royal Preston Hospital
Fulwood, Preston
PR2 9HT
Tel: 0177 252 2317

Appendix 10: Participant consent form

Lancashire Teaching Hospitals NHS
NHS Foundation Trust

Preston MND Care and Research Centre,
Department of Neurology,
Royal Preston Hospital, PR2 9HT.

Participant Consent Form

Title of Study: Enteral tube feeding for Motor Neurone Disease (MND) - Effect on quality of life and nutritional status.

Please complete this form after you have read the Information Sheet and/or listened to an explanation about the research.

Please sign in the boxes next to the statements that you agree with:

I confirm that I have read and understand the information sheet for the above study. I have had the opportunity to ask questions about it. Any questions that I have asked have been answered to my satisfaction.	☐
I understand that my participation is voluntary and that I am free to withdraw at any time, without giving reason and without my medical care being affected.	☐
I understand that relevant sections of any of my medical notes and data collected during the study, may be looked at by responsible individuals from the MND care centre, from regulatory authorities or from the NHS Trust, where it is relevant to my taking part in this research. I give permission for these individuals to have access to my records.	☐
I understand the information from the study will be published as a report, without my name attached and that every attempt will be made to ensure my confidentiality and anonymity. I agree to the use of anonymised quotes in publications.	☐
I agree to my GP being informed of my participation in the study.	☐
I agree to participate in this research project.	☐

Name of Participant	Date	Signature
Name of witness	Date	Signature
Name of Researcher/MND staff	Date	Signature

Appendix 11: Amyotrophic Lateral Sclerosis Functional Rating Scale – Revised

Lancashire Teaching Hospitals NHS
NHS Foundation Trust

Amyotrophic Lateral Sclerosis Functional Rating Scale – Revised (ALSFRS-R)

Patient Code Number:

Evaluation Date :						
Speech						
4	Normal speech process					
3	Detectable speech disturbances					
2	Intelligible with repeating					
1	Speech combined with non vocal communication					
0	Loss of useful speech					
Salivation						
4	Normal					
3	Sight but definite excess of saliva in mouth; may have night time drooling					
2	Moderately excessive saliva;may have minimal drooling					
1	Marked excess of saliva with some drooling					
0	Marked drooling; requires constant tissue or handkerchief					
Swallowing						
4	Normal eating habits					
3	Early eating problems – occasional choking					
2	Dietary consistency changes					
1	Needs supplemental tube feeding					
0	NPO (exclusively parental or enteral feeding)					
Handwriting						
4	Normal					
3	Slow or sloppy; all words are legible					
2	Not all words are legible					
1	Able to grip pen but unable to write					
0	Unable to grip pen					
Cutting food and handling utensils (patients without gastrostomy)						
4	Normal					
3	Somewhat slow and clumsy, but no help needed					
2	Can cut most foods, although clumsy and slow; some help needed					
1	Food must be cut by someone, but can still feed slowly					
0	Needs to be fed					
Cutting food and handling utensils (alternate scale for patients with gastrostomy)						
4	Normal					
3	Clumsy but able to perform all manipulations independently					
2	Some help needed with closure and fasteners					
1	Provides minimal assistance to caregiver					
0	Unable to perform any aspect of task					

Dressing and Hygiene						
4	Normal Function					
3	Independent and complete self-care with effort or decreased efficiency					
2	Intermittent assistance or substitute methods					
1	Needs attendant for self-care					
0	Total dependence					
Turning in bed and Adjusting bed clothes						
4	Normal					
3	Somewhat slow and clumsy, but no help needed					
2	Can turn alone or adjust sheets, but with great difficulty					
1	Can initiate, but not turn or adjust sheets alone					
0	Helpless					
Walking						
4	Normal					
3	Early ambulation difficulties					
2	Walks with assistance					
1	Non-ambulatory functional movement					
0	No purposeful leg movement					
Climbing stairs						
4	Normal					
3	Slow					
2	Mild unsteadiness or fatigue					
1	Needs assistance					
0	Cannot do					
Dyspnoea (new)						
4	None					
3	Occurs when walking					
2	Occurs with one or more or the following: eating; bathing; dressing (ADL)					
1	Occurs at rest, difficulty breathing when either sitting or lying					
0	Significant difficulty, considering using mechanical respiratory support					
Orthopnoea (new)						
4	None					
3	Some difficulty sleeping at night due to shortness of breath, does not routinely use more that two pillows					
2	Needs extra pillows in order to sleep (more than two)					
1	Can only sleep sitting up					
0	Unable to sleep					
Respiratory insufficiency (new)						
4	None					
3	Intermittent use of NIV					
2	Continuous use of NIV during the night					
1	Continuous use of NIV during the night and day					
0	Invasive mechanical ventilation by intubation or tracheostomy					

Appendix 12: Amyotrophic Lateral Sclerosis Assessment Questionnaire-40 (ALSAQ - 40)

Lancashire Teaching Hospitals NHS
NHS Foundation Trust

Quality of Life Questionnaire (1)

This questionnaire consists of a number of statements about difficulties that you may have experienced **during the last 2 weeks**. There are no right or wrong answers, your first response is likely to be the most accurate for you. **Please tick the box which best describes your own experience or feelings.**

Please try to answer every question even though some may seem rather similar to others, or may not seem relevant to you.

All the information you give will be treated in the strictest confidence.

How often during the last 2 weeks have the following been true? (Please tick one box for each question)

	Never	Rarely	Sometimes	Often	Always or Cannot walk at all
1. I have found it difficult to walk short distances e.g. around the house	☐	☐	☐	☐	☐
2. I have fallen over whilst walking	☐	☐	☐	☐	☐
3. I have stumbled or tripped whilst walking	☐	☐	☐	☐	☐
4. I have lost my balance whilst walking	☐	☐	☐	☐	☐
5. I have had to concentrate whilst walking	☐	☐	☐	☐	☐

How often during the last 2 weeks have the following been true? (Please tick one box per question)

	Never	Rarely	Sometimes	Often	Always or Cannot do at all
6. Walking has tired me out	☐	☐	☐	☐	☐
7. I have had pains in my leg whilst walking	☐	☐	☐	☐	☐
8. I have found it difficult to go up and down the stairs	☐	☐	☐	☐	☐
9. I have found it difficult to stand up	☐	☐	☐	☐	☐
10. I have found it difficult to get myself up out of chairs	☐	☐	☐	☐	☐
11. I have had difficulty using my arms and hands	☐	☐	☐	☐	☐
12. I have found turning and moving in bed difficult	☐	☐	☐	☐	☐
13. I have found picking things up difficult	☐	☐	☐	☐	☐
14. I have found holding books or newspapers, or turning pages difficult	☐	☐	☐	☐	☐
15. I have had difficulty writing clearly	☐	☐	☐	☐	☐
16. I have found it difficult to do jobs around the house	☐	☐	☐	☐	☐

Page 01 GC/HM 18/01/12 Department of Clinical Audit & Effectiveness

How often during the last 2 weeks have the following been true? (Please tick one box per question)

	Never	Rarely	Sometimes	Often	Always or Cannot do at all
17. I have found it difficult to feed myself	☐	☐	☐	☐	☐
18. I have had difficulty combing my hair or cleaning my teeth	☐	☐	☐	☐	☐
19. I have difficulty getting dressed	☐	☐	☐	☐	☐
20. I have had difficulty washing at the hand basin	☐	☐	☐	☐	☐
21. I have had difficulty swallowing	☐	☐	☐	☐	☐
22. I have had difficulty eating solid food	☐	☐	☐	☐	☐
23. I have found it difficult to drink liquids	☐	☐	☐	☐	☐
24. I have found it difficult to participate in conversations	☐	☐	☐	☐	☐
25. I have felt that my speech has not been easy to understand	☐	☐	☐	☐	☐
26. I have slurred or stuttered whilst speaking	☐	☐	☐	☐	☐
27. I have had to talk very slowly	☐	☐	☐	☐	☐
28. I have talked less than I used to	☐	☐	☐	☐	☐
29. I have been frustrated by my speech	☐	☐	☐	☐	☐
30. I have felt self-conscious about my speech	☐	☐	☐	☐	☐

How often during the last 2 weeks have the following been true? (Please tick one box per question)

	Never	Rarely	Sometimes	Often	Always
31. I have felt lonely	☐	☐	☐	☐	☐
32. I have been bored	☐	☐	☐	☐	☐
33. I have felt embarrassed in social situations	☐	☐	☐	☐	☐
34. I have felt hopeless about the future	☐	☐	☐	☐	☐
35. I have worried that I am a burden to other people	☐	☐	☐	☐	☐
36. I have wondered why I keep going	☐	☐	☐	☐	☐
37. I have felt angry because of the disease	☐	☐	☐	☐	☐
38. I have felt depressed	☐	☐	☐	☐	☐
39. I have worried about how the disease will affect me in the future	☐	☐	☐	☐	☐
40. I have felt as if I have no freedom	☐	☐	☐	☐	☐

Appendix 13: Letter to General Practitioner

Lancashire Teaching Hospitals NHS
NHS Foundation Trust

Preston MND Care and Research Centre,
Department of Neurology,
Royal Preston Hospital
Sharoe Green Lane,
Preston,
PR2 9HT
Tel: 0177 252 2545

To,
GP Address

Dear Dr……

Re: Patient name, DOB.

Your patient with a diagnosis of Motor Neurone Disease has consented to participate in a study entitled "Enteral tube feeding for Motor Neurone Disease (MND): Effect on quality of life and nutritional status" following her/his recent decision to undergo gastrostomy insertion.

The study participants will be requested to complete a PEG questionnaire and answer one question about the impact of the gastrostomy on their quality of life at 3 months, 6 months and 12 months post gastrostomy insertion. The questionnaire will be posted to the participants four weeks before the scheduled follow up appointment. The participants will be requested to bring the completed questionnaires to the appointment. There will be no other deviation from routine clinical care.

Please find enclosed a copy of the patient information sheet for your information. If you require any further information or have any comments about this please feel free to contact us on the details listed above.

Yours sincerely,

Dr. Suresh Chhetri
Specialist Registar in Neurology,
Royal Preston Hospital,
Sharoe Green Lane,
Preston, PR2 9HT

Appendix 14: Liverpool PEG questionnaire

Lancashire Teaching Hospitals NHS
NHS Foundation Trust

Preston MND Care and Research Centre,
Royal Preston Hospital, Preston.

Liverpool PEG Questionnaire

In the last 3 months how much of a problem was the PEG to you: (please circle)

	Not at All	A Little	Quite a bit	Very much
Pain / Discomfort	1	2	3	4
Leakage	1	2	3	4
Dirtying of your clothes by leakage	1	2	3	4
Redness / irritation	1	2	3	4
Blockage	1	2	3	4
Bleeding	1	2	3	4
Infection	1	2	3	4
Tube splitting	1	2	3	4
Falling out	1	2	3	4
Keeping the PEG and PEG site clean	1	2	3	4
Appearance	1	2	3	4
Types of clothes worn	1	2	3	4
Difficulties using the PEG tube	1	2	3	4
Interference with family life	1	2	3	4
Interference with intimate relationships	1	2	3	4
Interference with social activities	1	2	3	4
Interference with hobbies or leisure time	1	2	3	4
How much has the PEG tube affected your overall quality of life	1	2	3	4
How much do you think about your PEG	1	2	3	4
Do you wish the PEG could be removed	1	2	3	4

Lancashire Teaching Hospitals NHS
NHS Foundation Trust

Preston MND Care and Research Centre,
Royal Preston Hospital, Preston.

How much did / do you use your PEG for feeds?

Not at all Very occasionally ☐ Often Frequently ☐ All the time ☐

In TOTAL how many times has your PEG tube needed to be replaced

Once ☐ Twice ☐ Three times ☐ Four or more times ☐

What other comments you wish to make about your PEG?

.....
.....
.....
.....

How would you describe your quality of life since the insertion of your feeding tube?

.....
.....
.....
.....
.....
.....
.....
.....
.....

Thank you for completing the questionnaire, we are very grateful.

Completing this questionnaire is entirely voluntary and will not alter your care in any way. Please bring the completed questionnaire to your next appointment. If there is anything that is not clear or you would like further information regarding this study, please free to contact the researcher (Dr. Suresh Chhetri, Telephone Number 0177 252 2317) or a staff member of the Preston MND Care and research centre team at 0177 252 2545.

Appendix 15: Poster Presentation at the 25th International Symposium on ALS/MND held at Brussels in December 2014

References:
1. Miller RG *et al.* Neurology 2009; 73(15):1218–1226.
2. Gregory S *et al.* Neurology 2002; 58(3):485–487.

DOI: 10.3109/21678421.2014.960177/071

P72 ENTERAL TUBE FEEDING AND SURVIVAL PATTERN OF 407 PATIENTS WITH MOTOR NEURONE DISEASE

CHHETRI SK[1,2], BRADLEY BF[2], MAJEED T[1], LEA RW[2]

[1]*Preston MND care and Research centre, Lancashire Teaching Hospitals NHS Foundation Trust, Preston, UK,* [2]*University of Central Lancashire, Preston, UK*

Email address for correspondence: suresh.chhetri@lthtr.nhs.uk

Key words: enteral feeding, nutrition, percutaneous endoscopic gastrostomy (PEG)

Background: Motor Neurone Disease (MND) patients with dysphagia and impaired nutritional status are usually offered enteral feeding (EF). The findings of prospective and retrospective studies investigating the impact of EF on survival have demonstrated little consensus (1, 2).

Objective: To assess the impact of enteral feeding on survival of patients with MND.

Methods: We conducted a retrospective review of the MND database and case notes of MND patients between 2005 and 2012. We identified cases that had undergone gastrostomy tube placement for EF. Statistical analyses of association between clinical manifestation, survival and gastrostomy tube insertion were evaluated using SPSS version 21. A forward stepwise cox regression was used to evaluate whether EF offers survival advantage. We also assessed survival in the bulbar and limb onset subgroups with and without EF using log-rank analysis.

Results: A total of 407 patients were identified. 345 cases with complete data were analysed of which 213 were limb onset, 130 bulbar onset and 2 respiratory onset. 93 patients (31 limb onset, 61 bulbar onset and 1 respiratory onset) received enteral feeding. After adjusting for effects of gender, onset age, onset site, age at diagnosis and riluzole treatment, EF was not associated with a statistically significant survival advantage ($\chi 2$ (1) = 1.96, p = 0.16). Log-Rank analysis revealed no significant difference in survival times between bulbar onset and limb onset illness, either with or without EF (Log-Rank $\chi 2$ (1) = 0.56, p = 0.45). Median (95% CI limits) survival times for limb onset MND with and without EF were 777 days (498.67-1055.13) and 715 days (620.47-809.53) respectively. Median survival times for bulbar onset with and without EF were 799 days (677.64-920.36) and 645 days (414.77-875.24) respectively.

Discussion and conclusion: There are no appropriately designed trials to inform decisions on nutritional management of MND patients and clinical practice is largely guided by expert clinical opinion and consensus. Our retrospective review did not find a survival advantage with enteral feeding. However the effect of enteral feeding on quality of life, an important objective of any management strategy, remains unknown. The retrospective nature of our study and lack of randomisation are potential limitations. A prospective study to evaluate impact of enteral feeding on survival and quality of life in this challenging clinical population would provide further evidence to inform and influence best clinical practice.

References:
1. Miller RG. *et al.* Neurology 2009; 73:1218–26.
2. Katzberg H, Benatar M. Cochrane Database Syst Rev. 2011; 19 (1):CD004030.

DOI: 10.3109/21678421.2014.960177/072

Appendix 16: Publications on Motor Neurone Disease

Research Letter

PALLIATIVE MEDICINE

Palliative Medicine
1–2

DOI: 10.1177/0269216315570412
pmj.sagepub.com
SAGE

Choosing the place of death: Empowering motor neurone disease/amyotrophic lateral sclerosis patients in end-of-life care decision making

Suresh Kumar Chhetri[1,2], Belinda Fay Bradley[2], Pauline Callagher[1], Robert Addison-Jones[1], Wendy Bennett[1], Joyce Gardham[1], Amy Parkes[1], Robert William Lea[2] and Tahir Majeed[1]

Motor neurone disease/amyotrophic lateral sclerosis (MND/ALS) is a fatal neurodegenerative disease that requires special attention at the end-of-life, particularly because disability is relentlessly progressive and death generally occurs in a predictable fashion.[1,2] In the absence of a cure, palliative care and advance care planning (ACP) are key management strategies.[1,2] The quality of care provided throughout the illness profoundly influences the end-of-life care (EOLC).[1–3] The 'End of Life Care Strategy' aims at promoting excellence in EOLC.[3] The central aspect of this strategy concerns patients' preference for place of death. There is little in the literature about enabling MND/ALS patients to make choices about their EOLC, particularly relating to the preferred place of death (PPD).

Honouring patient's choice for PPD is important, and this can be achieved through ACP.[2,3] The Preferred Priorities for Care (PPC) document is a patient-held dynamic record that can be used as an ACP tool to promote discussion and documentation of wishes, preferences and priorities for care in relation to end-of-life issues.[3,4] The Preston MND care and research centre serving a population of 1.6 million in North West England offers PPC document to all MND/ALS patients.

We reviewed the case notes of patients who died in 2012 and 2013 to investigate whether completion of PPC document affected actual place of death or hospital use towards end-of-life. There were a total of 99 deaths, of which 33 (33.3%) occurred in hospital. PPC document was completed by 52 patients (52.5%); 29 (55.8%) identified home as a PPD and the rest identified hospice/home ($n=11$; 21.2%), hospice ($n=10$; 19.2%) or nursing home ($n=2$; 3.8%). None identified hospital as a PPD. The majority of patients completing the document (completers) died at home ($n=18$; 34.6%) or hospice ($n=16$; 30.8%); 12 (23.1%) died in hospital and 6 (11.5%) died at nursing home. PPC document was not completed in 47 cases (47.4%). Majority of those who did not complete (non-completers) the document died in hospital ($n=21$; 44.7%), while 16 (34%) died at home, 6 (12.8%) at nursing home, 3 (6.4%) at hospice and 1 (2.1%) while on holiday (Figure 1). A chi-squared test demonstrates statistically significant difference between whether patients completed the document and where they died ($\chi^2(16)=71.06$, $p<0.001$). Odds ratios indicate that non-completers were 1.96 times more likely to die in hospital. In contrast, completers were 4.84 times more likely to die in a hospice.

The main reason for admission in both groups was respiratory failure/shortness of breath (12 non-completers; 6 completers); 4 non-completers and none of the completers were admitted with general deterioration. Other causes for admission included falls, breakdown of care and other medical reasons. The major reason for non-completion of PPC document was reluctance or refusal by the patient to discuss EOLC issues (51%). Other reasons included late diagnosis, inability to make wishes known due to cognitive impairment and unexpected deterioration.

Majority of people would prefer to die at home, but unfortunately, this is not the reality they experience.[3] Healthcare towards end-of-life places a major resource burden on the health service.[3,5] A retrospective study of 1600 hospitalisations in patients with MND/ALS demonstrated prolonged and expensive admissions, a high in hospital mortality rate and few routine discharges.[5] Most of our patients who completed the PPC document were

[1]Preston MND Care and Research Centre, Department of Neurology, Royal Preston Hospital, Lancashire Teaching Hospitals NHS Foundation Trust, Preston, UK
[2]University of Central Lancashire, Preston, UK

Corresponding author:
Suresh Kumar Chhetri, Preston MND Care and Research Centre, Department of Neurology, Royal Preston Hospital, Lancashire Teaching Hospitals NHS Foundation Trust, Preston PR2 9HT, UK.
Email: chhetri@doctors.org.uk

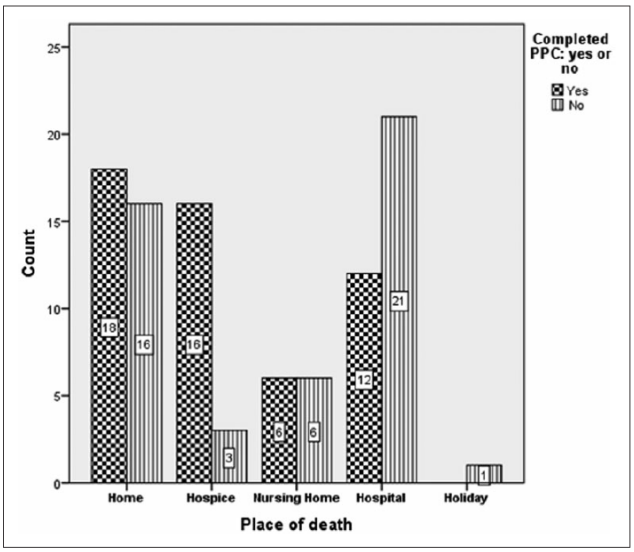

Figure 1. Actual place of death of patients who completed the PPC document ($n = 52$) as compared to those that did not ($n = 47$).

able to achieve their PPD. Completion of document was associated with significantly reduced hospital deaths and increased hospice deaths: 44.7% of non-completers died in hospital. This value is strikingly similar to MND/ALS deaths in hospitals (45.1%) in England.[6] A significant proportion of these patients could potentially be cared at home, if their care preferences are known. The PPC document thus facilitates multi-agency collaborative working including involvement of specialist palliative care team and enables MND/ALS patients to die in their PPD. ACP has also been shown to yield positive experiences in caregivers of patients with MND/ALS and reduce grief related symptoms in the bereavement phase.[2] Patients/relatives feel empowered by participating in decisions about EOLC, and shared decision making is valued at the end-of-life.[1–3]

We demonstrate that the use of PPC document empowers patients to gain control over their EOLC when dealing with an uncontrollable cruel illness, enables delivery of personalised care and reduces hospital admissions. EOLC should be discussed early and throughout the disease trajectory as an integral part of holistic care in MND/ALS. The PPC document is commonly used in the field of oncology but not in MND/ALS. Our study supports the view that PPC document should also be offered to MND/ALS patients as a standard of care.

Declaration of conflicting interests

The authors declare that there is no conflict of interest.

Ethics

The study was approved by the clinical governance and audit department, Lancashire Teaching Hospitals NHS Foundation Trust.

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Amyotrophic Lateral Sclerosis and Frontotemporal Degeneration, 2014; 15: 145–147

REPORT

Amyotrophic lateral sclerosis and Huntington's disease: Neurodegenerative link or coincidence?

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Introduction

Huntington's disease (HD) is an autosomal dominant neurodegenerative disorder characterized by progressive cognitive, behavioural and motor dysfunction (1). It is a trinucleotide repeat disorder associated with expansion of a CAG repeat mutation in the *huntingtin* gene located on the short arm of chromosome 4 (1). Amyotrophic lateral sclerosis (ALS) is a relentlessly progressive neurodegenerative disease characterized by loss of motor neurons in the spinal cord, brainstem and motor cortex. The two conditions are clinically and neuropathologically distinct. The median survival time after onset in ALS varies from 20 to 48 months with 10–20% of the patients surviving 10 years or more (2). The median survival in HD is 16.2 years (range 2–45 years) with approximately 20% of the patients surviving more than 23 years (3). We describe a patient with genetically confirmed HD who later developed rapidly progressive ALS. This case adds to the increasing literature on the co-occurrence of HD and ALS.

Case report

A white British male with a strong family history of HD requested predictive testing for HD at the age of 46 years. His brother and mother had died of HD in their fifties. There was no family history of ALS. He was asymptomatic and first neurological examination was unremarkable. Following appropriate genetic counselling in accordance with the standard guidelines for HD predictive testing (4), he underwent HD mutation screening. A PCR based test for detecting the CAG triplet repeat expansion revealed an expanded allele (>39 CAG repeats), confirming the HD gene mutation. Over the next two years he exhibited behavioural changes consistent with psychiatric manifestations of HD. He was noted to be unusually irritable with temper outbursts. Anxiety and cognitive slowing were evident at age 48 years. Lack of motivation became a significant and refractory problem from the age of 51 years. He was increasingly reliant on his wife to carry out all domestic duties, although he was able to manage his personal care. At the age of 57 years he developed spasms in his lower limbs, dysarthria and dysphagia. Clinical examination demonstrated generalized wasting, fasciculations, pseudobulbar dysarthria and a brisk jaw jerk. There was mild spastic paraparesis with diffuse hyperreflexia and bilateral extensor plantar responses.

Magnetic resonance imaging (MRI) of the brain showed generalized cerebral atrophy. Electromyography showed acute, subacute and chronic motor denervation and fibrillation potentials in the cranial, cervical, thoracic and lumbosacral segments consistent with the diagnosis of ALS. The patient deteriorated rapidly and the family opted for palliative care. He died three months after the onset of ALS. No adventitious movements were noted during life.

Discussion

There are 10 cases in the literature describing the coexistence of ALS with genetically confirmed HD (Table I) (5–11). In patients with both ALS and HD, the conditions have not occurred together in another family member. Although muscle atrophy

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Table I. Case reports describing the co-existence of ALS with HD.

Reference	Age/ Gender	CAG repeats	Presenting symptoms (age of presentation)	Sequence of illness (age in years)	ALS phenotype	Family history
Rubio 1996 (5)	81/M	45	Personality changes (57 years)	HD (57) only. ALS histopathological diagnosis.	Not applicable	ALS (mother) Neuropsychiatric Disorder (maternal uncle)
Papageorgiou 2006 (6)	72/F	40	Chorea of the head and extremities (72 years)	HD (72) followed by ALS 18 months later.	Limb onset	Involuntary movements (brother)
Kanai 2008 (7)	48/M	46	Left upper limb amyotrophy (41 years)	ALS (41) followed by HD 12 months later.	Limb onset	Involuntary movements (father and siblings)
Phukan 2009 (8)	56/M	≥40	Right upper limb weakness (56 years)	ALS (56) followed by HD 7 months later.	Limb onset	HD (paternal first cousin) Parkinson's disease (mother)
Mandrioli 2010 (9)	67/F	43	Chorea of the head and extremities (63 years)	HD (63) followed by ALS 3 years later.	Bulbar onset	Clinical diagnosis of HD (mother) HD (sister)
Sadeghian 2011(10)	69/M	40	Memory problems (67 years)	HD (67) followed by ALS 2 years later.	Limb onset	Non-contributory
Tada 2012 (Case 1) (11)	61/F	46	Chorea in all limbs, emotional liability (mid 50s)	HD (mid 50's) followed by ALS at the age of 59 years.	Limb onset	Chorea (paternal grandmother)
Tada 2012 (Case 2) (11)	58/F	47	Chorea and cognitive changes (mid 30s)	HD (mid 30s) only. ALS histopathological diagnosis.	Not applicable	HD (father, sister, paternal grandfather and other relatives)
Tada 2012 (case 3) (11)	67/F	42	Chorea in all limbs and trunk(mid 50s)	HD (mid 50s) followed by ALS at the age of 66 years.	Bulbar onset	HD (mother, maternal grandmother, three siblings and other relatives)
Tada 2012 (case 4) (11)	58/F	39	Dysarthria	ALS (56) only. HD mutation carrier	Bulbar onset	HD (father)
Chhetri 2013	57/M	>39	Irritability	HD (48) followed by ALS 9 years later.	Bulbar onset	HD (mother and brother)

may occur in HD, the two conditions are clinically and neuropathologically distinct. HD is an autosomal dominant disorder while ALS is usually sporadic, although 5–10% of cases are transmitted as a familial autosomal dominant trait. The most frequent mutations are found in the superoxide dismutase-1 gene, chromosome 9 open reading frame 72 (C9orf72), TAR DNA binding protein 43 gene and the fused in sarcoma/translocated in liposarcoma gene (12). In the absence of a clear family history, our patient was not tested for ALS mutations. Distinct examination findings in HD may include oculomotor dysfunction comprising impaired initiation of saccades, slowed hypometric saccades, distractibility and impersistence of gaze and generalized chorea. The tongue may exhibit chorea but no fasciculations. Neuroimaging studies including MRI may demonstrate bilateral atrophy of the head of the caudate nucleus and putamen.

The coexistence of pathological features of HD and ALS has been demonstrated in several studies (5,11). It has been suggested that cellular dysfunction due to polyglutamine aggregation and toxicity could be responsible for motor neuronal loss in genetically predisposed patients (5,7). A hexanucleotide repeat expansion in C9orf72 is the most common genetic cause of ALS identified to date, thought to account for approximately 30% of familial ALS. However, a study demonstrated no significant association between the CAG repeat length and ALS, indicating two distinctive neurodegenerative processes (12). Although the clinical sequence of illness is variable, ALS is more often preceded by HD (5,6,9–11).

Although a causative link between HD and ALS remains unclear, the possibility of a genetic or epigenetic relationship cannot be discounted. The relatively mild HD phenotype in our patient meant that the diagnosis of ALS was not difficult. However, as dysphagia, dysarthria and amyotrophy are common to both of these conditions, identifying ALS in patients with advanced or severe HD may prove challenging. Many such cases may simply go unreported and it remains unclear whether the co-occurrence of ALS and HD is coincidental. There has been no systematic attempt to estimate the prevalence of both conditions in the same patient; however, assuming a prevalence rate of 5 per 100,000 for ALS and 10 per 100,000 for HD, one would expect to see them occurring together in only 5 per billion and even fewer, if some die of ALS before the onset of HD. Moreover, 20% of the reported cases had only histopathological evidence of ALS suggesting that not all co-occurrent cases are recognized. The frequency of the reported cases (Table I) may suggest that the concurrent incidence of both conditions

occurs more often than one would expect by chance alone.

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VERY HIGH TITERS OF VOLTAGE-GATED POTASSIUM CHANNEL ANTIBODIES IN A PATIENT WITH AMYOTROPHIC LATERAL SCLEROSIS

Voltage-gated potassium channel (VGKC) antibodies have been implicated in a spectrum of immunotherapy-responsive neurological conditions, including peripheral nerve hyperexcitability (PNH), a heterogeneous syndrome that may present with fasciculations, cramps, and stiffness.[1,2] These antibodies are reported rarely in association with amyotrophic lateral sclerosis (ALS).[2–4] We report the case of a patient with very high titers of VGKC antibodies.

A 61-year-old man presented with a 9-month history of impaired right hand dexterity and a 2-month history of right hand weakness and limb cramping. He had no leg weakness or bulbar disturbances. Examination demonstrated fasciculations in all limbs, mild wasting of both first dorsal interossei, and grade $4^+/5$ weakness of the palmar and dorsal interossei bilaterally, but no tongue wasting or fasciculation. Reflexes were generally brisk. Sensory examination was normal. Nerve conduction studies were unremarkable, but electromyography (EMG) showed profuse fasciculation potentials and myokymic discharges in both upper and lower extremities suggestive of PNH. The right genioglossus, right deltoid, and bilateral tibialis anterior muscles showed moderately reduced recruitment with some discrete motor unit potentials (MUPs) of normal amplitude and duration firing at abnormally rapid rates. No fibrillation potentials or positive sharp waves were seen. The combination of fasciculation potentials and reduced recruitment raised concerns about ALS. VGKC antibodies were strongly positive at 1028 pM (0–100). A comprehensive work-up for malignancy, which included serum paraneoplastic antibodies and positron emission tomography, was unremarkable. Cerebrospinal fluid examination was normal. Carbamazepine eased the cramps, but the weakness progressed to involve all limbs despite a 6-month trial of intravenous immunoglobulin (2 g/kg) administered every 6 weeks. Repeat VGKC antibody titers were 1343 pM.

EMG repeated 6 months later showed myokymic discharges but also fibrillation potentials and positive sharp waves in the right abductor hallucis, bilateral tibialis anterior, and right rectus abdominis muscles. Long-duration, high-amplitude, rapidly firing, discrete MUPs were present in muscles innervated by cranial, cervical, thoracic, and lumbosacral segments. These electrodiagnostic findings were indicative of ALS with superimposed PNH. His symptoms have continued to worsen, but there is no clinical bulbar involvement 26 months into the illness. The reflexes remain brisk. There has been no cognitive impairment or seizures to suggest limbic encephalitis.

A number of autoimmune conditions have been described in association with ALS.[5] A potential association between VGKC antibodies and ALS has been reported in a retrospective cohort of 54 patients.[3] Sixteen (29.6%) patients had an antibody titer of >100 pM, with a maximum of 439 pM. The mean titers were also higher in ALS patients than in a cohort with peripheral nervous system disorders.[3] VGKC antibodies have been implicated in axonal dysfunction after spinal cord injury, indicating a potential spinal cord substrate for expression of VGKC antibodies.[6] Similarly, axonal hyperexcitability has been shown to be neurotoxic in experimental animals.[7] A causal relationship between VGKC antibody-associated PNH and ALS remains uncertain. It is possible that VGKC autoimmunity is an epiphenomenon, particularly because immunomodulatory therapies have been ineffective in halting progression of the patient's disease.

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TWO, THREE, OR FOUR-LIMB TESTING? OR THE DIFFICULTIES OF OPTIMIZING ELECTRODIAGNOSIS FOR SUSPECTED CIDP

I read with great interest the study by Vo et al. who retrospectively compared 3-limb with 2-limb electrophysiological testing in chronic inflammatory demyelinating polyneuropathy (CIDP).[1]