Improving early recognition of Motor Neuron Disease in primary care: 
Research Protocol

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1 Study Protocol

1.1 Aim

The aim of this study is to quantify combinations of clinically recognised symptoms and signs associated with a diagnosis of MND. The research will inform the evidence base for the subsequent development of tools in GP systems (such as alerts, templates and protocol) to improve the early recognition of MND.

1.2 Background

MND is believed to affect approximately 5000 people in the UK at any one time. Most people with MND are aged between 50 and 70. It tends to affect more men than women (risk ratio 1.25). MND causes progressive muscular weakness that may first present as isolated and unexplained symptoms. It is difficult to diagnose in primary care since it is both a rare disease and the symptoms (such as clumsiness, weakness or slurred speech) may be due to other conditions. Patients may delay consulting their GP and the GP may not consider MND as a potential cause of the symptoms resulting in delays in diagnosis and hence delays in starting treatments.

Recent NICE guidance (NG42) prioritises the recommendation that there are “robust protocols and pathways to inform health professionals about MND and how it may present”. All UK general practices use electronic health record systems to record clinical information and these computer systems have advanced features which are used to help identify patients at risk of medical conditions or to prompt GPs to consider diagnoses such as cancer. In theory, it would be possible to build tools into the clinical systems which can be used to help identify patients with possible MND earlier. However, before this can be done, research is needed to identify which, of the many symptoms of MND, are the most important ones which are likely to be recorded on GP systems and which symptoms (or combination of symptoms) increase the likelihood that a patient has MND. The important thing here is to ensure that any potential tool has an appropriate balance between sensitivity and specificity, so that patients with MND are identified without too many alerts being generated for patients who do not have the disease.

1.3 Objectives

Our main research objectives are

1. To describe the characteristics of patients with a diagnosis of MND using the QResearch database linked to hospital data.
2. To identify which Read and Snomed Codes are commonly used to record red flag symptoms and signs for MND in electronic health records.
3. To identify which of the known red flag symptoms separately or in combination are significantly and independently associated with a diagnosis of MND.
4. To quantify the sensitivity, specificity and predictive power of each of the significant red flag symptoms (alone and in combination) for MND.
1.4 Classification of type of MND

<table>
<thead>
<tr>
<th>Type</th>
<th>Median survival time from start of symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amyotrophic lateral sclerosis (ALS)</td>
<td>2–5 years</td>
</tr>
<tr>
<td>Primary lateral sclerosis (PLS)</td>
<td>8–10 years</td>
</tr>
<tr>
<td>Progressive muscular atrophy (PMA)</td>
<td>2–4 years</td>
</tr>
</tbody>
</table>

1.5 Study design

Nested case-control study. The nested case-control design is an established efficient approach for investigating exposure-disease associations in a study population. This design has been used successfully in a number of highly cited studies which have subsequently led to changes in guidelines or clinical practice. By drawing a sample of matched controls for each case, the number of study subjects for whom symptom information needs to be obtained is reduced. This is important for a relatively uncommon condition such as MND. In our study, cases and controls will be matched on age, sex, practice and calendar time. Matching on age at diagnosis will control for age which is known to be strongly associated with risk of MND. Matching on practice will help control for practice and demographic factors which are not included in the other risk factors and which might give rise to unmeasured confounding. Matching by calendar time will also control for changes in recording of symptoms over time. A matched, nested case control study is likely to be the best practical study design to obtain detailed unbiased estimates.

1.6 Study period


1.7 Setting

QResearch is a large validated research database including the records of 30 million patients registered with approximately 1500 English GP practices using the EMIS Health Clinical System including data since 1989 offering longitudinal data for over 20 years. The database includes event level detailed information on patient demographics (year of birth, sex, ethnicity, deprivation), prescribed medications, clinical diagnoses, referrals, clinical values, laboratory investigations. All 1500 practices have been linked at individual patient level to cancer registrations data (from 1990 onwards), mortality records (from 1997 onwards) and to hospital admissions data (from 1998 onwards). QResearch is representative of the population in England and the database has been used extensively for research including cancer epidemiology, health services research, the development of risk prediction models and evaluation of drug safety. It has an excellent track record of high impact research papers published in leading journals including studies using the linked datasets. (http://www.qresearch.org/SitePages/publications.aspx).
1.8 Study population

We will identify an open cohort of men and women aged 18 years and over registered during the study period. Patients with an existing diagnosis of MND at the start of the study will be excluded. The entry date to the study cohort will be the latest of: 18th birthday, date of registration with the practice plus one year, date on which the practice computer system was installed plus one year, or the beginning of the study period (1st January 1998). The right censor date will be the earliest of the following: date of diagnosis of MND, date of 100th birthday, date of death, date of leaving the practice, date of the latest download of data or the study end date (31st Dec 2017). Person years will be calculated between the study entry date and the right censor date.

1.9 Identification of cases

Cases will be patients in the study cohort with a new diagnosis of MND on either GP, hospital records or deaths between 1998 and 2017. A feasibility analysis identified at least 5,000 patients with MND on QResearch since 1998.

1.10 Identification of Controls

Controls will be people of the same age, sex and practice as their matched case but without a diagnosis of MND. We will match each MND case with up to 10 controls who are alive & registered at the time of the MND diagnosis of the case (index date). Controls will be matched with cases by practice, age, sex and calendar time using incidence density sampling. Each control will be allocated an index date which will be the date of first diagnosis of MND for their matched case. We will exclude cases and controls who have less than three years of computerised data available to ensure that the data are complete for a minimum of three years before the index date.

1.11 Clinically recognised symptoms and signs of MND

Data will be extracted for all relevant symptoms recorded on the database in cases and controls before the index date.

1.11.1 MNDA Red flags


1.11.1.1 Bulbar Features

- Dysarthria
- Dysphagia
- Sialorrhoea
- Tongue Fasciculations

1.11.1.2 Limb Features

- Focal weakness
- Falls
- Loss of Dexterity
• Muscle Wasting
• Muscle Fasciculations
• Cramps

1.11.3 Respiratory Features
• Hard to Explain Respiratory Symptoms
• Shortness of Breath on Exertion
• Excessive Daytime Sleepiness
• Fatigue/tiredness
• Early Morning Headache
• Orthopnoea

1.11.2 Cognitive Features (rare)
• Behavioural change
• Emotional Lability
• Fronto-temporal dementia

1.11.3 Additional Clinically Recognised Symptoms and Signs of MND

These symptoms and signs were found from the NICE Guideline (NG42) on Motor Neuron Disease²
• Appetite Loss
• Muscle Stiffness
• Loss of Dexterity
• Trips
• Nightmares
• Poor Sleep
• Confusion
• Hallucinations
• Quinine

The following symptoms and signs were found from a search of MND patients from JB’s practice.
• Weight loss
• Wide based gait
• Incoordination/ataxia
• pathological crying
• dysphasia and aphasia
• dropped foot
• loss of inhibition
• Babinski sign (upgoing plantar reflexes)
• spasticity or increased tone
• dry mouth

Additional symptoms and signs from the Literature¹¹
• Wasting of tibialis anterior
• Flattening of thenar eminence
• Wasting of dorsal interossei
• Heaviness of legs
• Dropping objects
• Difficulty climbing stairs

1.11.4 Non-red flag symptoms

We will also identify the symptoms which are NOT usually indicative of MND as specified on the list on the MND website such as
• impairment of the senses
• double vision/ptosis
• bladder and bowel problems
• sexual dysfunction.

1.12 Analysis and statistical reporting

We will present a descriptive analysis comparing characteristics of cases with MND and controls without MND. We will describe the proportions of cases and controls with ‘red flag’ symptoms which occurred prior to the diagnosis of MND in cases/index date in controls. We will examine different time periods e.g. 12 months prior to diagnosis; 1-2 years; 3-4 years; 5 or more years before diagnosis/index date.

We will undertake a univariate analysis examining each red flag symptom and each risk factor in turn. We will then include all the red flag symptoms in a multivariate analysis using conditional logistic regression and use backwards elimination to remove ones which are not significant on multivariate analysis. This will determine which red flag factors remain important and statistically significant (p<0.01) when all the factors are taken into account simultaneously. We will undertake analyses to look for co-linearities and interactions between variables. This process will help identify key red flags and combinations of symptoms and also the relevant time periods prior to diagnosis.

We will then undertake a cohort analysis to calculate the sensitivity and specificity values and positive and negative predictive values for the significant red flag symptoms, both alone and for combinations of symptoms. The cohort will be based on the population identified as described above. We will use Cox proportional hazard models to estimate the coefficients for each risk factors. The time frame over which the analysis will be conducted will be informed by the results of the case control analysis. The results of this cohort analysis will be presented in the form of a chart showing absolute risk values for symptoms alone and in combination.

A feasibility study identified over 5,000 patients with MND in the last 20 years in QRResearch. With 5000 cases and 10 matched controls per case we will be able to detect an odds ratio of 1.26 or more for a symptom recorded in 5% of controls, with 90% power and 1% significance. For a symptom recorded in 1% of controls we will be able to detect an odds ratio of 1.59 or more.
1.13 Limitations

It is important to note, however, that all observational research studies have limitations such as bias and confounding. For example, not all symptoms will be reported by patients to the GP and not all reported symptoms/signs will be coded on in the patient’s electronic health record. Similarly, there may be patients with MND who do not have a diagnosis on their record (false negative) and the occasional patient with a false positive diagnosis. This is likely to result in a degree of misclassification bias which tends to bias the odds ratio towards unity. However, the results are likely to be applicable to the setting of ‘real world’ general practice which is a strength.

1.14 Outputs

There will be two main outputs from the study.

- We will produce a report which lists the relevant clinical codes which are used to record ‘red flag’ symptoms for MND in primary care. These code lists can then be used to develop further tools to help alert GPs to the possibility of MND.
- There will be a research paper suitable for publication in a peer reviewed medical journal.

5 References


