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A hospital based epidemiological study of genetically determined muscle disease in south western Norway

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Abstract

We determined the prevalence of genetically determined neuromuscular diseases in adult Norwegian patients from Hordaland County. We identified patients using International Classification of Disease codes registered in our hospital database and reviewed patient notes to ensure diagnostic accuracy. To ensure maximal ascertainment, we screened both inpatient and outpatient contacts from two 5-year periods 01.01.2005 to 31.12.2009 and 01.01.2008 to 01.01.2013, and used the second data set to define prevalence.

Myotonic dystrophy was the commonest adult muscle disorder with a minimum prevalence of 11.84/100,000 followed by facioscapulohumeral muscular dystrophy at 6.42/100,000. Genetically confirmed limb-girdle muscular dystrophies had a prevalence of 4.2/100,000 with *CAPN3* mutations being the commonest followed by mutations in *ANO5* and *FKRP*. Becker muscular dystrophy was rare (0.4/100,000). For the purposes of comparison, we also ascertained adults with spinal muscular atrophy (SMA) and found a prevalence of 4.42/100,000.

The impact of neuromuscular disease is enormous both for the patient and for society. Progressive weakness and increasing dependency together with pulmonary and cardiac complications require specialised, multidisciplinary follow up. The provision of such care places substantial demands on health service resources. Thus, precise understanding of both type of neuromuscular disease and numbers of patients is essential in order to manage individuals appropriately and plan future health service needs.

Keywords: Epidemiology; Muscle disease; Prevalence.

1. Introduction

Diseases affecting muscle, whether primary or secondary e.g. to disturbance elsewhere in the motor unit, lead to weakness and motor disability. The majority of primary muscle disorders are progressive and associated with increasing functional decline and dependency. Moreover, the impact of muscle disease is not limited to the patient, but extends to the patient's family, other caregivers and to society.

Currently, few cures are available and symptomatic treatments, particularly those directed at maintaining function and preventing complications such as contractures and ventilatory insufficiency are the mainstays of management. Care of patients with muscle disease requires interdisciplinary cooperation usually involving neurologists, physiotherapists, occupational therapists, lung and orthopaedic surgeons [1].

Improved understanding of the consequences of neuromuscular insufficiency, including for example the impact on nocturnal ventilation, has led to improved quality of life and survival [2]. New treatment paradigms offer even greater potential and, while the new genetic therapies may not cure, there is now good reason to hope they will extend and improve quality of life even further [3]. In order

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understand the implications of the new treatment modalities for both health care provision and society, and thus plan health service provision appropriately, it is necessary to have comprehensive data concerning the number of patients and type of muscle disease. To this end, we performed the first epidemiological study of inherited muscle disease in the Norwegian population.

2. Materials and methods

The study was performed at Haukeland University Hospital. This is the only neurological centre serving Hordaland County. Typically, all adult patients with muscle disease are referred to this hospital, and patients with childhood onset disorders are referred to our centre when reaching adulthood. We used the International Classification of Disease version 10 (ICD-10) codes to ascertain patients through our hospital database, which records all in-patient and outpatient contacts linked to the patient's unique identity number. Our primary focus was inherited muscle disease, but we include data on spinal muscular atrophy for comparative purposes. The following ICD-10 codes were used: G120, 121, 122; G710, 711, 712, 713. To ensure any patients later re-classified were not missed, we also reviewed all those with the following: G718–720, G723–24, G728–729, G736, M30–332, M339, M600, M608–609, M628–629 looking for final diagnosis, and performed the search over two overlapping periods, 01.01.2005 to 31.12.2009 and 01.01.2008 to 01.01.2013. Only patients who were alive in the second period were included. Further, only patients who had their clinical diagnosis confirmed by one of the neurologists in our specialised muscle clinic (PSS, LAB) were included. Patients with no genetic mutation and an unclear phenotype or inconclusive biopsy findings were excluded. Some patients classified clinically as LGMD or a scapuloperoneal syndrome had their genetic diagnosis clarified after completion of our survey; where this was the case, we have simply included the patient in the relevant disease category.

We used postal address code to identify patients living in Hordaland County for which the whole population on 01.01.13 was 498,135 (Norwegian Central Bureau of Statistics; SSB). We recorded the following demographic and diagnostic data: age, gender, address; primary diagnosis (ICD-10) and any other additional diagnoses; method and date of diagnosis. The study was approved by the hospital as a Quality Assurance project (2010/3283).

3. Results

We used the whole population number of 498,135 as the denominator for calculating point prevalence on the 01.01.2013. Patients who had died during the second study period were not included in the point prevalence.

We identified 89 patients with an established or probable genetically determined muscular dystrophy/myopathy of whom 5 had died during the second 5-year period of study (Table 1). The major categories included FSHD, LGMD, dystrophin-linked disease and an assortment of other conditions including oculopharyngeal muscular dystrophy (OPMD), Laings myopathy and scapuloperoneal syndromes. One patient with biopsy proven Nemaline myopathy and one with an oculopharyngeal distal myopathy were not genetically clarified, but based on the presence of other affected family members were included as genetically determined disorders (Table 1). The largest single disease category was FSHD with 34 patients of whom two died during the ascertainment period giving a point prevalence on 01.01.13 of 6.42/100,000. The majority of these patients were FSHD type 1, however, two brothers were later found (after 2013) to have mutations in the SMCHD1 gene and were classified as FSHD type 2.

Table 1
Numbers of patients with muscular dystrophy and related conditions.

	Ascertained	Minus dead	per 100,000
FSHD	34	32	6.42
LGMD	29	28	5.62
Becker	2	2	0.40
DMD	11	10	2.01
Other	13	12	2.40
Total	**89**	**84**	**16.85**

Figures for the major categories of muscle disease (dystrophies and myopathies) derived from the second cohort with reference to the first cohort of patients. The category of LGMD includes all patients both with final genetic diagnosis and without. Only patients alive during the second period were used to generate prevalence (minus dead column).
Becker, Becker muscular dystrophy; DMD, Duchenne muscular dystrophy; FSHD, fasioscapulohumeral muscular dystrophy; LGMD, Limb Girdle muscular dystrophy. Other, Muscle-eye-brain disease; oculopharyngeal muscular dystrophy; scapuloperoneal syndromes; manifesting adult females with X-linked myotubular myopathy; oculopharyngeal distal phenotype.

Table 2
Numbers of patients with myotonia.

	Ascertained	Minus Dead	Per 100,000
DM1	58	54	10.84
DM2	6	5	1.00
Myotonia Congenita	14	14	2.81
Total	**78**	**73**	**14.65**

DM1 – myotonic dystrophy type 1; DM2 - myotonic dystrophy type 2.

The prevalence of LGMD was 5.62/100,000; excluding those without a clear genetic diagnosis lowered the figure to 4.22/100,000. Ten of 11 patients with Duchenne muscular dystrophy (DMD) were alive at the point of analysis giving a prevalence of 2.01/100,000. The prevalence of Becker muscular dystrophy was considerably less at 0.4/100,000.

Seventy-eight patients had a dystrophic or non-dystrophic myotonic disorder (G71.1) (Table 2) and the majority of these had myotonic dystrophy type 1 (DM1). Interestingly, we found 14 patients with myotonia congenita (MC) giving a point prevalence of 2.81/100,000. All of these had confirmed CLCN1 mutations, and the majority showed recessive inheritance.

We also ascertained adult patients with genetically confirmed (5q associated) spinal muscular atrophy attending our muscle clinic and found 23 of whom 22 were alive on

Table 3
Shows the overall impact of neuromuscular disease.

Disease group	Total ascertained	Alive	Per 100,000
Muscle diseases	89	84	16.86
Myotonic disorders	78	73	14.65
McArdles	6	4	0.80
Hypokalemic Periodic Paralysis	5	5	1.00
SMA (over 18)	23	22	4.42
Total	**203**	**190**	**37.73**

We have grouped the major categories together to provide insight into the numbers of patients with neuromuscular disease that attended our specialised muscle clinic.

01.01.13. Six patients with genetically confirmed McArdles and five with hypokalaemic periodic paralysis were also identified and while most of the latter were not genetically confirmed, they are included here to highlight the spectrum of diseases found.

The commonest limb girdle muscular dystrophies in our population were caused by Calpain (LGMDD4/LGMD2A/LGMDR1) and anoctamin 5 (LGMD2L/LGMDR12) mutations (Table 3). These would have been equally prevalent except that one patient with LGMD2L died during the study period. In all but two cases of *CAPN3* mutation, we found a heterozygous a 21-bp, in-frame deletion (c.643_663del21). One other patient was compound heterozygous for a known change and a probable pathogenic variant. The majority of LGMD2L patients carried the founder *ANO5* mutation c.191 dup A, while three were compound heterozygotes with other combinations. LGMD 2I was not as common in our cohort as either 2A or 2L; the commonest *FKRP* mutation was the c.826C > A.

The largest number of patients in whom we had no genetic diagnosis had a limb-girdle phenotype. With the advent of new sequencing techniques, many of these have been clarified since this study period ended including one with LGMD2B and homozygous dysferlin mutation and one who had *COL6A1* mutations and who has Bethlem myopathy and thus not LGMD. Five patients, who clinically had proximal weakness and biopsy findings consistent with a LGMD, remain genetically undiagnosed. Interestingly, no cases of Pompe disease were identified despite sequencing this gene in all the cases with a genetically undefined LGMD phenotype. While this may be due to this study's population size, we are aware that few cases of Pompe disease have been identified in the country as a whole.

We excluded patients with no genetic mutation and an unclear phenotype or inconclusive biopsy findings. While some of these may later turn out to have LGMD or other type of genetically determined muscle disease, we chose not to include them in this study. Patients classified as "other" included: two brothers with Muscle-eye-brain disease and mutation in *POMT1*, two with oculopharyngeal muscular dystrophy and *PABNA1* mutations, four with scapuloperoneal syndromes of whom 2 had mutation in *TRPV4* (father and daughter) and two had an *FHL1* mutation (mother and son); and two adult females with mutations in *MTM1* and manifesting X-linked myotubular myopathy. One patient with an oculopharyngeal distal phenotype has also not been genetically characterised.

Fig. 1. Map of Norway showing the county of Hordaland in red. (From Wikipedia, attribution: Creative Commons CC-BY-SA-2.5).

4. Discussion

Hordaland County (Fig. 1) is the third most populated county in Norway and contains one major city (Bergen), several smaller towns and a substantial rural population. The Department of Neurology, Haukeland University Hospital is the only neurological centre serving this population. While this means that ascertainment is good for muscular dystrophies, i.e. disorders that give progressive weakness, milder variants of myotonic dystrophy, myotonia congenita and FSHD, may have gone unrecognised. Our figures for these conditions are, therefore, estimates of minimum prevalence. This study focussed only on adult patients investigated and followed up in a specialised multidisciplinary outpatient clinic that caters for all types of neuromuscular disease including spinal muscular atrophy (SMA), but not ALS, myasthenia or peripheral neuropathies such as CMT.

We included patients registered with DMD. While ascertainment of these patients is likely to be incomplete, we felt this data was important to inform us about potential numbers attending our adult clinic and, since DMD has been studied more than most other muscle diseases, for comparative purposes [4]. The number of cases with Becker muscular dystrophy (BMD) appeared lower than we might have expected based on studies performed in Northern England, where the estimate was 7.29/100,000 [5]. Our figure of 0.4/100,000 is closer to that found in a study from Sweden that showed 1.6/100,000 [6].

We found an overall prevalence for LGMD of 5.62/100,000 and for those with a genetic diagnosis, the figure was 4.2/100,000. In a study performed in 2009 in Northern England, the estimated prevalence of LGMD was 2.27/100,000 [5]. While it is possible that there are major discrepancies between Northern European countries, it is also possible that the improvement of genetic testing has made it easier for us to classify these patients.

The spectrum of limb girdle muscular dystrophies is different to that we expected based on previous studies. In an earlier Norwegian study, the prevalence of LGMD2I was 1.85/100,000 [7]. We, therefore, expected this to be the most prevalent type, but this was not the case. The prevalence of LGMD2I was 0.8/100,000 while for LGMD2L it was 1.61/100,000. Patients with *CAPN3* mutations can have either dominant or recessive disease and in our population, the majority (7 of 9) had the recently described, dominantly inherited 21-bp, in-frame deletion (c.643_663del21) [8]. Only two had recessive disease and both were compound heterozygotes. Patients with the dominantly inherited form of calpainopathy had a typical LGMD phenotype albeit with predominant involvement of gait, and they tended to have a milder and later onset disorder.

Similar to other countries, FSHD is the second most common muscular dystrophy in our population. Compared to Holland, where they registered a figure of 12/100,000 [9], the prevalence in our population was lower at 6.42/100,000, but almost double that found in N.E England where the prevalence was estimated to be 3.95/100,000 [5]. FSHD manifests a wide range of severities from very severe, early onset associated with mental retardation and eye involvement (2 patients in our population), to patients with minor scapula winging who may never come to medical attention. It is likely, therefore, that ascertainment of this disorder is an underestimate. Two of our patients (brothers) had FSHD type 2 and this diagnosis was also made during the second period of assessment.

Myotonic dystrophy is the most common muscle disease in the adult population and our study confirms this. While our figure of 11.84/100,000 reflects minimum prevalence only, we have more than 60 adult patients with myotonic dystrophy in a population of just under 500,000. DM1 and DM2 are disorders that combine multisystem involvement and progressive disability with cognitive disabilities that mean that patients often neglect their disease. Even those with mild disease can experience major problems engaging in normal everyday activities. Potentially serious respiratory and cardiac complications that can affect even mildly affected, demand vigilance and regular follow up and show how important it is to perform prevalence studies such as these.

The number of patients with myotonia congenita (2.8/100,000) appears high [10], but is in fact lower than that found in another area of Norway. A study performed in Northern Norway [11] found a prevalence of 9/100,000 similar to that found in Northern Finland [12]. The Norwegian population may be atypical due to a potential bottleneck caused by the decimation caused by the plague in the 14 century, and by its geography that constrained population movement prior to the last century. While this is likely to affect recessive diseases more than dominantly inherited ones, with the exception perhaps of myotonia congenita, our figures are not markedly different to those produced elsewhere.

To get an idea of the overall demand for neurological service provision, we grouped the diseases together: adding the number with an established or probable genetically determined muscular dystrophy with myotonic dystrophy gave a prevalence figure 31.51/100,000. If we add to this those with SMA, the figure rises to 35.93/100,000. Adding those with hypokalemic periodic paralysis and McArdles brings the figure to 37.73/100,000. Including all those who died during the period, but who were at some point reviewed in clinic, the figure rises to 40.35. Treatment of these patients currently involves a combination of local services together with a wide range of hospital specialists including doctors from several specialities, physiotherapists, occupational therapists etc. The complexity of this is also changing with the introduction of new and, if the new treatment for SMA is any guide, very expensive medicines. While SMA treatment is currently reserved for those under 18 in Norway, the number of patients in our study that have survived into adulthood, provides an indication of the numbers we will be treating.

5. Conclusions

In this study of the prevalence of inherited neuromuscular diseases in Norway, we show that the number and range of neuromuscular disease is comparable to other European centres although interesting differences such as the prevalence of Becker and myotonia congenita exist. The accumulated minimum prevalence of muscular dystrophies, myotonic disorders and SMA of 1:2600 demonstrates that these disorders will continue to have major impact on heath service provision for the foreseeable future.

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