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A Population-Based Epidemiologic Study of Adult Neuromuscular Disease in the Republic of Ireland

By

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MRCPI

Thesis submitted to the National University of Ireland, Cork for the degree of Doctor in Medicine

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DECLARATION

I declare that this thesis in candidature for the degree of Doctor in Medicine has been composed entirely by myself. The work which is documented in this thesis was carried out by myself. All sources of information contained within which have not arisen from the results generated have been acknowledged.



Stela Lefter

ABBREVIATIONS

AAN - American Academy of Neurology

ACh - acetylcholine

AChE - acetylcholinesterase

AChR - acetylcholine receptors

AMAN - acute motor axonal neuropathy

AMSAN - acute motor-sensory axonal neuropathy

AP - action potential

ATS - Andersen-Tawil syndrome

CANOMAD - Chronic Ataxic Neuropathy Ophtalmoplegia IgM paraprotein Cold Agglutinins Disialosyl antibodies

CB - conduction block

CB - conduction block

CCD - central core disease

CFT - congenital fiber-type disproportion

CIDP - chronic inflammatory demyelinating polyradiculoneuropathy

CK - creatine kinase

CLCN1 - skeletal muscle voltage-gated chloride channel gene

CM - congenital myopathies

CMAP - compound motor action potential

CMS - congenital myasthenic syndrome

CMT - Charcot-Marie-Tooth disease

CNM - centronuclear myopathy

CNS - central nervous system

CPEO - chronic progressive external ophthalmoplegia

CR - capture-recapture

CSF - cerebral spinal fluid

CV - conduction velocity

DADS - distal acquired symmetrical demyelinating neuropathy

DGC - dystrophin glycoprotein complex

dHMN - distal hereditary motor neuropathies

DM1 - myotonic dystrophy type 1

DMD - Duchenne muscular dystrophy

DMPK - myotonic dystrophy protein kinase

EFNS/PNS - European Federation of Neurological Societies/Peripheral Nerve Society

EM - electron microscopy

EMG - electromyography

FAP - familial amyloid polyneuropathy

FSHD - facioscapulohumeral dystrophy

GBS - Guillain-Barré syndrome

GIS - Geographical Information Systems

GMD - genetic muscle disease

GSM - glycogen storage myopathy

HIPE - Hospital In-Patient Enquiry

HNPP - hereditary neuropathy with liability to pressure palsies

HSMN - hereditary sensory and motor neuropathy

Hyper PP - hyperkalaemic periodic paralysis

Hypo PP - hypokalaemic periodic paralysis

IR - incidence rate

KD - Kennedy's disease

KSS - Kearns-Sayre syndrome

LEMS - Lambert-Eaton myasthenic syndrome

LGMD - limb girdle muscular dystrophy

LSM - glycogen storage myopathy

MAD - myoadenylate deaminase deficiency

MADSAM - multifocal acquired demyelinating sensory and motor neuropathy

MAG - myelin-associated glycoprotein

MC - myotonia congenita

MD - muscular dystrophy

MDC - congenital muscular dystrophies

MDI - Muscular Dystrophy Ireland

MELAS - mitochondrial encephalomyopathy with lactic acidosis and stroke-like episodes

MFS - Miller-Fisher syndrome

MG - myasthenia gravis

MGUS - monoclonal gammopathy of undetermined significance

MMN - multifocal motor neuropathy

MUSK - muscle-specific tyrosine kinase

NCS - nerve conduction studies

NDM - non-dystrophic myotonias

NM - nemaline myopathy

NM - neuromyotonia

NMD - neuromuscular diseases

NMJ - neuromuscular junction

OPMD - oculopharyngeal muscular dystrophy

PAB2 - poly A binding protein 2

PDN - paraproteinaemic demyelinating neuropathy

PMC - paramyotonia congenita

PN - peripheral nerve

PNS - peripheral nervous system

POEMS - polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy, skin changes

PP - periodic paralyses

PR - prevalence rate

PROMM - proximal myotonic myopathy

RNS - repetitive nerve stimulation

ROI - Republic of Ireland

SF EMG - single fibre electromyography

sIBM - sporadic inclusion body myositis

SMA - spinal muscular atrophy

SMIC - skeletal muscle ion channelopathies

SNAP - sensory nerve action potential

SSEP - somatosensory evoked potential

VGCC - voltage gated calcium channels

VGKC - voltage gated potassium channel

X EDMD - X-linked Emery-Dreifuss dystrophy

ABSTRACT

This research project generates for the first time prevalence rates (PR) for all adult neuromuscular diseases (NMD) as well as the incidence rates (IR) for Guillain-Barre syndrome (GBS) in the Republic of Ireland (ROI). Multiple case ascertainment sources were used to achieve as complete as possible case ascertainment to accurately estimate the country-wide prevalence. Acquired demyelinating polyneuropathies represented the biggest cohort (26.0%) followed by muscular dystrophies (22.5%) and myasthenia gravis (19.7%). For GBS, in the 20 year period (1992 to 2012), comparable with other international studies, incidence rates of 0.3-1.3 per 100,000 person-years were attained. Higher PR figures for chronic inflammatory demyelinating polyneuropathy and sporadic inclusion body myositis were found (5.87 per 100,000 and 11.7 per 100,000 in those older than 50 year, respectively) compared with previous studies. The PR for myasthenia gravis in ROI is comparable with countries such as Australia, Italy and Norway but is lower than in Northern Ireland. The PR for Charcot-Marie-Tooth disease and limb girdle muscular dystrophies were similar with United Kingdom PR; however, a definite diagnosis was attained in only one third of Irish patients. Given the fact that paediatric cases were excluded from our study, lower PR figures were obtained for dystophinopathies. Interestingly, the PR for myotonic dystrophy type 1 and facioscapulohumeral muscular dystrophy (FSHD) in the ROI was lower than in United Kingdom but not considerably. A high PR for periodic paralysis (PP) was found in our study, nearly ten times higher for Hyper PP and as twice as high for Hypo PP when compared with figures from England; however, the ROI figures were derived from large families suggesting a founder effect. Of all the inherited NMD, 46% of cases had a definite histopathology and/or genetic diagnosis. The combined PR for inherited and acquired NMD was high, 62.6 per 100,000, when compared with other chronic neurological diseases in ROI. During the course of the study, a definite genetic diagnosis was achieved in families with rare previously unreported NMD in ROI, such as Laing distal myopathy, Andersen Tawil syndrome and FSHD2. This research defines the burden of NMD in the ROI, raises awareness of these conditions, will facilitate earlier intervention where appropriate and will provide a strong argument for service provision for these patients. This research project will serve as a useful originator for future research studies, especially with regard to obtaining genetic confirmation of currently undefined cases.

PUBLICATIONS AND PRESENTATIONS

PUBLICATIONS

1. Lefter S, Hardiman O, Ryan A.M. **Methodology and design of a national epidemiological study on adult neuromuscular disease.** Neuroepidemiology 2014;43:123-30

2. Lefter S, Hardiman O, Ryan A.M. **A Population-Based Epidemiologic Study of Adult Neuromuscular Disease in the Republic of Ireland**. Manuscript in preparation. December 2014

3. S. Lefter, O. Hardiman, R. L. McLaughlin, S.M. Murphy, M. Farrell, A.M. Ryan. **A novel MYH7 L1453P mutation resulting in Laing distal myopathy in an Irish family.** Neuromuscular disorders. Published Online: September 24, 2014.

4. S. Lefter, O. Hardiman, D. Costigan, B. Lynch, J. McConville, C.K. Hand, A.M. Ryan. **Andersen-Tawil syndrome with early fixed myopathy.** J Clin Neuromuscul Dis 2014;16:79-82.

PRESENTATIONS

1. S. Lefter, S. Murphy, M. Farrell, O. Hardiman. **An Autosomal Dominant Distal Myopathy in an Irish Family.** Irish Neuromuscular Association Meeting, IICN. Cork, Ireland. May 2012. **Oral presentation.**

2. S. Lefter, N Lynch, R. Galvin, O. Hardiman, A.M. Ryan. **An Autosomal Dominant Muscle Dystrophy with a novel mutation.** Irish Neuromuscular Association Meeting, IICN. Cork, Ireland. May 2012. **Oral presentation.**

3. S. Lefter, N. Bermingham, C. Keohane, B. McNamara, A.M. Ryan. **Sometimes, there is a good reason why women need new shoes!** Irish Neuromuscular Association Meeting, IICN. Cork, Ireland. May 2012. **Oral presentation.**

4. Lefter S, Hardiman O, Ryan A.M. **A Population-Based Epidemiologic Study of Adult Neuromuscular Disease in the Republic of Ireland – interim results.** Registrar's Prize in Clinical Neuroscience, IICN. Dublin. November 2012. **Oral presentation.**

5. Lefter S, Hand C, McConville J, Costigan D, Lynch B, Hardiman O, Ryan A. **U know who?** Registrar's Prize in Clinical Neuroscience, IICN. Dublin. November 2012. **Oral presentation.**

6. Lefter S, Hardiman O, Ryan A.M. **A Population-Based Epidemiologic Study of Adult Neuromuscular Disease in the Republic of Ireland.** 49th Annual Irish Neurological Association Meeting, IICN. Dublin. May 2013. **Oral presentation.**

7. Lefter S, Murphy K, Farrell M, Hudson J, Barresi R, Ryan A.M**. From Kerry to Rosses Point.** Registrar's Prize in Clinical Neuroscience, IICN. Dublin. November 2013. **Oral presentation.**

8. Lefter S, Hardiman O, Ryan A.M. **A Population-Based Epidemiologic Study of Adult Neuromuscular Disease in the Republic of Ireland.** Registrar's Prize in Clinical Neuroscience, IICN. Dublin, November 2013. **Oral presentation.**

9. S. Lefter, O. Hardiman, R. L. McLaughlin, S.M. Murphy, M. Farrell, A.M. Ryan. **A novel MYH7 L1453P mutation resulting in Laing distal myopathy in an Irish family.** 66th AAN Annual Meeting. Philadelphia, USA. April 2014. **Poster abstract.**

10. S. Lefter, O. Hardiman, A.M. Ryan. **A Population-Based Epidemiologic Study of Adult Neuromuscular Disease in the Republic of Ireland**. 66th AAN Annual Meeting. Philadelphia, USA. April 2014. **Poster abstract.**

Presentations at the Patient Orientated Meetings and Seminars

1. S. Lefter, O. Hardiman, A.M. Ryan. **A Population-Based Epidemiologic Study of Adult Neuromuscular Disease in the Republic of Ireland.** The 2012 Myasthenia Gravis Seminar. Myasthenia Gravis Association. Muscular Dystrophy Ireland. Dublin. March 2012. **Oral presentation.**

2. S. Lefter. **Limb Girdle Muscular Dystrophy in the neuromuscular clinic.** Limb Girdle Muscular Dystrophy Information Day. Muscular Dystrophy Ireland. Dublin. September 2012. **Oral presentation.**

3. S. Lefter, O. Hardiman, A.M. Ryan**. A Population-Based Epidemiologic Study of Adult Neuromuscular Disease in the Republic of Ireland – initial results.** Limb Girdle Muscular Dystrophy Information Day. Muscular Dystrophy Ireland. Dublin. September 2012. **Oral presentation.**

4. S. Lefter, O. Hardiman, A.M. Ryan. **A Population-Based Epidemiologic Study of Adult Neuromuscular Disease in the Republic of Ireland – interim results.** Annual General Meeting, Muscular Dystrophy Ireland. Muscular Dystrophy Ireland, Dublin. April 2013. **Oral presentation.**

5. S. Lefter, O. Hardiman, A.M. Ryan. **A Population-Based Epidemiologic Study of Adult Neuromuscular Disease in the Republic of Ireland – interim results.** All Ireland Research and Information Sharing Day. Muscular Dystrophy Ireland and the Northern Ireland Council of Muscular Dystrophy. Gormanstown, Co. Meath. September 2013. **Oral presentation.**

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DEDICATION

To my family, my beloved daughter Madalina and my partner Michael, for their love and understanding. They were a constant source of encouragement to 'keep going'. I can't thank them enough for their endless patience and enormous support in everything I do. To my beloved parents for their constant and unconditional love and from whom I learnt what is meant by diligence and perseverance and the benefit of cultivating a questioning mind. To my parents-in-law for their special source of love and support.

Chapter 1

Introduction

Neuromuscular disorders (NMDs) represent a complex group of heterogenous disorders, acquired or inherited, affecting the peripheral nervous system, which can be broadly divided into disorders affecting anterior horn cell (e.g. spinal muscular atrophy), peripheral nerve (e.g. Charcot-Marie-Tooth disease), neuromuscular junction (e.g. myasthenia gravis), skeletal muscle channel (e.g. periodic paralysis) and muscle (e.g. muscular dystrophies). All these disorders have different characteristics in terms of their symptoms, age of onset, inheritance pattern, genetic origin and epidemiology.

In recent years, a rapidly changing landscape in the area of NMDs has been witnessed. The new advances in the genetic area with easier access to genetic testing, an ever-increasing number of new genes being discovered and emerging potential gene therapies, have all opened exciting new prospects for these patients. With the already newly available treatments like enzyme replacement therapy for Pompe disease, and other prospective treatments in the pipeline for conditions such as inclusion body myositis, it is important to identify these patients in a timely fashion so that they can benefit from these new treatments. This forms the background underlying the recent re-emergence of interest in studying the epidemiology of these conditions.

The information gathered from epidemiological studies allows us to establish disease incidence and prevalence rates and monitor them over time. They also help to plan and budget future care services for these patients both at local community and national levels. Epidemiological studies also help to increase awareness of different conditions (particularly more rare ones) among other clinicians and throughout the wider community so that accurate and early diagnosis can be achieved and treatment, where available, is instituted.

In the past decade or so, numerous studies looking at the epidemiology of single-disorders in different age populations were published. However, an epidemiologic study of the broad spectrum of adult NMDs (both acquired and inherited) in order to identify 'the country-wide burden' was never studied, neither in the Republic of Ireland or any other country. This formed the background to undertaking this research study, the first of its kind in the Republic of Ireland.

In this chapter, I will describe general aspects of the anatomy of the peripheral nervous system followed by clinical aspects of NMDs with particular emphasis on the classification and diagnostic criteria of these conditions

1.1 The nervous system

The human nervous system consists of two main components, central nervous system (CNS), brain and spinal cord and peripheral nervous system (PNS), cranial and spinal nerves and autonomic system. The basic elements of the nervous system are the neurons (motor, sensory, and inter neurons) which contain three parts: soma or the cell body, dendrites which are filaments that receive neuron's input and an axon that carries the nerve signals away from soma (Figure 1). Neurons are electrically excitable cells which generate and conduct the repeating electrical signals called action potentials (AP).

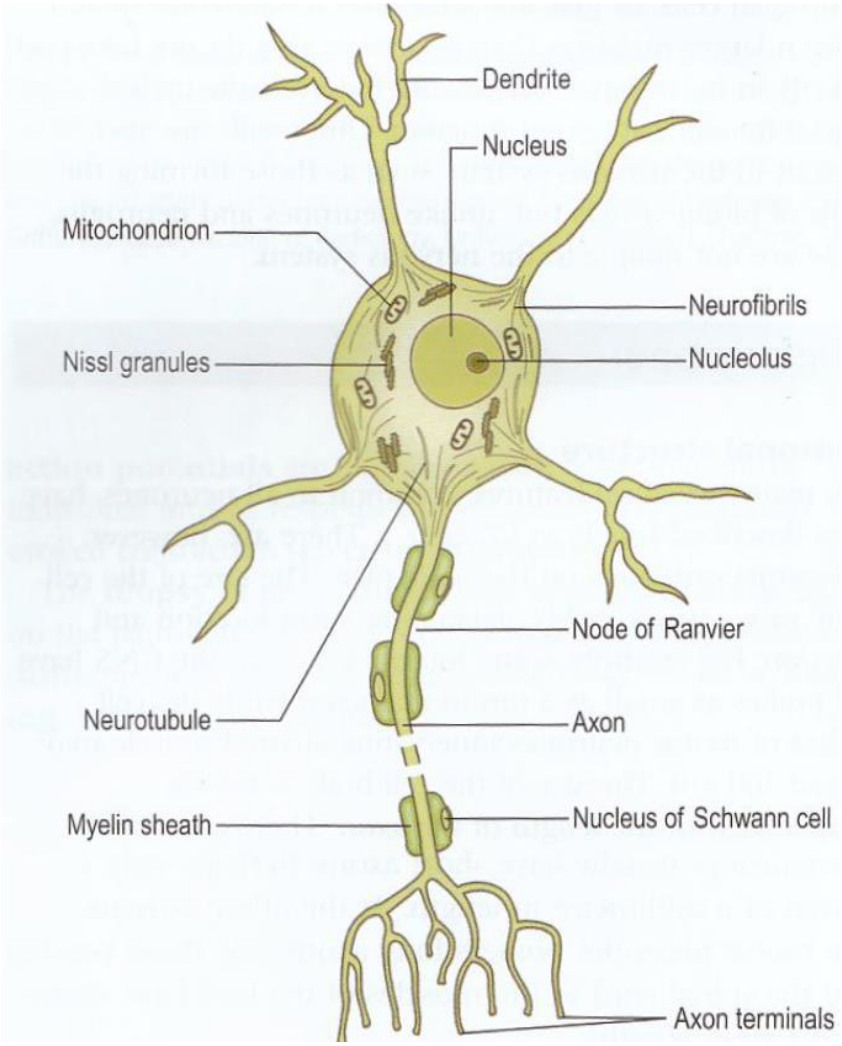


Figure 1 Diagram representing a myelinated motor neuron [1]

1.1.1 The peripheral nervous system

In the PNS, neurons processes are connected to the peripheral satellite cell, the Schwann cell. PNS includes the cranial nerves (except for the second cranial nerve), the spinal nerve roots, the dorsal root ganglia, the peripheral nerve trunks with their terminal ramifications and the peripheral autonomic system. There are two main types of peripheral nerves: somatic (motor and sensory nerves) and autonomic (sympathetic and parasympathetic nerves). Somatic motor nerves control muscles and sensory nerves carry heat, pain, and touch sensations to the CNS. The autonomic nerves control vital functions that are necessary for the maintenance of the homeostasis, including respiration, circulation, metabolism, body temperature, water balance, digestion, secretion, and reproductive function.

1.1.1.1 The axon

The axon, the central part of the nerve, spreads from the neuron to the target organ. In the peripheral nerves, Schwann cells form a layer called ”myelin sheath” which surrounds the axon and is arranged in segments called “internodes” (Figure 2). The small space of uncovered axon between sheaths is called the node of Ranvier, the site where the AP is transmitted. The AP bounces from node to node via a “saltation” mechanism, rather than propagating in a continuous conduction process. In contrast to myelinated axons, unmyelinated axons are partially enveloped by the membranes of Schwann cells.

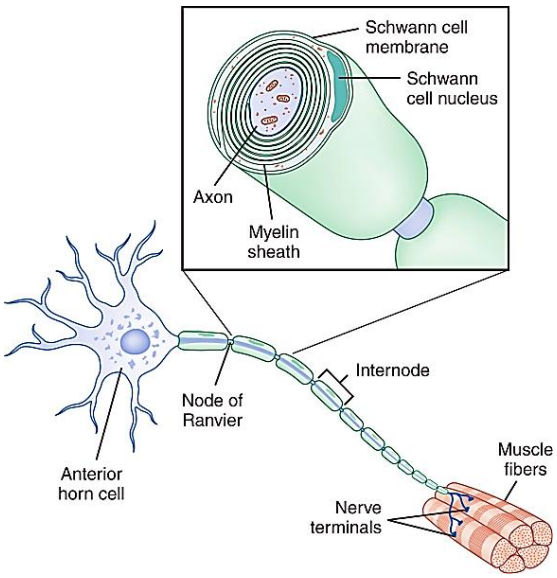


Figure 2 Anatomy of the peripheral nerve [2]

1.1.1.2 Peripheral nerve

Peripheral nerves (PN) can be divided into groups, depending on the direction they transmit the AP and depending on where they connect to CNS. Based on the direction they transmit the AP, the afferent nerves conduct signals from sensory neurons to the CNS and efferent nerves conduct signals from CNS along motor neurons to the peripheral organs such as muscles. Mixed nerves that have both afferent and efferent functions also exist. Based on where PN connect to the CNS, there are spinal nerves that start from the spinal cord and form the ventral roots (motor) and dorsal roots (sensory) and cranial nerves that connect directly to the brain. At cervical and lumbar levels, the spinal nerves join to form brachial and lumbosacral plexuses. The brachial plexus is formed by five spinal nerve ventral rami (C5-T1), each of which carries motor, sensory, and post-ganglionic sympathetic fibres to the upper limb. These five rami unite above the clavicle level to form three trunks which then contribute to the three cords (lateral, medial and posterior). The major nerves of the upper limb derive from the cords. Lateral cord contributes to formation of the median and musculocutaneous nerves. Similarly, after making its contribution to the median nerve, the medial cord continues as the ulnar nerve, medial cutaneous nerve of the arm and the medial cutaneous nerve of the forearm. The posterior cord divides into radial and axillary nerves and posterior cutaneous nerve of the arm. Also, from the cords, branches are distributed to the pectoralis major and minor muscles and to the subscapularis, latissimus dorsi and teres major muscles. Nerve branches to the serratus anterior, levator scapulae, rhomboids, and supraspinatus and infraspinatus muscles derive from more proximal levels of the plexus. The lumbar plexus is formed within the psoas major muscle by the anterior primary rami of lumbar spinal nerves L1, L2, L3 and L4. Branches of the lumbar plexus include the iliohypogastric and ilioinguinal nerves, lateral femoral cutaneous nerve of the thigh, genitofemoral nerve, femoral and the obturator nerves. The sacral plexus, derived from the anterior rami of spinal nerves L4, L5, S1, S2 and S3, contribute to tibial and peroneal portions of the sciatic nerve, posterior cutaneous nerve of the thigh and pudendal nerve. The superior and inferior gluteal nerves derive from the sacral plexus in the pelvis [3].
PN injury can be caused by different processes including inflammatory, metabolic, toxic, traumatic, inherited and paraneoplastic. Either motor or sensory nerves or both can be affected. The myelin sheaths or axons can be affected separately or concurrently resulting in axonal degeneration or demyelination or both. Large myelinated PN may react to injury or disease in three pathways: Wallerian degeneration, segmental demyelination and axonal degeneration [2].

1.1.1.3 Neuromuscular junction

The components of the neuromuscular junction (NMJ) are illustrated in Figure 3.
NMJ comprises acetylcholine receptors (AChR), acetylcholine (ACh) and acetylcholinesterase (AChE), which play an important role in neuromuscular transmission. ACh is synthesized in the motor nerve terminal and stored in vesicles as packets, or "quanta," each containing approximately 5000 to 10,000 molecules [4]. ACh combine with AChR on the postsynaptic membrane, generating miniature end-plate potentials (0.5 mV). A nerve AP, via voltage-gated calcium channels (VGCC), depolarizes the presynaptic membrane causing Ca^{2+} influx into the nerve terminal producing ACh release. Subsequently, the ACh disseminates into the synaptic cleft, where it can be hydrolyzed by AChE, and binds to AChR. As a result, channels open causing Na^{+} influx into the muscle fibre which activates voltage-gated Na^{+} channels, causing further Na^{+} influx and spreading of the AP along the muscle fibre. Other proteins involved in AChR clustering include Rapsyn, muscle-specific tyrosine kinase (MuSK) and agrin [5]. Rapsyn, a peripheral membrane protein exposed on the cytoplasmic surface of the postsynaptic membrane, is necessary for clustering of AChR, with which it coclusters. Rapsyn causes clustering of NMJ proteins other than the AChR, including MuSK [5]. MuSK, a postsynaptic transmembrane protein, is present prominently only at the NMJ, where it is part of the receptor for agrin. Agrin is a protein synthesized by motor neurons and secreted into the synaptic basal lamina. The signalling mediated by agrin / MuSK interaction triggers and maintains rapsyn-dependent clustering of AChR and other postsynaptic proteins [6].

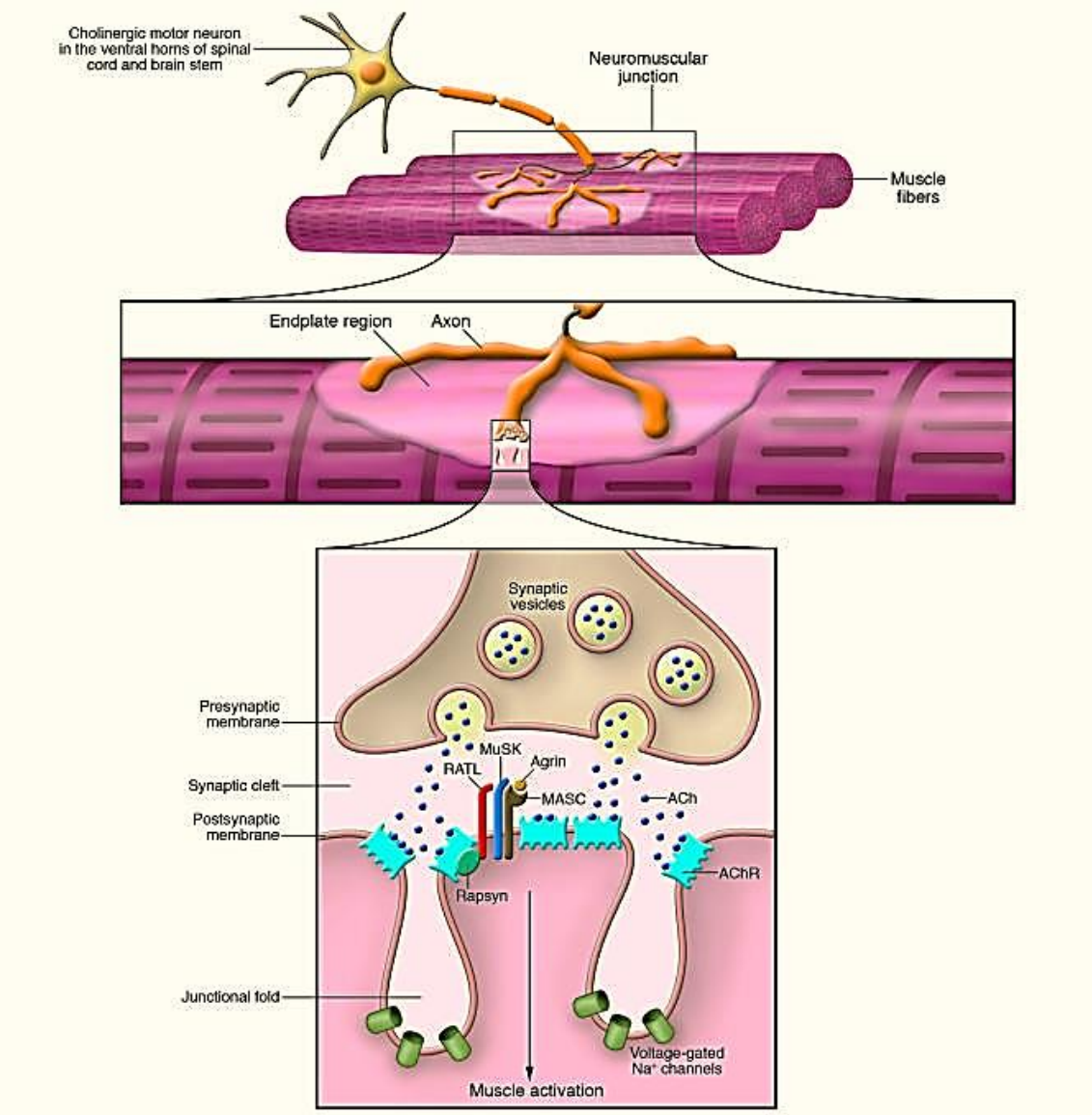


Figure 3 Neuromuscular junction structure [5]

1.1.1.4 Skeletal muscle

Skeletal muscle consists of thousands of muscle fibres which differ in their physiological and biochemical properties. Three fibre types can be identified in normal muscle (type 1, 2A, 2B) with an additional subtype of 2C that is an immature fibre type. Type 1 fibres, "slow twitch", have high oxidative and low glycolytic activity and type 2 fibres, "fast twitch", have low oxidative and high glycolytic activity [7]. The individual muscle fibres are surrounded by connective tissue (endomysium) which contains capillaries and nerve fibres. Muscle fibres are bound into groups or fascicles by collagen sheets (perimysium), which also bind together groups of fascicles and surround the entire muscle (epimysium). The muscle fibres are attached to tendons, in order to connect with the bone (Figure 4). Each muscle fibre is wrapped by an inner plasma membrane (sarcolemma), beneath which are the subsarcolemmal nuclei, and an outer basement membrane. The cytoplasm (sarcoplasm) of the cell contains myofibrils and organelles. Each myofibril is wrapped in the sarcoplasmic reticulum which by expanding into the fibre forms the transverse tubular system (T tubules), which are channels of communication between the extra- and intracellular sarcoplasmic reticulum (Figure 5). The myofibrils, composed of longitudinally orientated 'thin' and 'thick' filaments of actin and myosin, are organised in a repeated unit, called the sarcomere. Diverse biochemical processes, together with calcium ions produce contraction and relaxation of the muscle. Muscle contraction occurs via innervation. Each muscle fibre receives an axon from a motor neuron in the anterior horn of the spinal cord or nucleus of a cranial nerve. The nerve axon connects to the muscle fibre at the NMJ or motor end plate. A group of muscle fibres which have mutual innervation from one anterior horn cell represents the motor unit. During a lifetime, skeletal muscle is exposed to recurrent cycles of contraction and relaxation which relies on specific connection between the subsarcolemmal cytoskeleton and extracellular matrix elements. Muscular dystrophies are caused by a disruption between the extracellular matrix and the cytoskeleton or by aberrations in matrix components [8].

The Dystrophin Glycoprotein Complex (DGC)

Dystrophin is a large cytoskeletal protein that lies on the cytoplasmic face of the plasma membrane. It interacts with the actin cytoskeleton and other dystrophin-associated proteins producing dystrophin-associated glycoprotein complex (DGC) (Figure 6). DGC is believed to act as a link between the extracellular matrix and the cytoskeleton, stabilizing the membrane during contraction [9]. Dystroglycan, the principal element of the DGC, is made

up of 2 protein types: alpha- and β-dystroglycan [10]. DGC stability relies on alpha-dystroglycan glycosylation. Dystrophin is absent in patients with Duchenne's muscular dystrophy [11] and partially expressed in Becker muscular dystrophy [12, 13].

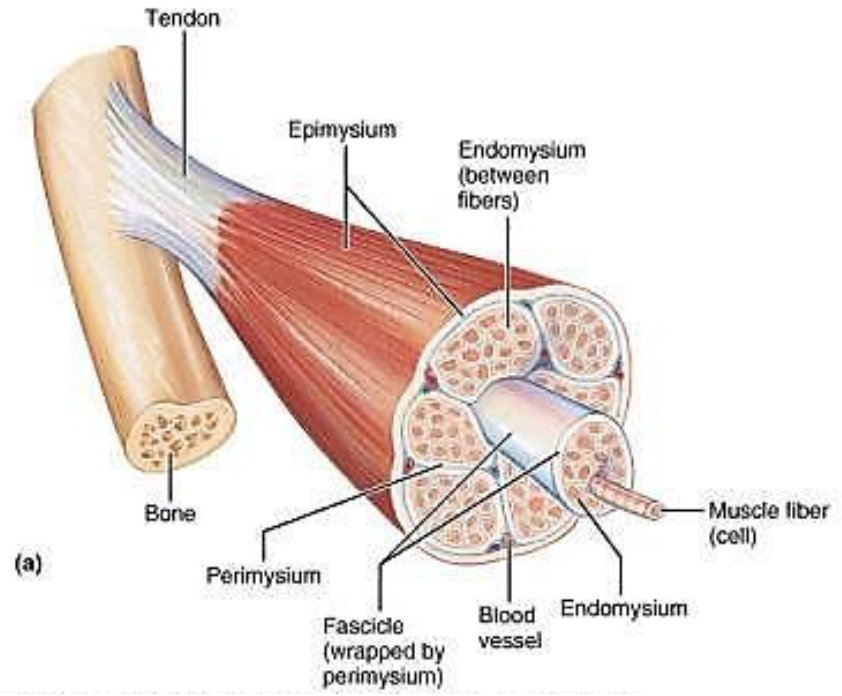


Figure 4 Diagram of skeletal muscle. Skeletal muscle enveloped by epimysium and comprised of fascicles made up of muscle fibres. Each muscle fibre is surrounded by endomysium. http://faculty.etsu.edu/forsman/Histologyofmuscleforweb.htm

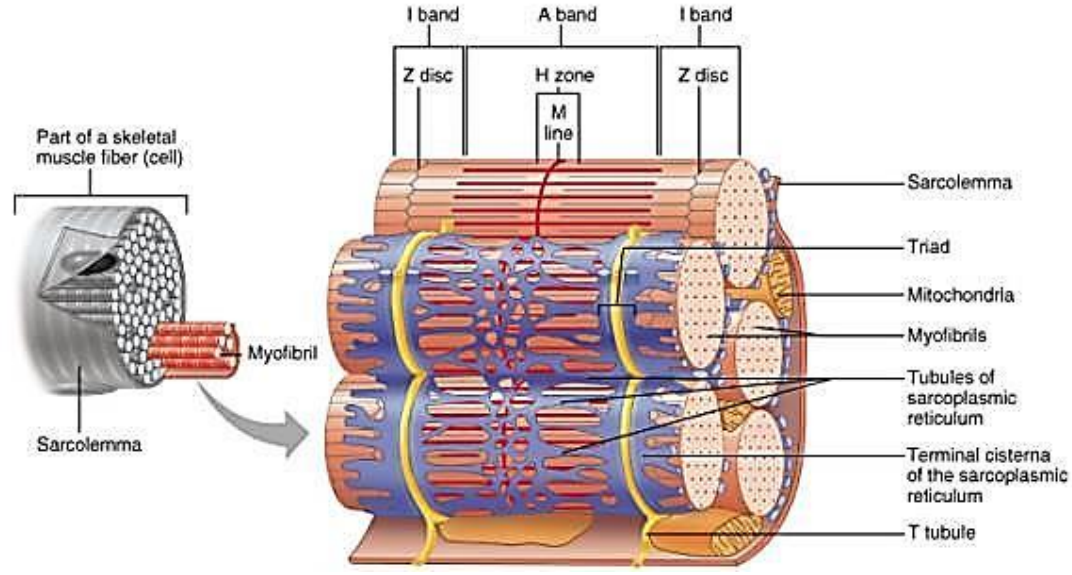


Figure 5 Amplified myofibril. Myofibrils are composed of individual contractile proteins, thick and thin myofilaments, giving the striated appearance of skeletal muscle http://faculty.etsu.edu/forsman/Histologyofmuscleforweb.htm

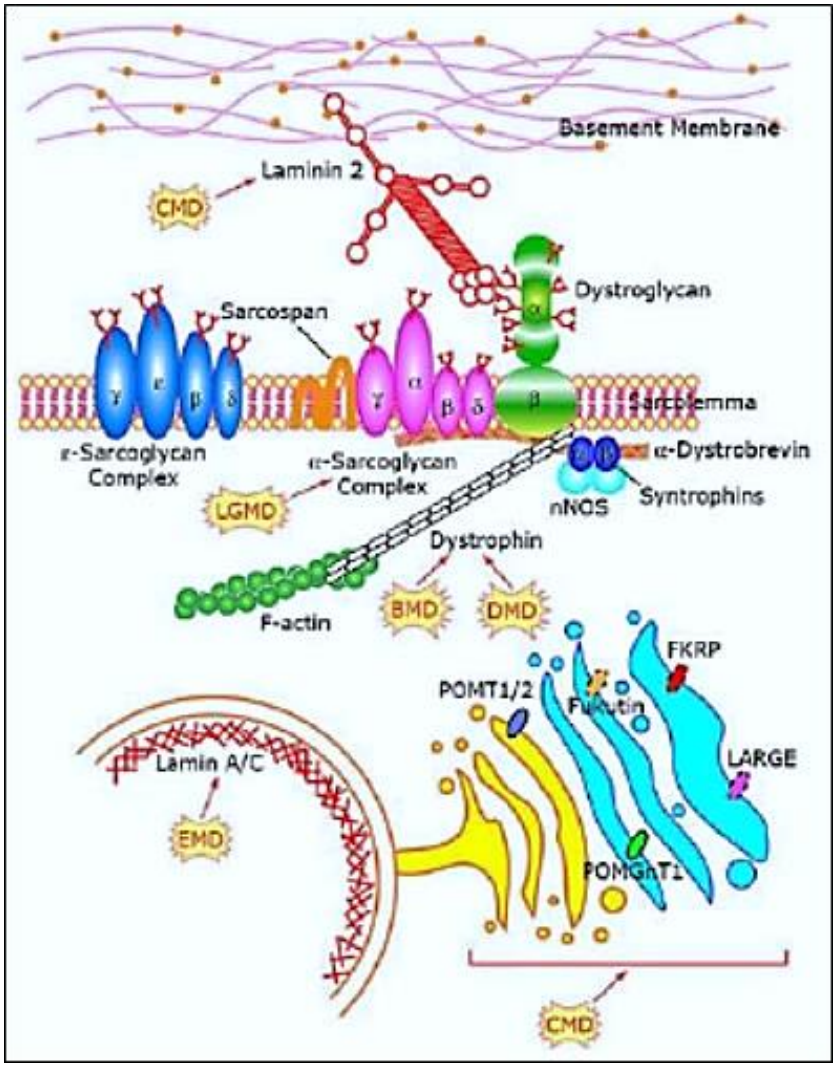


Figure 6 Diagram illustrating protein interaction in the Dystrophin Glycoprotein Complex and proteins affected in muscular dystrophies

https://www.sanger.ac.uk/research/projects/vertebratedevelopment/muscle.html

1.1.1.5 Electrodiagnostic studies

Electrodiagnostic studies (nerve conduction studies and electromyography) represent an extension of the neurological / neuromuscular examination. They assist in distinguishing between disorders of nerve and muscle, localising the lesion, establishing the correct diagnosis (e.g. differentiating between axonal and demyelinating neuropathy) and providing information about prognosis.

Nerve conduction studies (NCS)

NCS entail stimulating motor or sensory nerves via electrical impulses and recording the nerve responses at a position remote from the stimulation site. It can help with accurate localization of a focal lesion or with detection of a more widespread PNS disease process. The NCS most commonly performed are compound muscle action potentials (CMAPs) for motor nerves, sensory nerve action potentials (SNAPs) for sensory nerves, compound nerve action potentials (CNAPs) for mixed (sensory and motor) nerves and late responses (primary F-waves and H-reflexes). Important AP components that are used in analysis include latency, conduction velocity (CV), CMAP amplitudes and duration (Figure 7) [14].

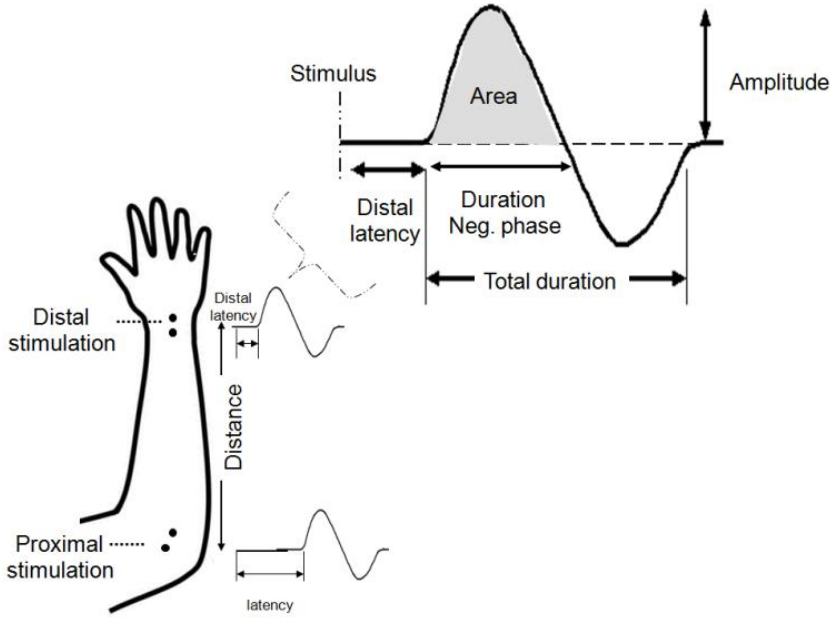


Figure 7 Diagram illustrating CMAP parameters assessed in motor NCS [14]

Electromyography (EMG)

EMG involves inserting a needle into a muscle. By analysing muscle's electrical activity, it can distinguish between a myopathic and a neurogenic process. Additionally, by determining the distribution of neurogenic abnormalities, it can differentiate between focal nerve, plexus or radicular processes and it can provide supportive evidence in distinguishing between axonal degeneration or demyelination [15].

Repetitive Nerve Stimulation (RNS) and Single Fibre Electromyography (SF EMG)
RNS tests neuromuscular transmission and is abnormal in about 75% of patients with generalised myasthenia gravis (MG) and 50% of patients with ocular MG [16]. SFEMG is helpful in the diagnosis of MG by revealing abnormal jitter in 95%–99% of patients, if appropriate muscles are examined, but its specificity is limited, with increased jitter in other disorders of nerves, muscles and NMJ [15, 16].

1.1.1.6 Muscle biopsy

When the clinical findings and/or electrodiagnostic features suggest a muscle disorder, a muscle biopsy may be appropriate to confirm the diagnosis. While many inherited muscle conditions can now be diagnosed with genetic testing, in many cases the biopsy remains a critical element of the diagnostic workup. It is essential to choose the right muscle to biopsy; severely weak muscles (MRC grade ≤3) are avoided as the results are likely to show only "end-stage" disease. Also, recently EMG-studied muscles are avoided because of potential artefacts. Sometimes, imaging tests (e.g., magnetic resonance) are useful in appropriate muscle selection.

Biopsy samples can be analysed by light microscopy, electron microscopy (EM), biochemical studies and immune staining. For general histology, the hematoxylin and eosin (H&E) and modified Gomori trichrome are the most useful. Myopathic features (central nuclei, small and large hypertrophic fibres, split fibres, necrotic and regenerating fibres, increased connective tissue) and inflammatory features are easily spotted on H&E. Gomori trichrome is helpful in detecting ragged-red fibres suggesting a mitochondrial disorder. Enzyme histochemistry distinguishes two main fibre types and a common relationship between glycolytic and oxidative enzyme activity in individual muscle fibres [17]. Fibre types are distinguished based on the appearance following staining for adenosine triphosphatase (ATPase), with and without preincubation at acid pH [18]. Myosin heavy chain isoforms (slow and fast) are having an increasing role in classifying fibre types [7, 19]; these are used as a standard histochemical reaction in neuropathology laboratories in Cork University Hospital and Beaumont Hospital, Dublin. Other standard reactions are oxidative enzyme stains: NADH, SDH and COX (identifies myofibrillar and mitochondrial abnormalities), Periodic acid-Schiff, PAS (identifies glycogen storage disease) and Oil Red O stains (in lipid storage disease). Biochemical enzymes stains are carried out when myophosphorylase (McArdle's disease), phosphofructokinase (Tarui disease) or myoadenylate deaminase (MAD)

deficiency are suspected. Lastly, immunohistochemical methods can stain for various muscle membrane or nuclear proteins which could be absent / deficient in some muscular dystrophies. In addition, Western blot can be performed for specific muscle proteins. EM examines the ultrastructural elements of muscle fibre and is sometimes important in the diagnosis of congenital myopathies, myofibrillar myopathies and mitochondrial disorders.

1.1.1.7 Muscle MRI

In recent years MRI has become more widely used in patients with NMD because the extent and localisation of muscle pathology can provide useful information for the diagnostic workup of patients. In a number of diseases the pattern of selected muscle involvement detected by MRI can almost be pathognomonic and can therefore guide genetic testing, besides the advantage of targeting the optimal muscle for biopsy [20-22].

1.2 Neuromuscular diseases. Clinical overview and diagnostic criteria

1.2.1 Acute Inflammatory Demyelinating Polyradiculoneuropathy

Clinical features

The classical form of acute inflammatory demyelinating polyradiculoneuropathy (AIDP) or Guillain-Barré syndrome (GBS) is a non-seasonal illness that affects individuals of all age, males are more often affected than females (1.5:1). A preceding event such as upper respiratory or gastrointestinal infection, surgery or vaccination 1 to 4 weeks before the onset of neurological symptoms is reported by approximately two thirds of patients [23]. While the cause for the prodromal illness often remains unknown, the most common detectable organism associated with GBS and especially with its axonal forms is *Campylobacter jejuni*. Patients with classic GBS may initially present with an ascending symmetrical lower limbs weakness with or without sensory symptoms, which subsequently spreads to involve upper limbs, facial and bulbar muscles and in severe cases, respiratory muscles. Whereas hyporeflexia or areflexia are the consistent GBS findings, these may be normal early in the disease. Interscapular or low back pain with radiation into the legs (moderate-severe)

occurs in 85% of patients and dysesthetic pain (burning or tingling) of the limbs is present in approximately 50% of patients. Autonomic dysfunction has been reported in 65% of patients admitted to the hospital [24]. Uncommon variants such as pharyngeal-cervical-brachial variant and confined to lower limb weakness variant, similar to a cauda equina lesion have been described. By GBS definition, clinical evolution ends by 1 to 4 weeks into the illness. If the progression continues for 4 to 10 weeks, the condition is called subacute inflammatory demyelinating polyradiculoneuropathy; if it continues longer than 10 weeks or has multiple relapses, the condition is called chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) [25].

Laboratory studies

To confirm the diagnosis of GBS, cerebral spinal fluid (CSF) examination and sequential electrophysiological studies are essential. CSF protein may be normal in the first week of symptoms but is elevated thereafter. The CSF protein may remain normal throughout the illness in approximately 10% of patients. NCS are abnormal in 90% of cases and consistent with a developing picture of multifocal demyelinating neuropathy associated with secondary axonal degeneration. The most common electrophysiological findings include prolonged distal motor and F-wave latencies, absent or non-persistent F waves, conduction block (CB), reduction in distal compound motor action potential (CMAP) amplitudes with or without temporal dispersion, and slowing of motor conduction velocities (CV) [26]. Initial electromyography (EMG) shows decreased motor unit recruitment. Two to four weeks after onset, if axonal degeneration occurs, fibrillation potentials appear. Electrodiagnostic features are the most reliable prognostic indicators.

Classification and diagnostic criteria

The diagnosis of GBS depends on clinical criteria supported by electrophysiological studies and CSF findings (Table 1) [27]. It is well known that not all GBS cases are due to demyelination and that an axonal immune-mediated process may also produce a similar clinical features. The axonal form is called acute motor-sensory axonal neuropathy (AMSAN) and is known for its severity and poor recovery. A pure motor axonal form called acute motor axonal neuropathy (AMAN) also exists. AMAN was closely related to the presence of antibodies against the ganglioside GD1 [28]. A classification of GBS subtypes, based on the clinical picture, electrophysiological and pathological findings is illustrated in Table 2 [29].

Table 1 Diagnostic criteria for Guillain-Barre syndrome [27]

Features required for diagnosis

- Progressive weakness of both legs and arms
- Areflexia

Clinical features supportive of diagnosis

- Progression over days to 4 weeks
- Relative symmetry or signs
- Mild sensory symptoms or signs
- Cranial nerve involvement (bifacial palsies)
- Recovery beginning 2-4 week after progression ceases
- Autonomic dysfunction
- Absence of fever at onset
- Laboratory features supportive of diagnosis
- Elevated cerebrospinal fluid protein with < 10 cells/μL
- Electrodiagnostic features of nerve conduction slowing or block*

  * AMAN and AMSAN have axonal features

Table 2 Classification of Guillain-Barre syndrome subtypes [29]

• Acute inflammatory demyelinating polyradiculoneuropathy	AIDP	85-90%
• Acute motor axonal neuropathy	AMAN	
• Acute motor sensory axonal neuropathy (AMSAN)	AMSAN	3-8%
• Miller-Fisher syndrome (MFS)	MFS	6-7%
• Acute pandysautonomia		
• Sensory GBS		

1.2.2 Chronic immune-mediated neuropathies

1.2.2.1 Chronic Inflammatory Demyelinating Polyradiculoneuropathy

Both CIDP and AIDP have similar features, such as clinical presentation, CSF albuminocytological dissociation (elevated protein and normal cells), inflammatory demyelinating process on histopathology and demyelination on NCS. Differentiating features between the two conditions are the time evolution and their response to corticosteroids. In contrast to AIDP, CIDP is generally not associated with preceding infections, has a more prolonged clinical course and is steroid-responsive. An autoimmune culprit is suspected for both conditions [30]. Two temporal evolution patterns can be observed in CIDP: continuous progressive course over months to years (60% of patients) and relapsing course with partial or complete recovery between relapses (30% of patients).

Clinical features

CIDP can affect all age groups but it occurs most commonly in the fifth and sixth decades. Symptoms at onset are extremely variable; however, the majority of patients present with symmetrical motor - sensory involvement. Occasionally, a predominantly motor presentation can be observed. In order to meet CIDP diagnostic criteria, symptoms must be present for at least 2 months. A non-length dependent neuropathy involving proximal limb weakness, almost as severe as distal limb weakness, is characteristic for CIDP. Both upper and lower limbs can be affected but legs are usually more severely affected. Muscle wasting is not a prominent feature. All these clinical features are very useful in differentiating CIDP from axonal neuropathies. Widespread hyporeflexia/areflexia is essential. Pain is not common, whereas sensory symptoms (numbness or tingling) in a stocking-glove distribution involving large-fibres are a frequent accompaniment.

Rarely, an atypical clinical variant with multifocal distribution of weakness and sensory deficits, called multifocal acquired demyelinating sensory and motor neuropathy (MADSAM) or Lewis-Sumner variant, can occur. In contrast to multifocal motor neuropathy (MMN), patients with MADSAM have both motor and sensory nerve involvement on clinical and electrophysiological exam, high protein in CSF and respond to corticosteroid treatment. A pure distal limb variant, meeting CIDP diagnostic criteria, is called distal acquired symmetrical demyelinating neuropathy (DADS). A chronic immune sensory

polyradiculopathy, involving sensory nerve roots, manifesting with a sensory ataxic syndrome but normal motor and sensory CV, response to IVIG treatment, has been described [31]. Involvement of the sensory nerve roots was indicated by abnormal somatosensory evoked potential (SSEP) responses, enlarged lumbar roots on MRI and high protein in CSF.

Several diseases have been associated with CIDP including diabetes mellitus, IgG or IgA monoclonal gammopathy of undetermined significance (MGUS), IgM monoclonal gammopathy without antibodies to myelin-associated glycoprotein (MAG), HIV infection, chronic active hepatitis, systemic lupus erythematosus, sarcoidosis, thyroid disease, inflammatory bowel disease, membranous glomerulonephritis, bone marrow or solid organ transplantation [2, 32]. The evidence is inadequate to consider CIDP associated with these diseases different from idiopathic CIDP [32].

Diagnostic criteria

For CIDP, electrodiagnostic, clinical and supportive diagnostic criteria are illustrated in Tables 3-5.

Table 3 Electrodiagnostic criteria for CIDP (EFNS/PNS 2010) [32]

1. **Definite**: at least one of the following:

- Motor distal latency prolongation ≥50% above ULN in two nerves (excluding median neuropathy at the wrist from carpal tunnel syndrome), or
- Reduction of motor conduction velocity ≥30% below LLN in two nerves, or
- Prolongation of F-wave latency ≥30% above ULN in two nerves (≥50% if amplitude of distal negative peak CMAP <80% of LLN values), or
- Absence of F-waves in two nerves if these nerves have distal negative peak CMAP amplitudes ≥20% of LLN + ≥1other demyelinating parametera in ≥1 other nerve, or
- Partial motor conduction block (CB): ≥50% amplitude reduction of the proximal negative peak CMAP relative to distal, if distal negative peak CMAP ≥ 20% of LLN, in two nerves, or in one nerve + ≥1 other demyelinating parametera in ≥1 other nerve, or
- Abnormal temporal dispersion (>30% duration increase between the proximal and distal negative peak CMAP) in ≥2 nerves, or
- Distal CMAP duration (interval between onset of the first negative peak and return to baseline of the last negative peak) increase in ≥1 nerve (median ≥ 6.6 ms, ulnar ≥ 6.7 ms, peroneal ≥ 7.6 ms, tibial ≥ 8.8 ms) + ≥1 other demyelinating parametera in ≥1 other nerve

2. **Probable**

- ≥30% amplitude reduction of the proximal negative peak CMAP relative to distal, excluding the posterior tibial nerve, if distal negative peak CMAP ≥ 20% of LLN, in two nerves, or in one nerve + ≥1 other demyelinating parametera in ≥1 other nerve

3. **Possible**

- As in (1) but in only one nerve

To apply these criteria, the median, ulnar (stimulated below the elbow), peroneal (stimulated below the fibular head), and tibial nerves on one side are tested. If criteria are not fulfilled, the same nerves are tested at the other side, and/or the ulnar and median nerves are stimulated bilaterally at the axilla and at Erb's point. Motor conduction block (CB) is not considered in the ulnar nerve across the elbow and at least 50% amplitude reduction between Erb's point and the wrist is required for probable CB. Temperatures should be maintained to at least 33◦C at the palm and 30◦C at the external malleolus. CMAP = compound muscle action potential; ULN = upper limit of normal values; LLN = lower limit of normal values.

Table 4 Clinical diagnostic criteria for CIDP (EFNS/PNS 2010) [32]

Inclusion criteria

(a) Typical CIDP

- Chronically progressive, stepwise, or recurrent symmetric proximal and distal weakness and sensory dysfunction of all extremities, developing over at least 2 months; cranial nerves may be affected; and
- Absent or reduced tendon reflexes in all extremities

(b) Atypical CIDP (still considered CIDP but with different features)

- One of the following, but otherwise as in (a) (tendon reflexes may be normal in unaffected limbs):
- Predominantly distal (distal acquired demyelinating symmetric, DADS) or
- Asymmetric [multifocal acquired demyelinating sensory and motor neuropathy (MADSAM), Lewis-Sumner syndrome] or
- Focal (e.g., involvement of the brachial or lumbosacral plexus or of one or more peripheral nerves in one upper or lower limb)
- Pure motor or
- Pure sensory (including chronic immune sensory polyradiculopathy affecting the central process of the primary sensory neuron)

Exclusion criteria

- Lyme disease, diphtheria, drug or toxin exposure probably to have caused the neuropathy
- Hereditary demyelinating neuropathy
- Prominent sphincter disturbance
- Diagnosis of multifocal motor neuropathy
- IgM monoclonal gammopathy with high titre antibodies to MAG
- Other causes for a demyelinating neuropathy including POEMS syndrome, osteosclerotic myeloma, diabetic and nondiabetic lumbosacral radiculoplexus neuropathy, PNS lymphoma and amyloidosis

Table 5 Supportive criteria for CIDP (EFNS/PNS 2010) [32]

- High CSF protein with leukocyte count <10/mm3 (level A recommendation)
- MRI showing gadolinium enhancement and/or hypertrophy of the cauda equina, lumbosacral or cervical nerve roots, or the brachial or lumbosacral plexuses (level C recommendation)
- Abnormal sensory electrophysiology in at least one nerve (Good Practice Points):
  - Normal sural with abnormal median (excluding median neuropathy at the wrist from carpal tunnel syndrome) or radial SNAP amplitudes; or
  - CV < 80% of lower limit of normal (<70% if SNAP amplitude < 80% of lower limit of normal); or
  - Delayed SSEP without CNS disease
- Objective clinical improvement following immunomodulatory treatment (level A recommendation)
- Nerve biopsy showing unequivocal evidence of demyelination and/or remyelination by electron microscopy (EM) or teased fibre analysis

1.2.2.2 Multifocal Motor Neuropathy

MMN is an immune-mediated motor neuropathy, treatable but incurable, which displays some clinical similarity to motor neuron disease (lower motor neuron type). It is unknown whether MMN is a separate condition or simply a multifocal motor variant of CIDP.

Clinical features

MMN is more frequent in men, mainly affecting young adults less than 45 years of age. A number of diagnostic criteria for MMN have been proposed, sharing the following features: progressive, asymmetrical, predominantly distal limb weakness in the distribution of two or more peripheral nerves developing over months to years, with a striking predilection for the upper extremities, and particularly hands, without upper motor signs [33, 34]. Muscle bulk is initially not affected, in spite of profound weakness and tendon reflexes are depressed or absent. Common features are muscle cramps and fasciculations. A slow or stepwise course progressing over months to years but without progression to generalized immobility is common.

Laboratory studies

In MMN, the CSF protein is normal, whereas it is elevated in CIDP. Approximately 50% of patients with MMN have elevated serum antibodies against gangliosides, especially GM1 [35]. The diagnosis relies on NCS which show focal motor conduction block (CB), defined as 50% reduction in amplitude or area of the proximally stimulated muscle evoked response compared with distally stimulated response, in one or more motor nerves at sites not prone to compression. Unique MMN features are: restriction of the CB to motor axons and normal SNAPs and sensory CV [34]. Certain conditions must be considered in a patient presenting with progressive limb weakness and wasting lacking sensory symptoms, such as amyotrophic lateral sclerosis, progressive muscular atrophy, bi-brachial motor neuron disease, CIDP and MMN (Table 6) [25].

Table 6 Differential diagnosis of multifocal motor neuropathy

FEATURES	MMN	CIDP	ALS
LMN weakness	Distal or proximal, asymmetrical	Proximal and distal, usually symmetrical	Progressive
UMN signs	Absent	Absent	Present
Sensory loss	Absent	Present	Absent
Motor conduction block	100%	Frequent	Rare and transient
Sensory conduction	Normal SNAP	Low to absent SNAP	Normal SNAP
CSF protein	Normal (70%)	Elevated	Normal
Anti-GM_1 antibodies	80%	Absent	<15%

1.2.2.3 Paraproteinaemic demyelinating neuropathies

IgM gammopathy

Neuropathies associated with IgM gammopathy are frequently demyelinating in nature. Approximately half of patients with IgM gammopathy have an antibody against myelin-associated glycoprotein (MAG) [36]. The typical presentation is of a chronic progressive distal limb paraesthesia, sensory loss, gait ataxia and tremor. Usually, weakness is mild or absent in the early stage of the disease. NCS show features of a sensory-motor demyelinating neuropathy. These patients respond poorly to usual treatments for CIDP

(IVIg, plasmapheresis, corticosteroids). The results of a randomized controlled trial in a small group of patients showed a potential benefit of Rituximab [37].

Patients with MAG-negative IgM gammopathy are more diverse; some have IgM antibodies against other neural antigens, for instance GM1. In these patients, hematologic diseases such as Waldenstrom macroglobulinemia, lymphoma, amyloidosis or cryoglobulinemia are common. These patients without MAG antibody may respond to usual CIDP treatments (IVIg, corticosteroids or plasmapheresis).

IgG or IgA gammopathy

There is insufficient evidence to support a direct role of the IgG or IgA paraprotein in the pathogenesis of neuropathy. As in some cases, the gammopathy is found long after the onset of neuropathy, it is possible that the paraprotein develops as a response to the nerve injury or may be coincidental. Both IgG and IgA gammopathy may present with either a demyelinating or axonal neuropathy. The demyelinating type is similar to CIDP and responds to conventional treatments (IVIg, plasmapheresis or corticosteroids). Axonal neuropathies are more challenging due to their possible coincidental finding in gammopathy and there is no evidence to support specific treatments apart from symptomatic management.

POEMS

POEMS (polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy, and skin changes) is a rare paraneoplastic syndrome usually associated with osteosclerotic myeloma, Waldenstrom macroglobulinemia or plasmacytoma but some patients may have no malignancy. The most common paraprotein is IgG or IgA or λ chain. Patients manifest a CIDP-like clinical and electrophysiological presentation featuring symmetrical distal and proximal weakness, diminished or absent reflexes and mild sensory loss. Vascular endothelial growth factor (VEGF) levels may be markedly elevated [38] and papilledema may develop in the course of the disease, features which are not seen in CIDP. This neuropathy responds to corticosteroids and antineoplastic treatment but is resistant to IVIg and plasmapheresis.

1.2.3 Inherited neuropathies

The inherited neuropathies, a group of clinically and genetically heterogeneous conditions, in which an accurate genetic diagnosis is becoming increasingly possible, can be broadly

classified into two groups: those in which the neuropathy is the sole or primary part of the disease (e.g., Charcot-Marie-Tooth disease) and those in which the neuropathy is part of a general neurological or multisystem disorder [39].

Classification of the genetic neuropathies:

1. Neuropathies in which the neuropathy is the sole/primary part of the disorder
- Charcot-Marie-Tooth disease (CMT)
- Hereditary neuropathy with liability to pressure palsies (HNPP)
- Hereditary sensory and autonomic neuropathies/hereditary sensory neuropathies
- Distal hereditary motor neuropathies (dHMN)
- Hereditary neuralgic amyotrophy

2. Neuropathies in which the neuropathy is part of a widespread neurological or multisystem disorder
- Familial amyloid polyneuropathy (FAP)
- Disturbances of lipid metabolism (e.g., adrenoleukodystrophy)
- Porphyrias
- Disorders with defective DNA (e.g., ataxia telangiectasia)
- Neuropathies associated with mitochondrial diseases
- Neuropathies associated with hereditary ataxias

3. Miscellaneous

1.2.3.1 Charcot-Marie-Tooth disease

General findings

CMT, the most common inherited disorder of the PNS, can have autosomal dominant, autosomal recessive or X-linked inheritance pattern. The classical clinical presentation is: distal weakness with initial involvement of the lower limbs spreading to the upper limbs as the disease progresses, decreased reflexes, sensory loss and foot deformities. Walking difficulties with steppage gait are the most common presenting symptoms. Motor symptoms are usually more prominent than sensory symptoms. Cranial nerve involvement, scoliosis, vocal fold and diaphragm paralysis are less frequent features. Symptom onset is usually during the first decades of life with a very slowly progressive course.

Classification

In 1968, Dyck and Lambert separated CMT into two types (CMT1 and CMT2) based on clinical, pathological, electrophysiological and genetic heterogeneity among 31 patients [40]. They also proposed the term hereditary motor and sensory neuropathy (HMSN) that includes a broader spectrum of inherited neuropathies. CMT is now preferred but both terms are used. Later studies supported this classification by distinction based on the median motor nerve CV, with a cut-off value of 38 m/s to differentiate between the two types (CV<38 m/s in CMT1 patients and >38 m/s in CMT2 patients) [41, 42]. Nevertheless, both axonal and demyelinating CMT ultimately develop axonal loss. Intermediate CVs have also been described in CMT patients [43-45]. Clinical features are similar in both CMT1 and CMT2 and therefore it is often impossible to distinguish between them based on neurological examination only. With recent improvement in genetic testing for CMT, its classification continues to expand with a total of around 40 subtypes recognised currently (Table 7 and Figure 8) [39, 46, 47].

Table 7 Classification of Charcot-Marie-Tooth disease [39]

Type	Gene/Locus	Specific Phenotype
Autosomal dominant		
(AD) CMT1		
CMT1A	Dup 17p *(PMP22)*	Classic CMT1
	PMP22 (point mutation)	Classic CMT1/DSS/CHN/HNPPs
CMT1B	*MPZ*	CMT1/DSS/CHN/intermediate/CMT2
CMT1C	*LITAF*	Classic CMT1
CMT1D	*EGR2*	Classic CMT1/DSS/CHN
CMT1E	*NEFL*	CMT2 but can have slow MNCVs in CMT1 range early-onset severe disease
HNPP	Del 17p *(PMP22)*	Typical HNPP
	PMP22 (point mutation)	Typical HNPP
X-linked CMT1 (CMT1X)		
CMT1X	*GJB1*	Intermediate patchy MNCVs
Autosomal recessive (AR) demyelinating CMT (CMT4)		
CMT4A	*GDAP1*	Demyelinating or axonal, usually early onset and severe/vocal cord and diaphragm paralysis described/rare AD CMT2 families described

CMT4B1	*MTMR2*	Severe CMT1/facial/bulbar/ focally folded myelin
CMT4B2	*SBF2*	Severe CMT1/glaucoma/focally folded myelin
CMT4C	*SH3TC2*	Severe CMT1/scoliosis/cytoplasmic expansions
CMT4D (HMSNL)	*NDRG1*	Severe CMT1/gypsy/deafness/tongue atrophy
CMT4E	*EGR2*	Classic CMT1/DSS/CHN
CMT4F	*PRX*	CMT1/more sensory/focally folded myelin
CMT4H	*FGD4*	CMT1
CMT4J	*FIG4*	CMT1
CCFDN	*CTDP1*	CMT1/gypsy/cataracts/dysmorphic features
HMSN-Russe	10q22Yq23	CMT1
CMT1	*PMP22* (point mutation)	Classic CMT1/DSS/CHN/HNPPs
CMT1	*MPZ*	CMT1/DSS/CHN/intermediate/CMT2
ADCMT 2		
CMT2A	*MFN2*	CMT2/usually severe/optic atrophy
CMT2B	*RAB7A*	CMT2 with predominant sensory involvement
CMT2C	12q23Yq24	CMT2 with vocal cord and respiratory involvement
CMT2D	*GARS*	CMT2 with predominant hand wasting/weakness or dHMN V
CMT2E	*NEFL*	CMT2 but can have slow MNCVs in CMT1 range /early-onset severe disease
CMT2F	*HSPB1*	(HSP27) Classic CMT2 or dHMN II

CMT2G	12q12Yq13.3	Classic CMT2
CMT2L	*HSPB8 (HSP22)*	Classic CMT2 or dHMN II
CMT2	*MPZ*	CMT1/DSS/CHN/intermediate/CMT2
CMT2 (HMSNP)	3q13.1	CMT2 with proximal involvement
AR CMT2 (also called AR CMT4)		
AR CMT2A	*LMNA*	CMT2 proximal involvement and rapid progression described/also causes muscular dystrophy/cardiomyopathy/lipodystrophy
AR CMT2B	19q13.1Y13.3	Typical CMT2
AR CMT2	*GDAP1*	CMT1 or CMT2 usually early onset and severe/vocal cord and diaphragm paralysis described/rare AD CMT2 families
Dominant intermediate CMT (DI-CMT)		
DI-CMTA	10q24.1Y25.1	Typical CMT
DI-CMTB	*DNM2*	Typical CMT
DI-CMTC	*YARS*	Typical CMT
Hereditary neuralgic amyotrophy (HNA)		
HNA	*SEPT9*	Recurrent neuralgic amyotrophy

Dup = duplication; PMP22 = peripheral myelin protein 22kD; DSS = Dejerine-Sottas syndrome; CHN = congenital hypomyelinating neuropathy; HNPP = hereditary neuropathy with liability to pressure palsies; MPZ = myelin protein zero; LITAF = lipopolysaccharide-induced TNF factor; EGR2 = early growth response 2; NEFL = neurofilament, light polypeptide; MNVCs = motor nerve conduction velocities; Del = deletion; GJB1 = gap junction protein beta 1, 32kDa; GDAP1 = ganglioside-induced differentiation-associated protein 1; MTMR2= myotubularin related protein 2; SBF2 = SET binding factor 2; SH3TC2 = SH3 domain and tetratricopeptide repeats 2; HMSNL = hereditary motor and sensory neuropathy-LOM; NDRG1 = N-myc downstream regulated 1; FGD4 = FYVE, RhoGEF and PH domain 4; FIG4 = FIG4 homolog, SAC1 lipid phosphatase domain containing S cerevisiae; CCFDN = congenital cataract, facial dysmorphism, and neuropathy syndrome; CTDP1 = CTD (carboxy-terminal domain, RNA polymerase II, polypeptide A) phosphatase 1; HMSN-Russe = hereditary motor and sensory neuropathy-Russe; MFN2 = mitofusin 2; RAB7A = RAB7A, member RAS oncogene family; GARS = glycyl-tRNA synthetase; dHMN = distal hereditary motor neuropathy; HSPB1 = heat shock 27kDa protein 1; HSPB8 = heat shock 22kDa protein 8; LMNA = lamin A/C; DNM2 = dynamin 2; YARS = tyrosyl-tRNA synthetase; HNA = hereditary neuralgic amyotrophy; SEPT9 = septin 9

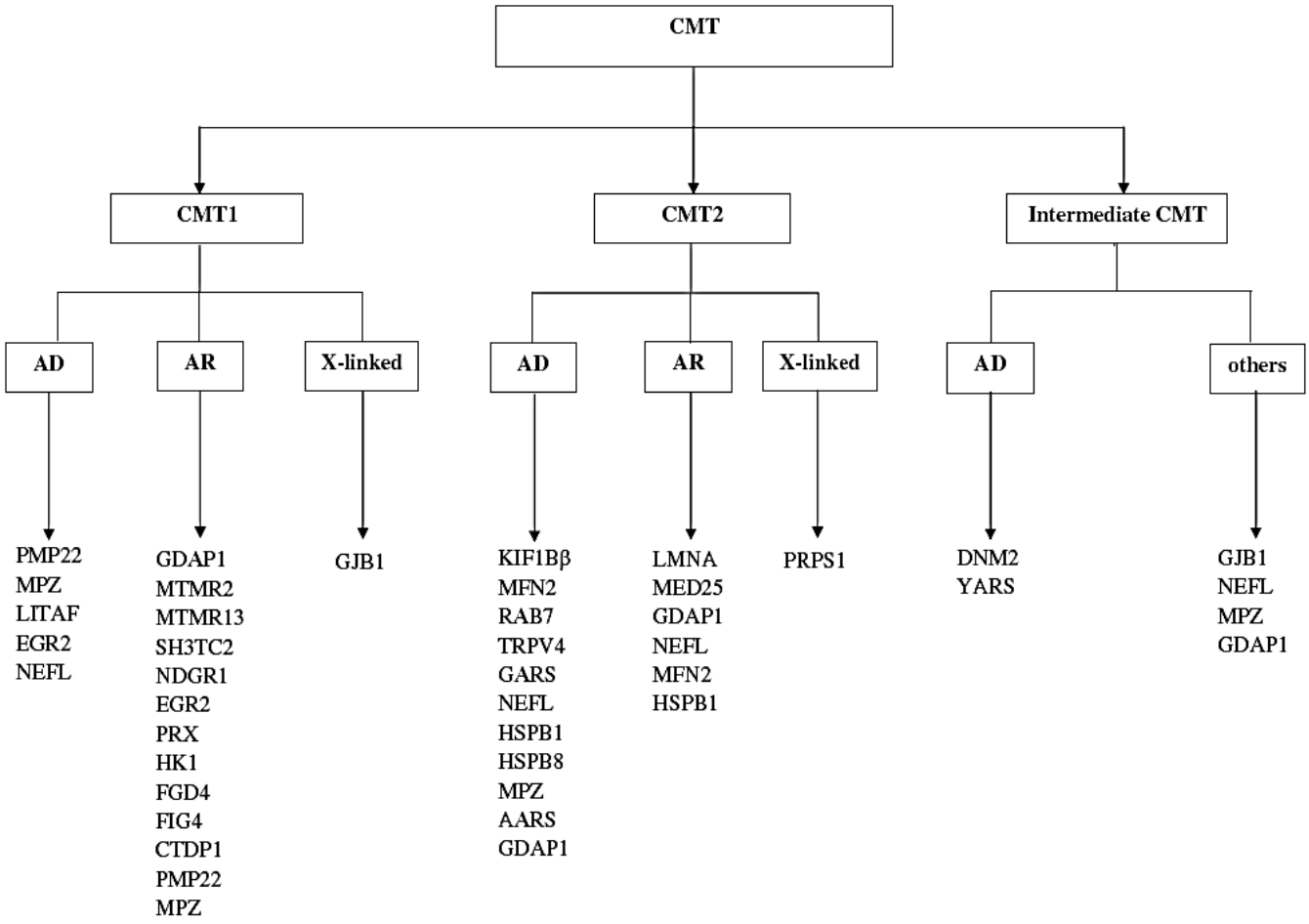


Figure 8 Genetic classification of Charcot-Marie-Tooth disease [47]

1.2.3.2 Hereditary neuropathy with liability to pressure palsy

HNPP is an autosomal dominant disease characterized by recurrent mononeuropathies in the nerves at sites of compression (e.g., median nerve at carpal tunnel, ulnar at the elbow and peroneal at fibular head). HNPP is caused by a deletion of the *PMP22* gene in chromosome 17p11.2 which affects myelin stability. Painless pressure palsies, usually in the 2nd and 3rd decades of life, is the most common presentation.

1.2.4 Spinal muscular atrophy

Spinal muscular atrophy (SMA) is an autosomal recessive NMD caused by homozygous deletion of exon 7 (with or without deletion of exon 8) in the survival motor neuron 1

(SMN1) gene. The disease is characterized by degeneration of alpha motor neurons in the anterior horn of the spinal cord, resulting in progressive generalised muscle weakness and atrophy especially in proximal limb muscles. Based on age of onset and achieved motor function, the phenotype is classified in four grades of severity (SMA 0, SMA I, SMAII, SMAIII, SMA IV) (Table 8) [48]. EMG studies show neurogenic features including fibrillations and fasciculations at rest and motor units with increased duration and amplitude. Muscle biopsy reveals neurogenic features including type 1 and type 2 muscle fibres group atrophy and angulated fibres.

Table 8 SMA – clinical classification and characteristics

	Age of onset	**Characteristics**
Type I (Werdnig-Hoffmann disease)	0-6 months	• manifests in the 1st months of life • quick and unexpected onset "floppy baby syndrome" • never sit • respiratory failure is the most frequent cause of death • do not usually live past 2 years of age • death occurs as early as within weeks in the most severe cases (sometimes termed *SMA type 0)* • with proper respiratory support, those with milder forms (10%) are known to live into adolescence and adulthood
Type II (intermediate)	7-18 months	• never able to stand/walk but able to sit • respiratory involvement is a major concern • Life expectancy is reduced but most patients live well into adulthood
Type III (Kugelberg-Welander disease)	> 18 months	• able to walk without support, although many later lose this ability • respiratory involvement is less common • life expectancy is normal/near normal
Type IV (adult)	2^{nd}-3^{rd} decade	• walk unaided • life expectancy is unaffected

SMA variants include:

1. Bulbar HMN I (Vialletto-van Laere syndrome) is an autosomal recessive syndrome that begins in the second decade of life. It is characterized by facial weakness, of bilateral sensorineural hearing loss dysphagia and dysarthria followed by facial weakness and compromised respiratory function [49].
2. Bulbar HMN II (Fazio-Londe disease) is characterized by progressive bulbar paralysis in the first decade of life. Patients present with stridor, dysarthria, and dysphagia. Cranial-nerve involvement leads to facial diplegia, ptosis, and ophthalmoplegia. Generalized weakness of the lower motor neurons and rare corticospinal-tract signs are sometimes observed [50].
3. Distal hereditary motor neuropathy (dHMN) is also referred to as distal spinal muscular atrophy (dSMA), a reflection of the commonly held but unproven belief that the pathology resides in the ventral horn of the spinal cord [51]. Despite advances in the identification of novel gene mutations, 80% of patients with dHMN have a mutation in an as-yet undiscovered gene. The causative genes include: *HSPB1, HSPB8, BSCL2, IGHMBP2, SETX, GARS, DYNC1H1, DCTN1 ATP7A and TRPV4* [51].
4. X-Linked Recessive Bulbospinal Neuronopathy (Kennedy disease) (see 1.2.5.)
5. Scapuloperoneal spinal muscular atrophy, caused by alterations in the *TRPV4* gene, is characterised by slowly progressive lower motor neuron loss associated with muscle weakness and atrophy in the shoulder girdle (with characteristic scapular winging) and the peroneal muscles [52, 53].

1.2.5 Kennedy disease

Kennedy disease (X-Linked Recessive Bulbospinal Neuronopathy) is an X-linked recessive late onset motor neuron disorder affecting men who usually remain asymptomatic until after the fourth decade. Besides slowly progressive spinal and bulbar muscular atrophy with fasciculations and generalized muscle weakness, patients may also show sensory symptoms, gynecomastia and impotence [54]. Early features may include hand tremor, dysarthria followed by muscle weakness, decreased or absent reflexes and muscle atrophy. Cramps and fasciculations can be prominent in the trunk and limbs and facial and perioral fasciculations are present in almost all patients. Significant bulbar symptoms are usually late manifestations [55]. Disease progression is very slow, most cases remain independent of assisting devices until fifth decade of life [56]. A mutation characterized by an increased size

of a polymorphic CAG repeat (40-60; normal 11-35 repeats) within the first exon of the androgen receptor gene is the cause of Kennedy disease [57]. CK levels may be elevated. NCS reveal reduced CMAP amplitudes in a third of patients and a sensory neuronopathy in 95% of patients. EMG shows features of chronic denervation. Unique findings are marked fasciculation potentials in the face, particularly in the perioral region, and in extremities.

Differential diagnoses include:

1. Clinical features such as progressive limb-girdle and bulbar weakness, muscle cramps and prominent fasciculations, resemble those of amyotrophic lateral sclerosis (ALS). However, characteristic features such as gynecomastia, perioral fasciculations, hand tremor and lack of upper motor neuron signs on physical examination should provide sufficient clues for Kennedy disease. Also, ALS progresses rapidly, whereas Kennedy's disease is a largely indolent disorder.
2. Kennedy's disease may also be easily mistaken for adult-onset SMA because of the slowly progressive limb-girdle weakness in both but bulbar involvement and gynecomastia are unlikely in SMA.
3. Hereditary sensorimotor neuropathy, limb-girdle dystrophy or facioscapulohumeral muscular dystrophy also may mimic Kennedy's disease. Careful clinical examination, neurophysiology and muscle/nerve biopsy analyses should distinguish these disorders.
4. Sporadic inclusion body myositis (sIBM) shares some clinical features with Kennedy disease such as asymmetric muscle weakness/wasting and difficulty swallowing. However, in sIBM fasciculation are absent and EMG demonstrates predominantly myopathic, rather than neurogenic changes. A muscle biopsy demonstrates characteristic features of sIBM (see 1.2.12).

1.2.6 Neuromyotonia (Isaac syndrome)

Neuromyotonia (NMT), also known as Isaac syndrome, is a disorder of generalized peripheral nerve hyperexcitability causing spontaneous continuous muscular activity of peripheral nerve origin [58]. Clinically, NMT presents with muscle twitching at rest (visible myokymia), painful muscle cramps triggered by voluntary or induced muscle contraction, and impaired muscle relaxation (pseudomyotonia) [59, 60]. Symptoms ranging from mere inconvenience to debilitating and progressive symptoms have been described [61]. Typical EMG findings are myokymic and neuromyotonic discharges (present during sleep and

general anaesthesia) which reflect spontaneous muscle activity driven by abnormal peripheral nerve firing [58, 59, 62]. NMT can be an isolated autoimmune disorder or seen in association with other conditions (myasthenia gravis without thymoma, diabetes mellitus, GBS, CIDP) [58]. About 40% of patients with acquired NMT will have detectable anti-voltage-gated potassium-channel (VGKC) antibodies located along peripheral motor axons and responsible for repolarization after AP firing [58, 63]. It can also be a paraneoplastic condition (thymoma with or without myasthenia gravis, small-cell lung carcinoma, lymphoma). The non-immune form is associated with ALS, peripheral neuropathies, toxins (e.g., herbicide, alcohol) or drugs (e.g., gold). Symptomatic treatment includes anticonvulsants such as phenytoin, carbamazepine, sodium valproate and lamotrigine; in severe symptoms, plasma exchange or intravenous immunoglobulin therapy have been used [58, 64].

1.2.7 Neuromuscular junction disorders

NMJ is a preferred site (either pre- or post-synaptic) for various disorders with autoimmune, genetic and toxic aetiology. Regardless of the aetiology, these disorders affect the ACh signal transmission from the presynaptic nerve to skeletal muscles, impairing muscle contraction and hence causing muscular weakness.

1.2.7.1 Lambert-Eaton Myasthenic Syndrome

LEMS is a rare acquired presynaptic disorder of NMJ transmission caused by impaired ACh release causing charcteristic clinical features such as proximal muscle weakness, depressed tendon reflexes, autonomic features and post-exercise facilitation. LEMS is classified into two subgroups: LEMS associated with small cell lung carcinoma (SCLC) (the most common cancer type association) and LEMS with no SCLC [65]. Irrespective of type, pathogenic antibodies against presynaptic voltage gated calcium channels (VGCCs) in the cell membrane of the motor nerve terminal are detected in 85% of patients. Clinical manifestations often precede cancer diagnosis. In most cases, the cancer is detected within the first 2 years after LEMS onset and, in almost all cases, within 4 years [65].

1.2.7.2 Myasthenia Gravis

MG, the most common primary disorder of neuromuscular transmission, is an acquired

autoimmune condition caused by the failure of neuromuscular transmission, resulting from the binding of autoantibodies to proteins implicated in signaling at the NMJ. These proteins include the nicotinic AChR or, less frequently, a muscle-specific tyrosine kinase (MuSK) involved in AChR clustering [5]. Patients with MG present with specific symptoms of muscle weakness including ptosis or diplopia, difficulty chewing, swallowing or talking or limb weakness. Classically, myasthenic weakness fluctuates during the day, worsening as the day progresses, or during prolonged muscle exercise and improving after rest [66]. The usual disease course is progressive; if left untreated, after 15 to 20 years, weakness becomes permanent. When the symptoms are limited to extrinsic ocular muscles (EOMs), which occurs in 10% of MG patients, the condition is called ocular MG (OMG) [5]. MG incidence is influenced by gender and age; below 40 years of age, female: male ratio is 3: 1, whereas during puberty and between 40 and 50 years, it is roughly equal. Above 50 years of age, it is more common in males [67]. MG patients associated with thymoma almost always have serum AChR antibodies. However, AChR antibodies are absent in about 15% of generalized MG patients. In 40% of negative-AChR antibody subgroup, antibodies to MuSK and another postsynaptic NMJ protein are detected [68]. Patients with MuSK antibody MG have selective facial, bulbar, neck or respiratory muscle weakness with relative sparing of the ocular muscles.

Subtypes of MG [69]:

1. Early-onset MG: age at onset <50 years, usually females. Thymic hyperplasia
2. Late-onset MG: age at onset >50 years, mainly males. Thymic atrophy
3. Thymoma-associated MG (10%–15%)
4. MG with muscle-specific tyrosine kinase (MUSK) antibodies
5. Ocular MG (OMG): symptoms only affecting extraocular muscles
6. MG with no detectable AChR and MuSK antibodies

1.2.7.3 Congenital Myasthenic Syndromes

Congenital myasthenic syndrome (CMS) is a rare group of clinically and genetically heterogeneous disorders caused by mutations in the genes coding for pre-synaptic, synaptic

or post-synaptic proteins leading to NMJ transmission dysfunction. Characteristic symptoms include fatigable skeletal muscle weakness (e.g., ocular, bulbar, limb, respiratory muscles) with onset at or shortly after birth, in early childhood, or less commonly in late childhood [70, 71]. Respiratory difficulties including severe hypoventilation progressing to apnoea and acute respiratory events, triggered by infections, hot weather or stress have been encountered in patients with known mutations in *RAPSN, COLQ* and *CHAT* genes [70, 72]. Cardiac and smooth muscle are spared. The genes identified so far include *CHRNE, CHRNA1, CHRNB1, CHRND, Dok-7, ColQ, RAPSN, MuSK, CHAT, SCN4A, Agrin, LAMB2, GFPT1, DPAGT1, ALG2, ALG14 and LRP4 [73, 74].*

1.2.8 Muscular dystrophies

1.2.8.1 Dystrophinopathies

Duchenne's muscular dystrophy (DMD) is an X-linked recessive disorder with incidence of 1/3600 male births [75]. DMD phenotype is caused by frame shifting or nonsense mutations in the DMD gene on the X-chromosome p21.2-21.1 causing absence of dystrophin expression [11]. Partial protein expression resulting from mutations which preserve the open reading frame cause a milder disease variant, Becker muscular dystrophy (BMD) [13]. Clinically, DMD patients present with progressive proximal weakness, calf hypertrophy and elevated serum creatine kinase (CK) [76]. Molecular genetic analysis has eliminated the necessity for muscle biopsy in classic dystrophinopathies but immunoanalysis is still instrumental [77].

1.2.8.2 Limb Girdle Muscular Dystrophies

LGMDs are a group of heterogeneous conditions which usually present in the late first or second decade of life [78]. The classical presentation of LGMD is weakness and wasting confined to proximal more than distal limb muscles with sparing of the bulbar muscles. However, wide variation with regards to symptom onset and progression, weakness distribution and wasting is observed in different genetic subtypes. Muscle biopsy in LGMD typically shows dystrophic features and usually, but not always, accompanied by elevated serum CK. Absence or partial deficiency of any specific protein on biochemical analysis

(immunostaining or immunblotting) performed on a muscle biopsy can determine the diagnosis of many LGMDs which can then be confirmed by molecular genetic tests. Over recent years muscle imaging has been increasingly used in the diagnosis of many LGMDs [20, 21, 79-81]. LGMDs are classified into autosomal dominant (type 1) or recessive (type 2) forms, the former being much rarer. To date, there are at least eight forms of dominant LGMD and seventeen forms of autosomal recessive LGMD identified [82, 83], illustrated in Table 9. The sequence in which the condition appears in the alphabetical list is based on the order in which they were discovered.

Table 9 Current limb girdle muscular dystrophy classification [82, 83]

LGMD forms	Chromosome	Protein	Important Complications	Other diseases associated with this gene
Autosomal Dominant				
LGMD1A	5q31	Myotilin	Other forms of myofibrillar myopathies more associated with cardiac & respiratory complications	Myofibrillar myopathies, spheroid body myopathy
LGMD1B	1q11-21	Lamin A/C	High risk of arrhythmia with requirement for an implantable defibrillator, cardiomyopathy, respiratory failure	Many including AD Emery-Dreifuss MD and dilated cardiomyopathy
LGMD1C	3p25	Caveolin 3		Rippling muscle disease, hyperCKaemia, myalgia, hypertrophic cardiomyopathy
LGMD1D	7q 36.2	HSP-40		
LGMD1E	2q35	Desmin		Cardiomyopathy and conduction defect
LGMD1F	7q32	?		
LGMD1G	4p21	?		
LGMD 1H	3p25.1-p23	?		
Autosomal Recessive				
LGMD2A	15q15.1	Calpain 3		
LGMD2B	2p13	Dysferlin		Miyoshi myopathy
LGMD2C	13q12	γ- sarcoglycan	Cardiomyopathy & respiratory	
LGMD2D	17q21	α- sarcoglycan	Cardiomyopathy & respiratory	
LGMD2E	4q12	β- sarcoglycan	Cardiomyopathy & respiratory	
LGMD2F	5q33	δ- sarcoglycan	Cardiomyopathy & respiratory	
LGMD2G	17q12	Telethonin		
LGMD2H	7q31-q33	TRIM 32		Sarcotubular myopathy
LGMD2I	19q	FKRP	Cardiomyopathy & respiratory	Congenital muscular dystrophy type 1C (MDC1C), Walker-Warburg syndrome
LGMD2J	2q24.2	Titin		Heterozygous mutations cause AD tibial MD
LGMD2K	9q34	POMT1		Walker-Warburg syndrome
LGMD2L	11p14.3	Anoctamin 5		

LGMD2M	9q31	Fukutin		Fukuyama muscular dystrophy
LGMD2N	14q24	POMT2		Walker-Warburg syndrome
LGMD2O	1p34	POMGNT1		
LGMD2Q	8q24	PLEC1		
Recessive LGMD with primary alpha-dystroglycan defect	3p21	DAG1		
MD with congenital disorder of glycosylation	1q22	DPM3		

POMT, protein O-mannosyltransferase; MD, muscular dystrophy

1.2.8.3 Facioscapulohumeral dystrophy

FSHD is as an autosomal dominant condition caused in most patients by a deletion in a 3.3-kb repeating sequence, *D4Z4*, localized on the chromosome 4 (4q35) which is believed to cause partial demethylation (FSHD1) of the contracted allele. Rarely, patients have a form of the disease (FSHD2) in which demethylation is global, i.e., on all *D4Z4* elements throughout the genome [84]. Genetic testing is reliable, although some cases show no abnormality in the chromosome 4 sequence [85]. A generational effect suggests the presence of anticipation in FSHD [86]. In a classical FSHD patient, symptoms begin during adolescence with facial weakness (e.g., difficulty in blowing up balloons, whistling or drinking through a straw). The smile becomes flattened despite a well preserved facial expression. Shoulder girdle muscles, particularly involved in scapula fixation, biceps and triceps muscles are weak but deltoid muscles are usually preserved even in advanced disease. Ankle dorsiflexors, often asymmetric, are affected early in the disease and foot drop may be the presenting symptom. Hip flexor and quadriceps weakness is common. Occasionally, a LGMD - like presentation, with symmetrical pelvic girdle greater than shoulder girdle with sparing of facial muscles, can be seen. Deafness is frequent, particularly in severe FSHD forms, and in association with Coats' disease (retinal oxidative vascular degeneration). Serum CK is usually elevated and EMG shows myopathic potentials. Muscle biopsy may show dystrophy, neuropathic features or inflammatory changes. DNA analysis confirm the diagnosis.

1.2.8.4 Myotonic dystrophy

Myotonic dystrophy type 1 (DM1)

DM1, the most common adult form of muscular dystrophy, is an autosomal dominant disorder, characterized by wasting and weakness of the muscles accompanied by myotonia and a number of other systemic defects. It is caused by mutations in the untranslated region of the gene myotonic dystrophy protein kinase *(DMPK)*, which normally has 5 to 30 repeating sequences of three nucleotides (CTG), located on chromosome 19q13.3. In DM1, these CTG repeats expand into hundreds or thousands. Usually, patients present in teenage years with distal weakness (hand weakness and foot drop) which spreads to the proximal muscles as the disease progresses. A long face with hollowing of the temples and masseter and temporalis muscles wasting is noted. Gradually, muscle weakness becomes severe and the myotonia may disappear. Other organs are frequently involved in DM1. Cardiac disease (conduction disturbances and cardiomyopathy) is a common complication. Excessive

daytime somnolence is a frequent symptom [87]. Cataracts and endocrine abnormalities (thyroid, pancreas, hypothalamus and gonadic disorders), testicular atrophy in males and recurrent miscarriages and menstrual irregularities in females, are common.

Myotonic dystrophy type 2 (DM2)

DM2, referred to as proximal myotonic myopathy (PROMM) and later as DM2 [88], is a multisystemic disorder similar to the classic form of myotonic dystrophy but without a CTG expansion. The culprit mutation is a CCTG repeat expansion in the first intron of zinc finger protein 9 *(ZNF9)* on chromosome 3q21 [89]. DM1 and DM2 show similarities with regard to the clinical phenotype with some exceptions, i.e., no congenital presentation or mental retardation has been described in DM2.

1.2.8.5 X-Linked Emery-Dreifuss Dystrophy

The gene for X-Linked Emery-Dreifuss Dystrophy (X EDMD), encoding for emerin (nuclear membrane protein), is located at Xq28. The clinical features of EDMD include: wasting and weakness of the proximal upper limbs, shoulder girdle and anterior leg compartment muscles; early contractures, especially in the elbows, neck, paraspinal muscles and Achilles tendons. Cardiac complications, e.g. conduction block and cardiomyopathy, are common. DNA studies and skin biopsy showing absent emerin from the skin nuclei confirm the diagnosis.

1.2.8.6 Oculopharyngeal muscular dystrophy

Oculopharyngeal muscular dystrophy (OPMD) is an autosomal dominant disorder with an unequal geographical distribution (familial clustering) with centres of the illness reported in Quebec, Germany, Spanish-American inhabitants from Colorado and Arizona; however sporadic families appear all over the world. The disease is caused by GCG repeat expansion in poly A binding protein 2 *(PAB2)* gene, located on chromosome 14q11.2-13 [90, 91]. OPMD patients present in the fifth or sixth decade of life with weakness of the eye muscles and mild ptosis which eventually, as the muscles weaken, results in severe ptosis and ophthalmoplegia. Soon after the ocular symptoms onset, patients experience swallowing difficulty. In some patients, facial weakness also occurs and limb girdle weakness is common in the later stages. Muscle biopsy shows dystrophic features and rimmed vacuoles which are common in OPMD but also in inclusion body myositis and several hereditary distal

myopathies. Small intranuclear tubulofilaments are a hallmark of the disease and often abnormal mitochondria and nemaline rods, particularly in pharyngeal muscles, are present. Molecular diagnosis is definitive.

1.2.8.7 Distal myopathies

Distal myopathies are a group of muscle diseases which share the clinical pattern of predominant weakness in the feet and/or hands [92]. To date, more than 20 distinct disorders have been separated, yet many without genetic confirmation (Table 10). By combining the age at onset, mode of inheritance, pathology and muscle imaging, the number of candidate genes for a certain disease can be significantly reduced, which is of help for targeting the gene to be tested [93]. Recently published updated classification for distal myopathies and differential diagnostic algorithms are helpful to identify the specific gene (Table 10 and Figure 9).

Table 10 Genetically determined distal myopathies [92]

	Gene	Protein	Ref.
1. Late adult onset autosomal dominant forms			
a. Welander distal myopathy	*nd*	nd	Welander [94]
b. Tibial muscular dystrophy (TMD, Udd myopathy)	*TTN*	Titin	Udd [95]
c. Distal myotilinopathy	*TTID*	Myotilin	Penisson-Besnier et al. [96]
d. ZASPopathy (Markesbery–Griggs)	*LDB3*	ZASP	Griggs et al. [97]
e. Matrin3 distal myopathy (VCPDM, MPD2)	*MATR3*	Matrin3	Senderek et al. [98]
f. VCP-mutated distal myopathy	*VCP*	VCP	Palmio et al. [99]
g. Alpha-B crystallin mutated distal myopathy	*CRYAB*	aB-crystallin	Reilich et al. [100]
2. Adult onset autosomal dominant forms			
a. Desminopathy DES	*DES*	Desmin	Sjoberg et al. [101]
b. Distal ABD-filaminopathy	*FLNC*	Filamin-C	Duff et al. [102]
c. Finnish-MPD3	nd	nd	Mahjneh et al. [103]
d. Italian 19p13-linked distal myopathy	nd	nd	Servidei et al. [104]
e. US-Polish family	nd	nd	Felice et al. [105]
f. Oculopharyngeal distal myopathy	nd	nd	Durmus et al. [106]
3. Early onset autosomal dominant forms			

a. Laing distal myopathy (MPD1)	*MYH7*	Beta-MyHHC	Laing et al. [107]
b. KLHL9 mutated distal myopathy	*KLHL9*	KLHL9	Cirak et al. [108]
4. Early onset autosomal recessive forms			
a. Distal nebulin myopathy	*NEB*	Nebulin	Wallgren-Pettersson al. [109]
5. Early adult onset autosomal recessive forms			
a. Miyoshi myopathy	*DYSF*	Dysferlin	Miyoshi et al. [110]
b. Distal Anoctaminopathy	*ANO5*	Anoctamin-5	Bolduc et al. [111]
c. Distal myopathy with rimmed vacuoles	*GNE*	GNE	Nonaka et al. [112]
d. Oculopharyngeal distal myopathy, OPDM	nd	nd	Durmus et al. [106]
6. Adult onset autosomal recessive form			
a. Calf myopathy non-DYSF/ANO5	nd	nd	Linssen et al. [113]

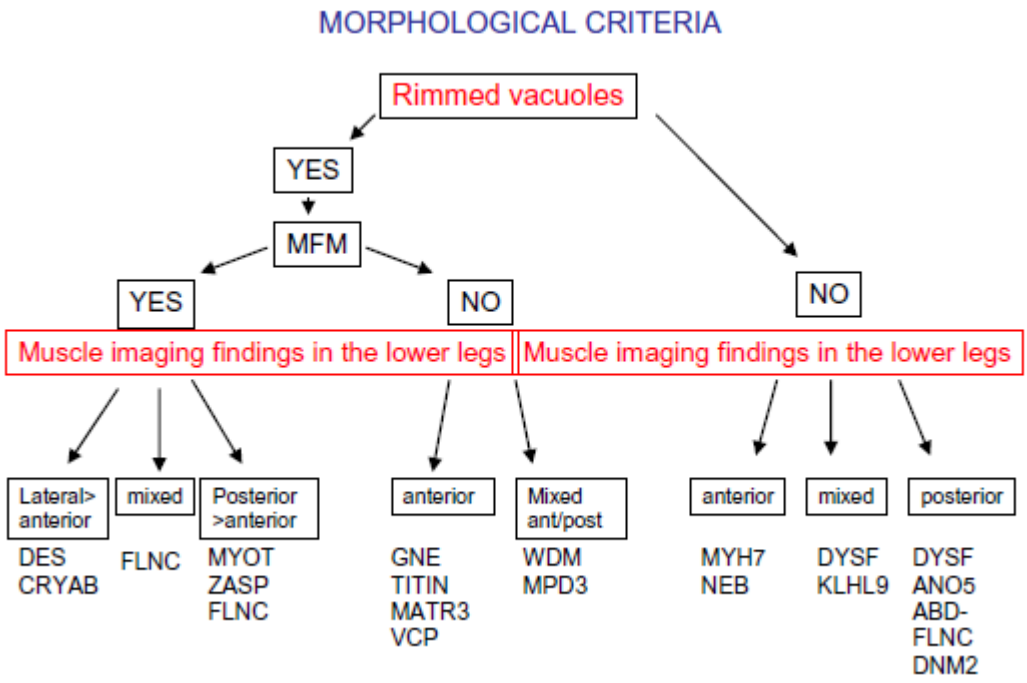


Figure 9 Distal myopathies diagnostic algorithm, using morphological data [92]

1.2.8.8 Congenital Muscular Dystrophies

Congenital Muscular Dystrophies (MDC), a group of autosomal recessive disorders, often manifest at birth with hypotonia, severe weakness of the trunk and extremities and nervous tissue involvement. Joint contractures, particularly of the ankles, knees, and hips are common. Mental retardation and signal increase in white matter is evident on brain MRI is common. Clinical and genetic features allow differentiation of several MDC forms, such as Fukuyama-type muscular dystrophy, Walker-Warburg disease and muscle-eye-brain disease. About 50% of the classic MDC cases are due to primary merosin or α2-laminin deficiency (MDC1A); the other half have mutations in *FKRP* (MDC1C) and integrin. Ullrich's congenital muscular dystrophy, caused by mutations in subunits of collagen type VI, is associated with neonatal weakness, joint contractures and distal hyperlaxity. It is allelic to a more benign form, Bethlem myopathy.

1.2.9 Congenital myopathies

Congenital myopathies (CM) are a group of inherited NMDs with early onset, defined by specific histopathological findings which include central cores, minicores, nemaline rods and central nuclei. Based on these features, CM classify as: Central Core Disease, Multi-minicore Disease, Nemaline Myopathy and Centronuclear Myopathy. CMs are genetically very heterogeneous group of muscle diseases which show a lot of overlap and muscle pathology can often be very unspecific. Even in the case of distinct findings on muscle biopsies, it can still be challenging to identify the underlying genetic cause. Characteristic patterns of muscle involvement on MRI helped to improve the diagnostic workup in some CMs [20].

Central Core Disease (CCD)

CCD is an autosomal dominant condition (but sporadic cases are also common), caused by mutation in the ryanodine receptor *(RYR)* gene on the long arm of chromosome 19 (19q13.1) and is allelic to hereditary malignant hyperthermia (MH). MH and CCD coexist in some families. The patient may be floppy soon after birth and congenital hip dislocation is common. Later on, delay in motor milestones accomplishment is a rule and generalised arm and leg weakness with mild facial and neck weakness occur. Skeletal abnormalities, such as high-arched palate, elongated face and high-arched feet are common. Serum CK is usually normal but mild elevation may occur. EMG shows nonspecific myopathic changes. Muscle biopsy reveals typical features, type 1 fibre predominance with central cores.

Nemaline Myopathy (NM)

Small, rod-like particles in muscle fibres are the hallmark of NM. It can be inherited in both autosomal and recessive fashion and is caused by gene mutations encoding for α-tropomyosin *(TPM3),* β-tropomyosin *(TPN2),* nebulin *(NEM2),* troponin T *(TnT1),* and α-actinin *(ACTA1*) [114]. Most common presentation is early hypotonia followed by diffuse limb weakness and mild facial and bulbar muscle weakness. These patients have an elongated face, high-arched feet, and often kyphoscoliosis. The disorder is mainly non-progressive, although some patients become weaker late in life. Respiratory failure out of proportion to the skeletal muscle weakness may develop. A more rare form, beginning in early adulthood, manifests with mild proximal weakness.

Centronuclear or Myotubular Myopathy (CNM)

The best-known form is a severe infantile myopathy, usually fatal during the first few months due to respiratory failure, manifesting with extraocular, facial and limb weakness [115]. X-linked myotubular myopathy results from mutations in the *MTM1* gene encoding for myotubularin-1[116]. A less common and milder form, autosomal dominant, occurs later in life, and manifests with ptosis, extraocular weakness, facial and moderate lower limb weakness. Muscle biopsy demonstrates typical findings: fibre size variation and type 1 fibre predominance with central nuclei.

Congenital Fiber-Type Disproportion (CFT)

Affected children are floppy at birth, have diffuse weakness with frequent face and neck muscle involvement which sometimes improves in early childhood. Contractures, congenital hip dislocation, deformities of the feet, high-arched palate, and kyphoscoliosis are common. Respiratory complications are common. When these children get older, they stay weak, short and have low weight. The muscle biopsy shows marked type 1 and type 2 fibre size disproportions with type 1 fibre atrophy and predominance. The diagnosis is only made when the difference between the type 1 and type 2 fibres is more than 45% and when more than 75% of the fibres are type 1. There is no causal gene for this condition.

1.2.10 Metabolic myopathies

Metabolic myopathies are divided into three categories: disorders of carbohydrate metabolism, lipid metabolism and mitochondrial function. Muscle fatigue is a shared symptom in metabolic myopathies but other symptoms such as muscle pain, muscle cramps

and myoglobinuria may occur [66].

1.2.10.1 Disorders of carbohydrate metabolism

Myophosphorylase deficiency (McArdle disease)

In the initial stage of exercise, carbohydrate stores from the muscles have an important role, before the compensatory mechanisms of increased blood-borne metabolites and increased lipid metabolism supply the demand [66]. McArdle disease is an autosomal recessive disorder caused by mutations in the *PYGM* gene which encodes for the muscle isoform of glycogen phosphorylase (myophosphorylase)[117]. Symptom onset is in childhood, during the first decade of life, with complains of tiredness, fatigue and pain with onset during the first few minutes of exercise. If exercise is continued, muscle pain becomes deep and aching which then gives a way to a hard and contracted muscle lasting for several hours and associated with an electrically silent EMG. A feature of McArdle disease is the development of the "second-wind phenomenon", associated with increase in fatty acid consumption. If, at the beginning of fatigue, the patient reduces speed but does not stop, the muscle pain may disappear and after that the patient may function as normal. If these patients gradually increase their exercise intensity, they may be able to get through the barrier and then may exercise at an acceptable intensity for longer periods [66]. A straightforward diagnostic test is the exercise forearm test which shows no increase in lactic acid level but increase in the ammonia level after exercise. Muscle biopsy may show glycogen increase and subsarcolemmal accumulations; myophosphorylase reaction is reduced or absent.

Phosphofructokinase (PFK) Deficiency (Tarui disease)

PFK deficiency is an autosomal recessive condition, caused by mutations in *PFK-M*, *PFK-L* and *PFK-P* genes, which is virtually indistinguishable clinically to McArdle disease, though the "second-wind phenomenon" is uncommon. Most attacks are associated with nausea, vomiting, and muscle pain.

Pompe's disease (PD)

PD is a rare lysosomal storage disorder caused by an absence or deficiency of the lysosomal enzyme acid a-glucosidase (GAA) which is essential for the glycogen degradation in the lysosomes. This enzymatic defect leads to increasing glycogen accumulation in many tissues, particularly in cardiac, skeletal and smooth muscle [118, 119]. Based on clinical

presentation with a range of phenotypes, PD is divided into infantile and late-onset forms [118, 119]. Infantile form is the most severe form and is characterized by generalized muscle weakness with hypotonia and organomegaly (cardio- and hepatomegaly). Cardiorespiratory failure as of cause of death by 1 year of age is typical [120]. The late-onset form, also recognized as childhood, juvenile or adult-onset, presents after 1 year of age. This form has a slowly progressive course leading to skeletal muscle weakness and respiratory insufficiency, the latter being the most common cause of death [118, 119, 121].

1.2.10.2 Disorders of lipid metabolism

Carnitine Palmitoyl Transferase (CPT) Deficiency

After about 20 - 30 minutes of endurance exercise, fatty acids, which are not used at the beginning of exercise, become gradually more principal, so that after an hour, they are the major energy source. Therefore, lipid metabolism defects cause symptoms after sustained exercise. CPT-II deficiency is an autosomal recessive condition caused by mutations in the *CPT-II* gene. Typically, it presents in young adulthood with weakness and myoglobinuria after strenuous exercise. Patients are particularly susceptible to these attacks if exercise occurs in a fasting state when the body is dependent on fatty acids. Unless the patient had a recent attack of muscle injury, the CK may be normal. The muscle biopsy in CPT deficiency is usually normal, unless a recent episode of muscle damage occurred which would cause myofibre necrosis. Biochemical testing of the muscle biopsy shows CPT deficiency. Forearm exercise testing is normal in CPT deficiency because the test stresses glycolytic pathways.

Carnitine Deficiency Myopathy

Primary carnitine deficiency is caused by mutations in the sodium-dependent carnitine transporter gene, *OCTN 2*. The most common clinical presentaion is a slowly progressive proximal limb muscle weakness (trunk, facial and bulbar may also occur) with a fluctuating course beginning during childhood or early teenage years. Fatigue and exercise-induced myalgia occur but generally are not the main complaints; myoglobinuria is usually not present. Muscle biopsy may show lipid droplet accumulations but the carnitine biochemical assay is necessary to confirm the diagnosis.

Myoadenylate Deaminase Deficiency (MAD)

About 1 - 2% of the population has myoadenylate deaminase (AMP deaminase) deficiency, resulted from the disruption of the purine nucleotide cycle. It is inherited in an autosomal

recessive fashion and is caused by mutations in *AMPD1* gene. These patients have myalgia or exercise intolerance but can also be asymptomatic. Reports of AMP deaminase deficiency vary in other NMDs. The interpretation of this entity remains difficult because of poor correlation between the enzyme defect and the clinical symptoms. Muscle biopsy is usually normal, although the biochemical analysis for AMPDA is absent. The forearm exercise test is helpful showing normal lactate but low or absent ammonia and hypoxanthine.

1.2.10.3 Mitochondrial myopathies

Mitochondrial diseases are a group of genetically and clinically heterogenous conditions caused by dysfunction of the mitochondrial respiratory chain. All organs which rely mostly on aerobic metabolism are potentially affected and nervous system involvement (described as mitochondrial encephalomyopathy) is common. The term mitochondrial myopathy is used when skeletal muscle is affected, either alone or with CNS disease. Mitochondrial myopathies can be classified according to whether the causative mutations affect mitochondrial (mt) DNA or nuclear DNA (Table 11) [122]. Each group can be further subdivided into mutations of genes that directly encode respiratory chain proteins and those that encode ancillary machinery (e.g., transfer/ribosomal RNA or proteins needed for the proper assembly or function of the respiratory chain proteins). In a significant number of patients however, particularly children, it is still not possible to identify the causative mutation [123]. The clinical classification of mitochondrial disease is challenging although recent developments in understanding the molecular basis have helped. Many patients exhibit a constellation of clinical features that fit in with a well-defined clinical syndrome (Table 12) [124, 125], such as Kearns-Sayre syndrome (KSS), chronic progressive external ophthalmoplegia (CPEO) [126], mitochondrial encephalomyopathy with lactic acidosis and stroke-like episodes (MELAS) [127], myoclonic epilepsy with ragged-red fibers (MERRF) [128], neurogenic weakness with ataxia and retinitis pigmentosa (NARP) [129], or Leigh syndrome (LS) [130]. However, poor genotype – phenotype correlation exists and many individuals do not belong to one specific category. For example, a group of patients with external ophthalmoplegia may be clinically identical, but some may have a large mtDNA deletion whereas others may have mtDNA point mutations (e.g., m.3243A>G) and others may have an autosomal dominant nuclear genetic mutation causing secondary mtDNA defects (e.g., *ANT1* mutations) [122]. Ragged red fibres (RRF), appearance due to the accumulation of abnormal mitochondria below the plasma membrane of the muscle fibre when muscle is stained with Gomori Trichrome, causing a "ragged" appearance of the

muscle fibre, may be present on muscle routine light microscopy. EM often shows distorted mitochondria.

Table 11 Genetic Classification of Human Mitochondrial Disorders [122]
Mitochondrial DNA Mutations
Rearrangements (deletions and duplications)
• Chronic progressive external ophthalmoplegia • Kearns-Sayre syndrome • Diabetes and deafness
Single nucleotide variants [1]
• Protein-encoding genes • Leber hereditary optic neuropathy (LHON) (m.11778G>A, m.14484T>C, m.3460G>A) • Neurogenic weakness with ataxia and retinitis pigmentosa / Leigh syndrome (m.8993T>G, m.8993T>C)
tRNA genes [1]
• MELAS (m.3243A>G, m.3271T>C, m.3251A>G) • MERRF (m.8344A>G, m.8356T>C) • Chronic progressive external ophthalmoplegia (m.3243A>G, m.4274T>C) • Myopathy (m.14709T>C, m.12320A>G) • Cardiomyopathy (m.3243A>G, m.4269A>G) • Diabetes and deafness (m.3243A>G, m.12258C>A) • Encephalomyopathy (m.1606G>A, m.10010T>C) • Nonsyndromic sensorineural deafness (m.7445A>G)
rRNA genes [1]
• Aminoglycoside-induced nonsyndromic deafness (m.1555A>G)
Nuclear DNA Mutations
Nuclear genetic disorders of the mitochondrial respiratory chain (mutated genes encoding structural subunits)
• Leigh syndrome with complex I deficiency (*NDUFS1, NDUFS4, NDUFS7, NDUFS8, NDUFV1*) • Leigh syndrome with complex II deficiency (*SDHA*) • Leukodystrophy with complex II deficiency (*SDHAF1*) • Cardiomyopathy and encephalopathy (complex I deficiency) (*NDUFS2*) • Optic atrophy and ataxia (complex II deficiency) (*SDHA*) • Hypokalemia and lactic acidosis (complex III deficiency) (*UQCRB*)
Nuclear genetic disorders of the mitochondrial respiratory chain (mutated genes encoding assembly factors)
• Leigh syndrome (*SURF1*, *LRPPRC*) • Hepatopathy and ketoacidosis (*SCO1*) • Cardiomyopathy and encephalopathy (*SCO2*) • Leukodystrophy and renal tubulopathy (*COX10*) • Hypertrophic cardiomyopathy (*COX15*) • Encephalopathy, liver failure, renal tubulopathy (with complex III deficiency) (*BCS1L*) • Encephalopathy (with complex V deficiency) (*ATPAF2*)
Nuclear genetic disorders of the mitochondrial respiratory chain (mutated genes encoding translation factors)
• Leigh syndrome, liver failure, and lactic acidosis (*GFM1*) • Lactic acidosis, developmental failure, and dysmorphism (*MRPS16*) • Myopathy and sideroblastic anemia (*PUS1*) • Leukodystrophy and polymicrogyria (*TUFM*) • Leigh syndrome and optic atrophy with COX deficiency (*TACO1*)
Nuclear genetic disorders associated with multiple mtDNA deletions or mtDNA depletion

• Autosomal progressive external ophthalmoplegia (*POLG, POLG2, C10orf2, SLC25A4*) • Mitochondrial neurogastrointestinal encephalomyopathy (thymidine phosphorylase deficiency) (*TYMP*) • Alpers-Huttenlocher syndrome (*POLG*) • Ataxia neuropathy syndromes [1] (*POLG, C10orf2, OPA1*) • Infantile myopathy / spinal muscular atrophy (*TK2*) • Encephalomyopathy and liver failure (*DGUOK*) • Hypotonia, movement disorder, and/or Leigh syndrome with methylmalonic aciduria (*SUCLA2*) • Hypotonia, encephalopathy, renal tubulopathy, lactic acidosis (*RRM2B*) • Mitochondrial encephalomyopathy with combined RC deficiency (*AIF1*) • Reversible hepatopathy (*TRMU*) • Myopathy with cataract and combined RC deficiency (*GFER*)
Other disorders
• Coenzyme Q_{10} deficiency (*COQ2, COQ9, CABC1, ETFDH*) • Barth syndrome (*TAZ*) • Cardiomyopathy and lactic acidosis (mitochondrial phosphate carrier deficiency) (*SLC25A3*)

1. Mitochondrial DNA nucleotide positions refer to the L-chain.

Table 12 Clinical syndromes of mitochondrial diseases [122]

Disorder	Primary features	Additional features
Alpers-Huttenlocher syndrome	• Hypotonia • Seizures • Liver failure	• Renal tubulopathy
Chronic progressive external ophthalmoplegia (CPEO)	• External ophthalmoplegia • Bilateral ptosis	• Mild proximal myopathy
Kearns-Sayre syndrome (KSS)	• PEO onset at age <20 yrs • Pigmentary retinopathy • One of the following: CSF protein >1g/L, cerebellar ataxia, heart block	• Bilateral deafness • Myopathy • Dysphagia • Diabetes mellitus • Hypoparathyroidism • Dementia
Pearson syndrome	• Sideroblastic anemia of childhood • Pancytopenia • Exocrine pancreatic failure	• Renal tubular defects
Infantile myopathy and lactic acidosis (fatal and non-fatal forms)	• Hypotonia in 1st year of life • Feeding and respiratory difficulties	• Fatal form may be associated with a cardiomyopathy and/or the Toni-Fanconi-Debre syndrome
Leigh syndrome (LS)	• Subacute relapsing encephalopathy • Cerebellar and brain stem signs • Infantile onset	• Basal ganglia lucencies • Maternal history of neurologic disease or Leigh syndrome
Neurogenic weakness with ataxia and retinitis pigmentosa (NARP)	• Late-childhood or adult-onset peripheral neuropathy • Ataxia • Pigmentary retinopathy	• Basal ganglia lucencies • Abnormal electroretinogram • Sensorimotor neuropathy
Mitochondrial encephalomyopathy with lactic acidosis and stroke-like episodes	• Stroke-like episodes at age <40 years • Seizures and/or dementia	• Diabetes mellitus • Cardiomyopathy (initially hypertrophic; later dilated)

(MELAS)	• Ragged-red fibers and/or lactic acidosis	• Bilateral deafness • Pigmentary retinopathy • Cerebellar ataxia
Myoclonic epilepsy myopathy sensory ataxia (MEMSA)	• Myopathy • Seizures • Cerebellar ataxia	• Dementia • Peripheral neuropathy • Spasticity
Myoclonic epilepsy with ragged-red fibers (MERRF)	• Myoclonus • Seizures • Cerebellar ataxia • Myopathy	• Dementia • Optic atrophy • Bilateral deafness • Peripheral neuropathy • Spasticity • Multiple lipomata
Leber hereditary optic neuropathy (LHON)	• Subacute painless bilateral visual failure • Males : females ~4:1 • Median age of onset 24 yrs	• Dystonia • Cardiac pre-excitation syndromes

1.2.11 Skeletal Muscle Ion Channelopathies

The genetic skeletal muscle ion channelopathies (SMIC) (non-dystrophic myotonias and periodic paralyses) are a group of conditions caused by mutations which mainly occur in voltage-gated ion channel genes (Figure 10).

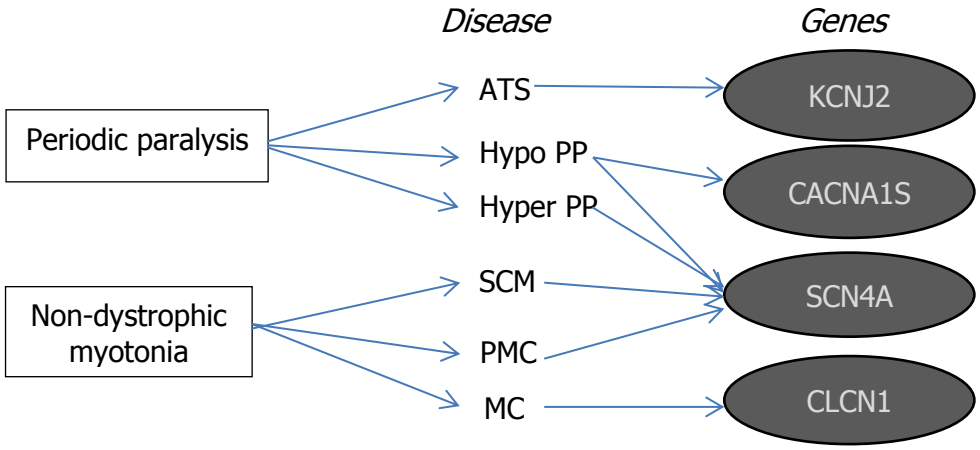


Figure 10 Classification of skeletal muscle ion channelopathies and causative genes [131]

ATS = Andersen-Tawil syndrome, Hyper PP = hyperkalaemic periodic paralysis, Hypo PP = hypokalaemic periodic paralysis, MC = myotonia congenital, PMC = paramyotonia congenital, SCM = sodium-channel myotonia, KCNJ2 = potassium-channel, CACNA1S = calcium-channel, SCN4A = sodium-cnannel, CLCN1 = chloride-channel

Periodic paralysis (PP)

The PPs are a group of autosomal dominant conditions characterized by episodic muscle weakness frequently associated with variations in potassium level. PPs are classified as hyperkalaemic periodic paralysis (Hyper PP), hypokalaemic periodic paralysis (Hypo PP) and Andersen-Tawil syndrome (ATS). The diagnosis of skeletal muscle channelopathies is achieved by a combination of clinical and electrophysiological investigations guiding efficient genetic analysis [131].

Hypo PP – the commonest form of PP, is associated with point mutations in both *CACNA1S* (Hypo PP1) and *SCN4A* (Hypo PP2). Nocturnal or early morning, focal or generalized paralytic attacks (tend to spare facial and respiratory muscles), lasting from hours to days, associated with low serum potassium at the start, are characteristic features. Attacks of paralysis begin in the first / second decade of life and are precipitated by carbohydrate load or rest after exercise. Some patients develop a fixed proximal myopathy [132]. Clinical distinction between Hypo PP1 and Hypo PP2 is difficult [131].

Hyper PP - is associated with point mutations in *SCN4A* gene; 9 common mutations account for 60% of cases. Hyper PP has an earlier onset, in the first decade. Paralytic attacks are usually briefer than in Hypo PP, lasting around 1-4 hours, with raised potassium at the onset and precipitated by potassium loading or rest after exercise. Fixed proximal myopathy is less common than in Hypo PP.

ATS - is characterized by a triad of cardiac abnormalities, distinctive facial and skeletal features and PP. Mutations in *KCNJ2* gene, encoding the inwardly rectifying potassium channel Kir2.1, accounts for 60% of diagnoses [133]. A novel causative gene for ATS, *KCNJ5,* was recently identified in a patient with typical ATS features [134].

Myotonia Congenita (MC)

MC, the most common of the SMIC group, is characterized by stiffness improving with exercise. Caused by mutations in the skeletal muscle voltage-gated chloride channel gene *(CLCN1)* (over 120 mutations) on chromosome 7, MC can be either dominantly or recessively inherited [135]. Dominant MC has an earlier onset and upper-limb-predominant symptoms, in contrast to the recessive form which has a later onset (4-12 years), more severe and lower-limb-predominant. Mexiletine is the most effective anti-myotonic agent.

Paramyotonia Congenita (PMC)

PMC is an autosomal dominant condition caused by mutations in the sodium-channel gene (*SCN4A)* on chromosome 17. It is characterized by impaired muscle relaxation, exacerbated by exertion or cold (paramyotonia), predominantly affecting the hands, face and tongue, and often accompanied by weakness which may persist for hours-days.

Sodium channel myotonia

SCM presents with pure myotonia (may be delayed post-exercise) but lacking paramyotonia or weakness and are cold-insensitive.

1.2.12 Sporadic Inclusion Body Myositis

Sporadic Inclusion Body Myositis (sIBM) is the most common idiopathic inflammatory myopathy after age 50 years. The causes of sIBM are still unknown, but are considered complex, with the contribution of multiple factors such as environmental triggers, ageing and genetic susceptibility [136]. Based on endomysial inflammation, sIBM was originally believed to be a primary inflammatory myopathy; however, there is a significant body of evidence in support of a neurodegenerative aetiology. Nevertheless, the exact contribution of these 2 pathways to the pathogenesis remains unknown [137].

In sIBM, wasting and weakness are most profound in long finger flexors, knee extensors and hip flexors (Figure 11, A and B) [138]. Swallowing difficulties are present in about 50% of cases [137] and respiratory failure requiring mechanical ventilation was reported in one case [139]. Muscle atrophy and weakness are often asymmetrical which may lead to an incorrect diagnosis of ALS. However, unlike ALS, there is no major wasting of the hand intrinsics, thenar and hypothenar muscles are spared, fasciculations are absent and deep tendon reflexes are normal or diminished [137]. In addition, muscle disorders similar to sIBM such as familial inclusion body myositis fIBM, hereditary inclusion body myopathies (hIBM) and other rimmed vacuolar myopathies (oculopharyngeal muscular dystrophy, X-linked recessive Emery-Dreifuss muscular dystrophy, LGMD type 1A, LGMD type 2G, LGMD type 1G, and rigid spine syndrome) are important to recognise [136].

sIBM is associated with moderate CK elevation and EMG shows features of a chronic irritative myopathy. Muscle biopsy in sIBM is characterised by the presence of typical pathological features of inflammation, degeneration and mitochondrial abnormality in

affected muscle fibres [136, 137]. Inflammatory changes include endomysial inflammation and upregulation of major histocompatibility complex (MHC) class I [140]. Degenerative changes include rimmed vacuoles (Figure 11, C), tubulofilaments seen on EM and the accumulation of many myotoxic proteins (amyloid, p62 and TAR DNA-binding protein-43 (TDP-43)) [141]. Mitochondrial abnormalities (RRF and mostly showing deficiency of COX activity) are another important pathological feature in sIBM and are more prevalent in sIBM than in polymyositis, dermatomyositis and normal ageing muscle fibres [102]. Revised 2010 IBM diagnostic criteria from MRC Centre for Neuromuscular Diseases are illustrated in Table 13.

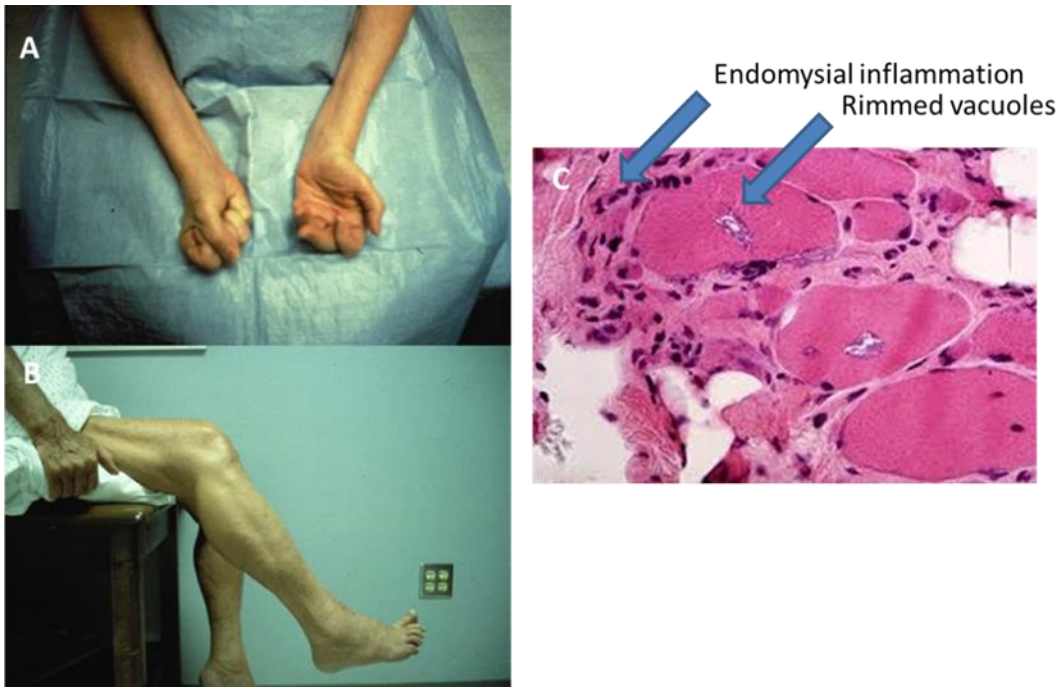


Figure 11 Clinical examination and muscle biopsy findings in a patient with sIBM. A and B, wasting/weakness of the long finger flexors in the left hand and knee extensors; C, muscle biopsy showing endomysial inflammation and rimmed vacuoles

Table 13 Modified IBM criteria 2010 [137]

Pathologically defined IBM	Conform Grigg's criteria [142]	Invasion of non-necrotic fibres by mononuclear cells, and rimmed vacuoles, and either intracellular amyloid deposits or 15–18 nm filaments
Clinically defined IBM	Clinical features	Duration weakness > 12 months Age > 35 years Weakness of finger flexion > shoulder abduction AND of knee extension > hip flexion
	Pathological features	Invasion of non-necrotic fibres by mononuclear cells or rimmed vacuoles or increased MHC-I,but no intracellular amyloid deposits or 15–18 nm filaments
Possible IBM	Clinical criteria	Duration weakness > 12 months Age > 35 years Weakness of finger flexion > shoulder abduction OR of knee extension > hip flexion
	Pathological criteria	Invasion of non-necrotic fibres by mononuclear cells or rimmed vacuoles or increased MHC-I, but no intracellular amyloid deposits or 15–18 nm filaments

1.2.13 Macrophagic myofasciitis

Macrophagic myofasciitis (MMF), first described in 1998 by a consortium of French myopathologists, is characterised by onset of diffuse myalgia, chronic fatigue and cognitive dysfunction which occurs in a small proportion of people previously immunised with vaccines containing aluminium oxyhydroxide (alum) adjuvant [143]. The time from last vaccination to first symptoms ranges from 2 to 72 months [144-146]. The pathognomonic features on muscle biopsy are long-standing alum-loaded macrophages which form a granulomatous lesion at the site of previous intra-muscular vaccination [147].

1.3 Epidemiology of neuromuscular diseases. Literature review

Epidemiologic studies that include a broad spectrum of NMDs, both acquired and inherited, are very rare whereas single-disorder studies are much more common [148-154]. A few studies looked at both acquired and inherited NMDs in children [155-157] but literature review has shown no such study in the adult population. A study analysed the PR of inherited NMDs in all age groups in Northern Ireland (NI) in 1994 which has similar demographics to ROI [158]. The NI data does provide a guide to the likely overall PR of inherited NMDs in ROI; however, NI study included the paediatric population and acquired conditions were not captured.

In this section, I will review the literature of reported international data on the incidence (IR) and prevalence (PR) of various NMDs included in this work.

1.3.1 Acute Inflammatory Demyelinating Polyradiculoneuropathy

Published IR estimates of GBS vary greatly depending mainly on case ascertainment, definitions and sample size [159]. The most common form is AIDP and accounts for 85–90% of GBS cases in Western countries [160]. The axonal variants, AMAN and AMSAN are most commonly encountered in other countries such as in China [23]. Population-based studies in Italy reported that MFS accounts for 6–7% of total cases of GBS, whereas in Taiwan this represented 18–19 %, suggesting geographical variation [23]. Rare variants such as acute pandysautonomia and polyneuritis cranialis are uncommon [161]. In the last four decades, most population studies showed that GBS appears to be evenly distributed all over the world, with an annual IR of about 1–2 per 100.000 population [23]. Some studies reported a wide IR range between 0.2 and 4.0 per 100,000 population. Males are more frequently affected than females (1.5:1) and there is an increase in IR with advancing age, with a minor peak in late adolescence and young adulthood and a second peak in the elderly [162]. In some studies, GBS cases were reported to be more common in the autumn and early winter, whereas others did not detect any seasonal difference [23]. Despite some reports suggesting GBS risk increase over time, the annual IR stayed stable from 1978 to 1993 in a large Swedish study [163] and even dropped from 1987 to 1996 in a study from Netherlands [164]. A meta-analysis of 13 articles on GBS IR from North America and Europe (of which 8

studies were from Italy and Spain) from 1966–2009 reported a IR ranging from 0.81 to 1.89 (median, 1.11) cases per 100,000 population [159]. In this analysis, the age-specific GBS IR increased from 0.62 cases per 100,000 person-years among 0-9-year-olds to 2.66 cases among 80-89-year-olds. A crude IR of 1.2 cases per 100 000 population and 1.5 per 100 000 when adjusted for undetected cases was reported in south east England in 1998 [165]. In a systematic literature review on data from 1980-2000, the IR rates found for GBS were between 1.1 - 1.8 per 100,000 per year with lower IR of 0.6 reported in children (<16 years) [166]. The majority of the studies included in this review were from Europe and North America where the majority of IR rates were between 0.84 in Finland [167] and 1.91 per 100,000 per year in Italy [168]. In comparison with IR data from Europe and North America, the IR was lower in China [169], Hong Kong [170], Brazil [171], Tanzania [172], Australia [173] and Japan [174] and slightly higher in the Middle East [175, 176] and Curaçao [177].

1.3.2 Chronic immune-mediated neuropathies

1.3.2.1 Chronic Inflammatory Demyelinating Polyradiculoneuropathy

Epidemiologic data on CIDP is limited. Previous studies reported variable results which may be ascribed to the use of different diagnostic criteria. The frequency of different CIDP subtypes is not well known. The last published study of a European population was performed in 2008 in Leicestershire and Rutland, UK. Using the 2006 clinical and electrophysiologic European Federation of Neurological Societies/Peripheral Nerve Society (EFNS/PNS) criteria, this UK study reported a CIDP PR of 4.77 per 100,000 population [33]. Using the 1991 American Academy of Neurology (AAN) criteria [178], the same UK study reported a PR of 1.97 [179]. These results were in-between the extremes of 1 and 7.1 found in the south-eastern UK [180] and northern Norway respectively [181]. In the study from Leicestershire and Rutland, 15.2% of patients had MADSAM and 23.9% had pure sensory onset. IR and PR rates reported from different geographic regions is shown in Table 14.

Table 14 International figures on Incidence and Prevalence of CIDP

Study[(Ref)]	Country	Population	Diagnostic criteria	PR x 10^5	Gender Ratio (M:F)
Lunn et al. 1999 [180]	Southeast England, UK	14,049,450	AAN	1.0	1.3:3
McLeod et al. 1999[182]	New South Wales, Australia	5,995,544	AAN	1.9	1.33:1
Mygland et al. 2001[181]	Vest-Agder, Norway	155,464	Albers and Kelly,1989	7.7	2.75:1
Chio` et al. 2007[148]	Piemonte and Valle d'Aosta regions, Italy	4,334,225	AAN	3.58	2.3:1
Iijima et al. 2008[183]	Japan	127,655,000	AAN, Saperstein et al., INCAT	1.61	1.63:1
Rajabally et al. 2008[179]	Leicestershire & Rutland,UK	963,600	AAN	1.97	2.8:1
Rajabally et al. 2008[179]	Leicestershire & Rutland,UK	963,600	EFNS/PNS	4.77	2.3:1

EFNS/PNS = European Federation of Neurological Societies/Peripheral Nerve Society, AAN = American Academy of Neurology

1.3.2.2 Multifocal Motor Neuropathy

MMN is a rare disorder thought to affect no more than 1–2 per 100,000 population, with men being more commonly affected than women (2.6:1) [29]. A recent study from 2013 reported a PR of 0.3 100,000 population in Japan [184]. However, detailed epidemiological studies of MMN in other populations have not been performed.

1.3.2.3 Paraproteinaemic demyelinating neuropathies

There is no published data on IR or PR of paraproteinemic neuropathies. A monoclonal gammopathy is present in 10% of patients with an idiopathic peripheral neuropathy, and 10–15% of patients with either IgM monoclonal gammopathy of undetermined significance (MGUS) or Waldenström macroglobulinemia suffer from a peripheral neuropathy [185].

1.3.3 Inherited neuropathies

1.3.3.1 Charcot-Marie-Tooth disease

CMT is the most common inherited PNS condition. The frequency of different CMT genotypes has been estimated in some clinic populations but PR data from the general population is lacking [186]. Studies from the pre-genetic era, 1921 – 1990, reported variable PR ranging between 14 and 282 per 100,000 [187]. In 1978, the PR of CMT disease (all types) in Northern England was reported to be 4.9 per 100, 000 [188]. A repeat study for the same region in 2012 estimated a PR of 9.8, twice as high as the former reported PR [149]. The highest PR in Europe had been reported in Norway: 41 per 100 000 in 1974 and 82.3 per 100 000 in 2011 [186, 189]. Table 15 illustrates the PR rates from different populations.

Table 15 Prevalence of CMT in different populations

Study(Ref)	**Population**	**PR X 10^5**
Skre et al. 1974[189]	West Norway	41.0
Davis et al. 1978[188]	North East England	4.9
Combarros et al. 1987[190]	North Spain	28.2
Holmberg et al. 1993[191]	North Sweden	20.1
MacMillan et al. 1994[192]	South Wales	16.7
Hughes et al. 1994[158]	Northern Ireland	3.1
Foley et al. 2010[149]	Northern England	9.8
Guthmundsson et al. 2010[193]	Iceland	12.0
Foley et al. 2010[149]	Newcastle upon Tyne	15.2
Nicolaou et al. 2010[194]	Cyprus	16.0
Braathen et al. 2011[186]	East Norway	82.3

1.3.3.2 Hereditary neuropathy with liability to pressure palsy

The PR data of HNPP is scarce. In 1997, a study from South West Finland reported the highest PR of 16 [195]. For comparison, a recent study reported a lower PR of 2.0 and 7.3 for North England and Newcastle upon Tyne respectively (Table 16).

Table 16 Prevalence of HNPP			
Study(Ref)	**Population**	**Cases**	**PR X 10^5**
HNPP alone			
Foley et al. 2010[149]	North England	59	2.0
Foley et al. 2010[149]	Newcastle upon Tyne	19	7.3
Meretoja et al. 1997[195]	South West Finland	69	16
CMT and HNPP combined			
Foley et al. 2010[149]	North England	352	11.8
Foley et al. 2010[149]	Newcastle upon Tyne	61	23.5

1.3.4 Kennedy disease

The PR of KD varies greatly in different parts of the world from 0.6 per 100,000 male population in Northern Ireland to 15.3 per 100,000 male in Western Finland (Table 17). A cluster of families in two communities surrounding the study area in Western Finland, suggested a founder effect [196]. A cohort of 113 families was reported from Japan with signs of a founder effect in that population group [197].

Table 17 Prevalence of Kennedy disease				
Study(Ref)	**Country**	**Cases**	**Population**	**PR X 10^{-5}**
Hughes et al.1994[158]	Northern Ireland	5	1,573,282 (all population)	0.3
Hughes et al.1994[158]	Northern Ireland	5	781,250 (male)	0.6
Udd et al.1997[196]	Western Finland	13	170,000 (male)	15.3
Guidetti et al.1997[198]	Reggio Emilia, Italy	7	438,588 (all population)	1.6
Guidetti et al.1997[198]	Reggio Emilia, Italy	7	214,224 (male)	3.3

1.3.5 Neuromuscular junction disorders

1.3.5.1 Lambert-Eaton Myasthenic Syndrome

LEMS is a very rare condition and therefore its epidemiology data is scarce. In 2003, based on a total number of 52 cases, a study from Netherlands found a PR for "all LEMS", "no SCLC" and "with SCLC" to be 2.5, 2.0 and 0.5 per million respectively [199].

1.3.5.2 Myasthenia Gravis

Estimated PR rates of MG vary widely ranging between 15 and 317 per million [200, 201] (Table 18). The earliest studies gave the lowest rates, likely due to underestimation of the true PR rate due to incomplete knowledge of the disease and limited diagnostic methods. However, a number of studies found an increase in the PR over time by comparing epidemiological data in the same region in different periods of time using a similar methodology [202-205]. This may suggest that increase in PR over time could not be explained only by differences in methodology and improvement in the diagnosis over time but also by a general trend towards increasing PR over time.

Table 18 Prevalence of myasthenia gravis (1951 – 2009)				
Study(Ref)	**Country**	**Population**	**Cases**	**PR x 10^{-6}**
Storm-Mathisen et al. 1951[202]	Norway	3,100,000	62	20
Gudmundsson et al. 1963[206]	Iceland	187,000	12	64
Oosterhuis et al. 1965[207]	Amsterdam, Holland	852,500	46	54
Okinaha et al. 1966[201]	Japan	608,000	9	15
Pirskanen et al. 1976[208]	Finland	4,700,000	264	56
Storm-Mathisen et al. 1981[202]	Norway	4,107,063	369	90
Phillis et al. 1984[209]	Virginia, USA	555,851	79	142
Giagheddu et al. 1986[210]	Sardinia, Italy	2,444,444	110	45
Yu et al. 1987[211]	Hong Kong	4,860,000	260	53.5
Ferrari et al. 1990[204]	Trento, Italy	444,879	37	83
Christensen et al. 1990[212]	Western Denmark	2,800,000	220	77.5
Guidetti et al. 1994[213]	Reggio Emilia, Italy	427,493	50	117
Robertson et al. 1997[214]	Cambridgeshire, UK	684,000	100	146
Poulas et al. 1997[215]	Greece	10,475,878	740	70.6
Oopik et al. 1997[216]	Estonia	1.462.130	144	99
Lai et al. 2007[217]	Taiwan	22,958,360	3205	140
Lavrnic et al. 2008[200]	Belgrade, Serbia	1,347,199 (>16 yrs)	425	317
Andersen et al. 2008[203]	Norway	4,700,000	619	131
Carr et al. 2008[218]	Northern Ireland	1,759,000	342	202.4
Gattellari et al. 2009[219]	Australia	21,960,000	2574	117.7
Pallaver et al. 2009[205]	Trento, Italy	524,826	68	129.6

1.3.6 Genetic muscle diseases

In 1954, Walton and Nattrass described 105 cases of muscle disease from Northumberland and Durham in the North of England [220]. Eighty-four patients were classified in the muscular dystrophy group: 48 Duchenne type, 18 limb girdle and 15 facioscapulohumeral. Those with 'myotonic syndrome' comprised 15 with dystrophia myotonica and 6 with myotonia congenita.

Fifty years later, in 2009, Norwood et al. undertook a comprehensive survey of genetic muscle disease cases in children and adults in the population of the same region (Table 19) [153]. In comparison with original study from fifty years ago, the recent study demonstrated an enhanced clarity regarding diagnostic categories and proportions of the affected population facilitated by molecular analysis. In Norwood's et al. study, based on their clinic population (over 1100 patients of all age groups), 31 separate muscle disease entities were molecularly defined and molecular genetic confirmation was achieved in 75.7% of cases. Per 100 000 population, the combined PR for all GMD in this clinic was 37. DM1 was the largest group, 28% of the whole cohort, giving a PR of 10.4. FSHD group accounted for 10.7% giving a PR of 3.95. Combined PR for the dystrophinopathies (DMD and BMD) gave a PR of 8.46. LGMDs involved 6.15% of the clinic population representing a combined PR of 2.27.

1.3.6.1 Myotonic Dystrophy type I

DM1 is the most common adult-onset form of muscular dystrophy with widely variable PR rates among world-wide epidemiological studies varying between 2 and 178 (Table 20). Increased use of molecular testing resulting in more frequent identification of asymptomatic carriers could explain the fact that recent studies yielded higher PR rates [221]. The Northern England study (2009) and the study from Northern Ireland (1994) revealed a PR of 10.4 and 8.4 respectively. An epidemiological study from Quebec, Canada which investigated the evolution of the PR of a large cohort of DM1 over a 25-year period (1985–2010) observed the highest so far PR of 178 in 1995 and 2000 and 158 in 2010 [222]. The high PR in this study is explained by the founder effects [223]. Fewer epidemiological studies were carried out on childhood onset DM1. In comparison with figures from the above studies which included all age population, a lower PR of 5 per 100 000 children (≤16 years) was reported in Western Sweden.

1.3.6.2 Facioscapulohumeral dystrophy

For FSHD, in the period from 1955 to 1990, world-wide studies reported differing PR rates varying from 0.2 to 6.6 per 100,000 [187] (Table 20). In the last 8 years, three separate studies from Netherlands, Northern England and Italy reported close PR rates of 5.0, 3.95 and 4.4 respectively. Interestingly, FSH is practically absent in southern and central Africa,

less prevalent in Southeast Asia, but more common in Western Europe, Japan, USA and Canada [224].

1.3.6.3 Dystrophinopathies

Not surprisingly, the PR figures for dystrophinopathies vary remarkably between paediatric and adult population. Previously reported PR rate for DMD was 8.2 per 100,000 males in 2 separate studies from Northern Ireland (1994) and Northern England (2009). The PR for BMD in Northern Ireland was half of the Northern England's PR rate - 3.26 and 7.29 per 100,000 males respectively. In paediatric population (≤ 16 years) from Western Sweden, PR for DMD is much higher, 16.8 per 100,000 males but lower for BMD, 1.6 per 100 000 males [155].

1.3.6.4 Limb Girdle Muscular Dystrophies

The overall PR of all the LGMDs has been estimated at 0.5-7 in several countries; however different populations have different frequencies of the various LGMDs. In Northern England, Norwood found a population PR of 2.27. In this study, LGMD2A (calpainopathy) was the most common, 26.5% of the total LGMDs, giving a PR of 0.6. LGMD2I was the next most common, 19% of the total LGMDs, giving a PR of 0.43. LGMD2B (dysferlinopathy) appears to be less frequent in the North of UK and no patient was found to have LGMD1A, 1C or 2G, H, J or K (Table 19). The next most common was LGMD2B accounting for 3-19%, followed by sarcoglycanopathies (LGMD2C-F) accounting for 3-18% as a group (with LGMD2D α-sarcoglycanopathy being the commonest). Worldwide, of all LGMDs, LGMD2I comprises 3-8%; however in certain parts of Northern Europe (including Denmark and parts of England) the prevalence of LGMD2I is higher. In this regard, LGMD2I represented 38% of all LGMDs in Denmark [225] and 19% in North of England [153], reflecting possible previous migration from Denmark to the Northern England. In all other European studies, LGMD2A is the commonest, representing 8-26% of all LGMDs cases [226, 227].

1.3.6.5 Congenital myopathies

Epidemiological data for many of the rarer genetic muscle diseases, such as congenital myopathies, is limited and either focused on single subgroups or limited to geographical areas [155, 158, 228, 229] (Table 20). In 1996, Northern Ireland's study estimated their PR

to be 3.5. In Western Sweden's study the PR was 5.0 per 100 000 children (≤16 years); NM was the most prevalent subtype. Another study in paediatric population (≤18 years) from southeastern Michigan, USA, estimated a PR of 3.8; CCD was the most common subgroup. The Northern England study estimated a lower combined PR of 1.37; CCD being the most common (Table 19). A retrospective study from Dubowitz Neuromuscular Centre, London, UK, assessed frequencies of individual congenital myopathies subgroups in their cohort of 66 patients and found that 54% patients had a core myopathy (central core disease, multi-minicore disease), 17% had NM, 13% had CNM and 4% had CFD [229]. It is believed that true PR of CM is underestimated, due to a substantial proportion of patients with mild clinical and/or non-specific histopathological features [229].

1.3.6.6 Spinal muscular atrophies

PR figure of 1.4 was reported in Northern Ireland (1994), 2.8 (in population ≤ 16 years) in Western Sweden (2000) and 1.87 in Northern England (2009). The higher PR in Western Sweden study is probably explained by higher frequency of this condition in the paediatric group. In Northern England study, 70% of the patients *SMN1* deletion and were either classified as SMA I, II or III. The rest of 30% of patients was given a diagnosis of SMA III based on clinical and neurophysiological findings and elimination of other diagnoses. The lower PR in Northern England may be explained by recent genetic advances which could have re-classified some of SMA patients to other categories [153]. In keeping with the previous literature, around 30% of SMA III patients from Northern England did not have an *SMN1* mutation [230].

1.3.6.7 X-linked Emery–Derifuss muscular dystrophy (X-EDMD)

Reported PR data for this condition is hard to find but generally it is much less common than autosomal dominant EDMD. Northern England's study estimated PR was 0.13.

1.3.6.7 Oculopharyngeal muscular dystrophy

Isolated families with OPMD have been reported all over the world but the highest PR was found in French, 1 in 100,000, French-Canadians in Quebec, 10 in 100,000 and Bukhara Jews from Israel, 1 in 600 [90, 231, 232].

1.3.6.8 Myofibrillar and distal myopathies

There have been much progress in the area of myofibrillar and distal myopathies in recent years but PR data is sparse [92, 233]. Tibial muscular dystrophy is the most common muscle condition in Finland with a PR of 20 per 100 000, but less frequent elsewhere [234]. Laing distal myopathy families and patients with sporadic *de novo* mutations are reported in many populations; based on experience from Finland, Spain and Norway the PR is greater than 0.1 [92]. Higher frequency, explained by founder mutations, of GNE-myopathy in Japanese and Middle Eastern populations has been reported; however the general mutations frequencies indicates a PR of less than 0.1 [92]. Only 0.9% of the Northern England's study genetic muscle disease cohort had a distal myopathy [153].

Table 19 Genetic muscle disease in Northern England [153]

Disease group	Cases based on clinical diagnosis	Cases confirmed according to diagnostic standard[153]	PR X 10^{-5}
Muscular dystrophies			
Duchenne (DMD)	124	124	8.29[a]
Intermediate	7	7	0.47[a]
Becker (BMD)	109	109	7.29[a]
Manifesting carriers	13	13	0.43
Total	253	253	8.46
Facioscapulohumeral	118	116	3.95
LGMD1B (AD EDMD)	6	6	0.20
LGMD2A	18	15	0.60
LGMD2B	4	2	0.13
LGMD2C	4	4	0.13
LGMD2D	2	2	0.07
LGMD2E	2	2	0.07
LGMD2I	13	12	0.43
LGMD unconfirmed	19	NA	0.64
Total LGMD	68	43	2.27
EDMD-X	4	4	0.13
Oculopharyngeal	4	4	0.13
Myotonic dystrophies			
DM1	311	311	10.4
DM2	5	5	0.17
Congenital Muscular Dystrophies			
MDC1A	18	18	0.60
Walker-Warburg syndrome	1	1	0.03
Ulrich muscular dystrophy	4	3	0.13
Rigid spine muscular dystrophy	4	1	0.13
Congenital myopathies			
Nemaline myopathy	6	5	0.20

Central core disease	12	10	0.40
Bethlem myopathy	23	18	0.77
Total	41	33	1.37
Distal myopathy	10	0	0.33
Myofibrillar myopathy	7	2 *(MYOT)*	0.07
		5 *(DES)*	0.17
Spinal muscular atrophies			
SMA type I	3	3	0.10
SMA type II	17	17	0.57
SMA type III	36	19	0.64
Total	56	39	1.87
Others			
Uncertain diagnosis/tests in progress	145	NA	NA
Patients with confirmed diagnosis	NA	836	NA
Total number of patients in database	1105	NA	37.0

Table 20 Prevalence of major genetic muscle disease from different studies

Study (Ref)	**Country**	**Cases**	**All age population**	**PR x 10^{-5}**
Myotonic dystrophy type 1				
Mathieu et al. 1983[222]	SLSJ, Quebec, Canada	405	285,211	142
Araki et al. 1983[235]	Japan	36	1,800,000	2
Hughes et al. 1994[158]	Northern Ireland	134	1,573,282	8.4
Darin et al. 1995[155]	Western Sweden	18	359,676 (≤ 16 years)	5
Leifsdottir et al. 2004[236]	Iceland	82	292,000	28
Mathieu et al. 2005[222]	SLSJ, Quebec, Canada	468	272,093	172
Norwood et al. 2009[153]	Northern England	311	2,990,000	10.4
Mathieu et al. 2010[222]	SLSJ, Quebec, Canada	432	273,641	159
Facioscapulohumeral muscular dystrophy				
Hughes et al. 1994[158]	Northern Ireland	50	1,573,282	3.1
Darin et al. 1995[155]	Western Sweden	3	359,676 (≤ 16 years)	0.8
Padberg et al. 1995[237]	Netherlands	772	15,459,000	5
Mostacciuolo et al. 2009[238]	Padova, Italy	40	871,190	4.4
Norwood et al. 2009[153]	Northern England	118	2,990,000	3.95
Duchenne muscular dystrophy				

Hughes et al. 1994[158]	Northern Ireland	67	781,250 (male)	8.2
Darin et al. 1995[155]	Western Sweden	31	185,000 (male ≤ 16 years)	16.8
Norwood et al. 2009[153]	Northern England	124	1,495,778 (male)	8.29
Becker muscular dystrophy				
Hughes et al. 1994[158]	Northern Ireland	25	781,250 (male)	3.2
Darin et al. 1995[155]	Western Sweden	3	185,004 (male ≤ 16 years)	1.6
Norwood et al. 2009[153]	Northern England	109	1,495,778 (male)	7.29
Limb girdle muscular dystrophies				
Hughes et al. 1994[158]	Northern Ireland	18	1,573,282	1.1
Darin et al. 1995[155]	Western Sweden	3	359,676 (≤ 16 years)	0.8
Norwood et al. 2009[153]	Northern England	68	2,990,000	2.27
Congenital myopathies				
Hughes et al. 1994[158]	Northern Ireland	57	1,573,282	3.5
Darin et al. 1995[155]	Western Sweden	18	359,676 (≤ 16 years)	5.0
Norwood et al. 2009[153]	Northern England	41	2,990,000	1.37
Amburgey et al. 2010[228]	Southeast Michigan, USA	46	1,211,100 (≤ 18 years)	3.8

Abbreviations: SLSJ - Saguenay-Lac-Saint-Jean region

1.3.6.9 Metabolic myopathies

McArdle disease

World-wide, the PR of McArdle disease is low and generally not well known, e.g. ~ 1 in the Forth Worth area, Texas, USA [239]. A recent study from Spain, based on a well-defined cohort of 239 cases, reported a PR of ~0.6 [152].

Late onset Pompe's disease (LOPD)

Accurate PR figures on LOPD in the general population are not available. PR rates differ between clinical forms and ethnic groups [240]. A high PR of 1 per 57, 000 and a much lower PR of 1 per 146,000 was estimated for LOPD in Dutch and Australian population respectively [241, 242]. Previously reported frequency of infantile-onset Pompe disease ranged from 1 in 33,333 to 1 in 138,000 among Taiwanese and Dutch populations, respectively [243] [242].

Mitochondrial disorders

A prospective study from Finland in 1998 studied the frequency of the mtDNA mutation at nucleotide 3243 in an adult population of 245,201 individuals. They screened for adult patients >20 years of age who had disorders such as diabetes mellitus, sensorineural hearing impairment, cardiomyopathy, brain infarct, epilepsy, ataxia, subjective visual disturbance and with radiological findings such as an occipital lesion, basal ganglia calcifications and cerebral white-matter lucencies. The mutation was found in 11 pedigrees (615 patients), and its PR was calculated to be 16.3 per 100,000 [244]. A study from Northern England which included mitochondrial DNA disease only (141 patients) found a PR of 9.2 per 100,000 adults of working age (16-60 years) but no specific figures for mitochondrial myopathy were reported [245]. A study from Madrid Health area 5, Spain studied 50 patients with all mitochondrial diseases in population over 14 years. Per 100,000, the overall estimated PR for mitochondrial disease in this area was 5.7, for mitochondrial myopathies the PR was 2.7, for CPEO was 2.5, for KSS and MELAS was 0.15 and for MERRF was 0.63 [246].

1.3.6.10 Skeletal Muscle Ion Channelopathies

A small number of studies estimated the PR of these disorders and most of them precede the genetic era. A most recent and comprehensive study from England in 2011 analysed the largest cohort of patients with SMIC reported so far (593 patients) and provided for the first time their overall PR of 1.12. This study revealed for the first time PR data on sodium channel myotonia, hyper PP and Andersen-Tawil Syndrome. The figures for myotonia congenita, paramyotonia congenita and hypo PP were similar to those previously observed in other areas (Table 21). Some studies reported significantly higher PR rates; however, most of them predate genetic testing, or were restricted to paediatric population, or were performed in areas with an unusually high population frequency of mutations due to founder effects and geographical factors (e.g., Northern Scandinavia or Germany) [151]. Percentages of dominant and recessive pedigrees were comparative in the English study, while previous studies found more recessive than dominant myotonia congenita [247, 248].

Table 21 Studies estimating the prevalence of Non–Dystrophic Myotonias and Periodic Paralyses

Date[(Ref.)]	Geographical area	Cases	Population	PR X 10^{-5}
Myotonia congenita				
1954[220]	North East England[a]	6	2,262,292	0.3
1954[249]	Rochester, USA	1	29,885	3.3
1956[224]	Switzerland*	18	4,714,992	0.4
1963[206]	Iceland	2	187,200	1.1
1979[250]	Turin, Italy*	10	1,160,686	0.9
1988[251]	Örebro, Sweden	3	269,341	1.1
1989[252]	Thugbah, Saudi Arabia	2	23,227	8.6
1990[187]	Ljubljana, Slovenia	10	1,996,377	0.5
1994[158]	Northern Ireland[b]	17	1,573,282	1.1
1995[155]	Western Sweden[c]	3	359,676	0.8
1997[253]	Assiut, Egypt	2	52,203	3.8
1998[247]	Northern Finland*	54	732,000	7.3
2001[248]	Northern Norway*	45	500,000	9.0
2001[254]	Hong Kong, China[d]	7	1,335,469	0.5
2011[151]	England*	277	53,012,500	0.52
Paramyotonia congenita				
1965[224]	West Germany*	160	57,000,000	0.3
1983[255]	Southern Norway[e]	1	573,762	0.2
1995[155]	Western Sweden[c]	4	359,676	1.1
2011[151]	England*	88	53,012,500	0.17
Hypokalemic periodic paralysis				
1978[256]	Denmark*[f]	66	5,096,959	1.3
1983[255]	Southern Norway[e]	3	573,762	0.5
1992[257]	Finland*[g]	21	4,998,478	0.4
2011[151]	England*	88	53,012,500	0.17
Hyperkalemic periodic paralysis				
2011[151]	England*	70	53,012,500	0.13
Sodium Channel Myotonia				
2011[151]	England*	30	53,012,500	0.06
Andersen-Tawil Syndrome				
2011[151]	England*	40	53,012,500	0.08

*Studies specifically conducted to evaluate the prevalence of the periodic paralyses or the non–dystrophic myotonias. [a]Total population from 1951 Census of England and Wales. [b]Prevalence of non–dystrophic myotonia. [c]Prevalence among children <16 years. [d]Prevalence among children <19 years. [e]Prevalence among children <18 years. [f]Only familial cases; total population data from Statistics Denmark. [g]Total population data from Statistics Finland.

Adapted from Horga A et al. Prevalence study of genetically defined skeletal muscle channelopathies in England. Neurology. 2013 April 16, 2013

1.3.6.11 Congenital Myasthenic Syndrome

Scarce data is available on epidemiology of CMS. PR rates of 0.6 per 100,000 in population ≤ 16 years and 0.82 per 100,000 all age population have been reported in Northern Ireland in 2009 [218] and Western Sweden in 1995 respectively [155].

1.3.7 Acquired muscle disease

1.3.7.1 Sporadic Inclusion Body Myositis

As shown in Table 22, the reported PR of sIBM varies worldwide from 0.07 in Turkey to 1.5 in Western Australia. The highest reported PR of 7 per 100,000 was in Olmsted County, USA; however this rate was based on a small cohort of 9 patients. It is believed that these figures are under-estimates due to incomplete case ascertainment, delayed disease diagnosis or misdiagnosis and therefore the true PR of sIBM may be substantially higher than previously thought [258, 259]. This speculation is given further weight by observing the PR figures in Western Australia which have increased from 0.9 per 100,000 in 2000 to 1.5 per 100,000 in 2008, probably reflecting improved case ascertainment [258]. There is a lack of published data on the PR of sIBM from Asian countries but the condition is considered to be rare in Turkey [260] and India [261]. sIBM has been found to be rarer in non-Caucasians (African-Americans, Australian aboriginals) further suggesting that genetic factors play an essential role in defining susceptibility to the disease [258]. For instance, the frequency of the allele HLA-DRB1*0301 (DR3) and the 8.1 MHC haplotype is higher in Europeans, North Americans and Australians, compared to Turkey, Thailand, African-Americans and Australian aboriginals where PR of sIBM is very low [258]. However, to truly define the PR of sIBM in diverse populatuons, much larger, multicentre epidemiological studies are needed which can also research the significance of relevant factors which might influence the PR of the disease (e.g., HLA genotype, genetic, environment) [259]. An international sIBM genetic study is ongoing and whole-exome sequencing will be applied in a large cohort of sIBM patients with the aim of working out important genetic risk factors for sIBM [136].

Table 22 International Prevalence figures for sIBM				
Study date [Ref]	**Country**	**Cases**	**PR X 10^5**	**PR X 10^5 (> 50 years)**
Oflazer et al. 2010 [260]	Turkey	9	0.07	0.4
Badrising et al. 2000[262]	Netherlands	76	0.5	1.6
Phillips et al. 2000 [263]	Western Australia	17	0.9	3.5
Needham et al. 2008 [264]	Western Australia	31	1.5	5.1
Felice et al. 2001 [265]	USA, Connecticut	35	1.1	2.9 (>45 years)
Wilson et al. 2008 [266]	USA, Minnesota	9	7	nd
Suzuki et al. 2003 [267]	Japan	1255	1	nd

nd = not done

1.3.7.2 Macrophagic myofasciitis

PR of MMF has never been reported in the literature. One French group reviewed the records of 457 adult MMF patients accumulated from 1994 to 2011 in the Neuromuscular Centre of Créteil. Isolated cases were reported in different countries [146, 268, 269].

1.3.8 Overall prevalence of neuromuscular diseases as a group

Table 23 Overall Prevalence of NMD from different studies					
Study [(Ref)]	**Country**	**Conditions**	**Cases**	**Population**	**PR x 10^{-5}**
Emery 1991[224]	150 surveys	Inherited NMD	150 surveys	150 surveys	33.3
Hughes et al. 1994[158]	Northern Ireland	Inherited NMD	543	1,573,282	34.5
Darin et al. 1995[155]	Western Sweden	Inherited NMD	191	359,676 (≤ 16 years)	53.1
Darin et al. 1995[155]	Western Sweden	All NMD	227	359,676 (≤ 16 years)	63.1
Norwood et al. 2009[153]	Northern England	Inherited muscle disease	1105	2,990,000	37.0

1.4 Objectives of the present study

There have been no previous population-based studies of adult neuromuscular diseases (NMD) in the Republic of Ireland (ROI). The main aim of this work was to accurately identify all cases of adult inherited and acquired NMD in the ROI with the future plan being to develop specific disease registries and care programmes for these patients. This project aimed to provide data on prevalence of these conditions and to analyse their geographical distribution and burden within ROI - information which will assist in future service planning/provision for these patients. Additional objectives were to analyse the proportion of patients with a genetic diagnosis, to explore their gene frequencies and finally, to compare the epidemiological figures from our study with those reported internationally. A particular interest was attributed to identification of conditions for which therapeutic options are now available.

Chapter 2

Materials and Methods

2.1 Study population

The study focused on the adult population of ROI, a geographically well-defined area comprising 26 counties (APPENDIX 1). The estimated total population is 4,588,252 with an overwhelmingly homogenous Caucasian population; adults (≥ 18 years) comprise 3,439,565 based on the 2011 ROI Census 2011 (Central Statistics Office Ireland; htpp://www.cso.ie/) (APPENDIX 2). In ROI, neurology patients are looked after by neurologists working in the public and private sector. Fifteen public hospitals and 8 private hospitals/clinics function as neurology referral centres in the country. Two dedicated neuromuscular clinics in two tertiary referral hospitals - Beaumont Hospital, Dublin and Cork University Hospital, Cork - serve as specialised referral centres for patients with NMD in ROI. These two tertiary referral hospitals have two neuropathology departments serving the whole ROI. However, not all neuromuscular patients are referred/followed up in the 2 specialized neuromuscular clinics; a significant number are followed up by neurologists locally in the public or private hospital in their own catchment area.

2.2 Incidence and Prevalence calculation

Incidence is the number of new cases of a certain condition occurring in a defined population in a specified time period. It can be expressed as cumulative incidence (CI) or incidence rate (IR), both equally valid. In our study we calculated the IR which was estimated for GBS only, estimated for each year from 1992 – 2012 (IR date was 1st January of each year) using relevant ROI Census data for each year (Central Statistics Office Ireland; htpp://www.cso.ie/) [270].

$$IR = \frac{\text{Number of new cases of NMD during a given time period}}{\text{Total person-time of observation}}$$

The prevalence rate (PR) measures the instantaneous number of NMD cases in a population at a given point in time. Prevalence may be expressed as a crude or age-adjusted rate. In our study we calculated crude prevalence (PR).

$$PR = \frac{\text{Number of cases of NMD at a given point in time}}{\text{Total number of at-risk individuals}}$$

IR and PR were expressed as cases per 100,000 of the population at risk, i.e., adult population (≥ 18 years) living in ROI at the time of data analysis. PR was estimated for: each condition in each county, each condition for the whole country and for all NMD as a group. For X linked conditions, PR was calculated per 100,000 male population. In addition, for sporadic inclusion body myositis (sIBM), the PR was calculated per 100,000 population at risk for this condition (≥ 50 years). The date and time used for PR estimation was midnight on 31st December 2013.

The 95% confidence intervals (CI) were calculated based on standard formula (normal approximation of the binomial): p +/- 1.96*sqrt(p(1-p)/n) [271].

2.3 Prevalence mapping of NMD

In order to create choropleth maps showing the distribution of the various NMDs across Ireland GIS (Geographical Information Systems) were used. GIS allows for the creation, management and visualisation of spatial data; in this case the PR of the various conditions at county level. In order to map the PR of the various conditions it was first necessary to calculate the PR for each condition using the population of the counties. The population data was downloaded from the Central Statistics Office (CSO) website and MS Excel (© 2010 Microsoft Inc.) was used to calculate the PR values. This data was then imported into the GIS and linked to county boundary data. Once the data had been imported and linked to boundary data it was possible to symbolise the data in order to highlight the variations in values across the country. The data was classified using the equal interval methodology, meaning the data values for each condition where divided into equal-sized sub-ranges, and a different shade varying from light to dark was assigned to the sub-ranges (the darker the colour the higher the PR of NMD in that county). Depending on the number of cases either 3 or 5 sub-ranges (classes) were used for the map. Once the data had been symbolised a layout was created for each map, including a scale bar, legend and north arrow and the completed maps were then exported. The described process is exemplified in the screenshot images (APPENDIX 6).

The PR data was mapped for each NMD and for all NMD as a group for each county where the patient lives. This is illustrated in the legend of each map (APPENDIX 6).

Of note, the mapped PR figures for each NMD and for all NMDs as a group for each county are unadjusted for age. The main purpose of the PR mapping was to show the burden and spread of various NMDs across the country and not to be used to compare the PR rates between counties as age structure may differ. Age adjusted PR calculation was performed for sIBM only (APPENDIX 3). The national age breakdown in 10 year bands has been given in APPENDICES 4 and 5 in order to facilitate the inter-county figure comparison if needed.

2.4 Study inclusion and exclusion criteria

Table 24 Study inclusion and exclusion criteria

Inclusion criteria

Adults (≥ 18 years) living in the Republic of Ireland ≥ 5 years with the following conditions:

1. Neuropathy
   - Acquired inflammatory demyelinating neuropathies (GBS, CIDP, MMN, PDN)
   - Inherited neuropathy (e.g. CMT, HNPP, dHMN, HMSN 5, FAP)
   - Spinal muscular atrophy (Types 3 & 4)
   - Kennedy's disease
   - Neuromyotonia
2. Neuromuscular Transmission Disorder
   - Myasthenia Gravis
   - Lambert-Eaton myasthenic syndrome
   - Congenital myasthenic syndrome
3. Muscle disease
   - Muscular dystrophies (e.g. DMD, BMD, LGMD, FSHMD, Myotonic dystrophy
   - Distal myopathy, myofibrillar myopathy
   - Congenital myopathy
   - Muscle channelopathy (myotonia congenita, paramyotonia congenita; periodic paralysis, ATS)
   - Inclusion body myositis, macrophagic myofasciitis
   - Metabolic myopathy (glycogen storage, fatty acid, mitochondrial*)

Exclusion criteria

1. Under 18 years of age
2. Acquired axonal neuropathy
3. Myalgia without muscle weakness
4. Polymyositis, Dermatomyositis
5. Post-Polio syndrome
6. ALS

** Only patients who had overt muscle involvement either as a sole manifestation of or as a feature of a mitochondrial disorder were included.*

Abbreviations: GBS = Guillain-Barré syndrome, CIDP = chronic inflammatory demyelinating polyneuropathy, MMN = multifocal motor neuropathy, PDN = paraproteinaemic demyelinating neuropathy, CMT = Charcot-Marie-Tooth disease, HNPP = hereditary neuropathy with liability to pressure palsies, dHMN = distal hereditary motor neuropathy, HMSN = hereditary motor sensory neuropathy, FAP = familial amyloid polyneuropathy, DMD = Duchenne muscular dystrophy, BMD = Becker muscular dystrophy, LGMD = limb girdle muscular dystrophy, FSHMD = facio-scapulo-humeral muscular dystrophy, ATS = Andersen-Tawil syndrome, ALS = amyotrophic lateral sclerosis

2.5 Diagnostic criteria of the conditions included in the study

Diagnostic criteria for inclusion and classification were the following: for CIDP, those proposed by EFNS/PNS published in 2006 and updated in 2010 [32]; for GBS, those described by Asbury [27]; for inherited neuropathies and inherited muscle disease, those established by the European Neuromuscular Centre in 1998 [11] and from more recent key references for individual conditions as proposed in 2013 version of the gene table of monogenic neuromuscular disorders [82]. Diagnosis of non-dystrophic myotonia and periodic paralysis was established by clinical, electrophysiologic features and gene confirmation. Diagnosis of IBM was based on Modified IBM criteria from MRC Center for Neuromuscular Diseases 2010 [272]. Diagnosis of myasthenia gravis was established by history and examination features with the result of at least 1 positive paraclinical test (antibody, electrophysiology or edrophonium). LEMS was established by demonstrating characteristic electrophysiologic features (idiopathic form) with additional evidence of an underlying neoplasm (paraneoplastic form) and supported by VGCC antibodies. Diagnostic standards for congenital myasthenic syndrome were those described by Kinali [70].

2.6 Case ascertainment

This study was conducted jointly between the two dedicated neuromuscular centres in ROI (Cork University Hospital and Beaumont Hospital, Dublin). All patients recruited through neuromuscular clinics had a full neurological examination and their medical notes and investigations/results were reviewed by one of the investigators. Neurology databases in 14 public hospitals (out of a total of 15) and 7 private hospitals/clinics (out of a total of 8), 2 neuropathology departments and 5 neurophysiology departments were searched (Figure 12). Two new databases (implemented in the last 3 years) in 2 major hospitals in Dublin were non-searchable because of inability to search these databases using the usual terms/identifiers.

The patient voluntary organization Muscular Dystrophy Ireland (MDI) informed all their members about the study and invited them to participate by a correspondence to each member and study advertisement on their website (www.mdi.ie). The fellow was freely contactable by people who might wish to be enrolled in the study and by all physicians by means of a dedicated mobile phone and email address. Details of the project were presented at multiple patient oriented meetings organised by MDI during a two-year study period. Permission was granted to search MDI database. Patients identified via MDI were recruited via referral to one of the neuromuscular clinics or by arranging a review by the fellow in the MDI office.



● Neurology department in public hospital (12 sites)

■ Neurology department + neuromuscular clinic in public hospital (2 sites)

o Private hospital/clinic (7 sites)

★ Muscular Dystrophy Ireland (1 site)

Figure 12 ROI map showing location of case ascertainment sites

The catchment area includes 26 counties with an estimated adult population (≥ 18) of 3,439,565.

In order to aid recruitment, multiple methods were used to increase awareness of this study with a view to achieving as complete ascertainment as possible. All adult and paediatric neurologists, neurophysiologists, neuropathologists, respiratory physicians, cardiologists and county physicians were notified in writing regarding the study aims. Referrals by these physicians of existing neuromuscular patients or patients suspected of exhibiting features of NMD to the two neuromuscular clinics were encouraged. General practitioners were notified about the study by an advertisement article in the Irish College of General Practitioners national journal. The fellow presented the project at the national neurology meetings and neurology intradepartmental educational meetings in hospitals across the country. The study was advertised in local medical newspapers.

The HIPE was searched in four major adult hospitals for discharges from 1st January 1990 until 31st August 2013 with diagnoses under the following ICD codes: ICD-9-CM: 33510 - 33511, 3560 - 3562, 3570, 3578, 3580 - 3581, 3588, 3590 - 3592, 3598, 3596 and ICD-10-AM: G121, G129, G600, G610, G618, G708, G700, G702, G710 - G713, G736, G724. Cases identified through HIPE system have been crosschecked with patient medical notes for diagnosis verification and further disease classification purposes. For patients identified from the HIPE system and neurology databases, supportive data from preceding investigations in the course of diagnostic evaluation were used where possible.

The following demographic variables were recorded: full name, date of birth, gender, hospital number, patient address, country of birth, name of the treating neurologist, name of the hospital patient is attending, source/sources where patient was ascertained. The NMD group (e.g., acquired neuropathy, inherited neuropathy, neuromuscular junction disorder, muscular dystrophy, skeletal muscle channelopathy, acquired muscle disease) followed by more specific diagnosis (e.g., AIDP, CIDP, CMT, myasthenia gravis, limb girdle muscular dystrophy, periodic paralysis, myotonia congenital, sIBM) were recorded. Where available the precise genetic or other (e.g. immune-mediated) diagnosis was recorded (99 entities). The following relevant diagnostic investigations were obtained: for AIDP – neurophysiology, cerebrospinal fluid protein level, ganglioside antibodies; for CIDP - neurophysiology, cerebrospinal fluid protein level, ganglioside antibodies (GM1), anti MAG, serum paraproteins and where available sural nerve biopsy; for inherited neuropathies – neurophysiology and where available genetic tests; for neuromuscular junction disorders – relevant autoantibodies, neurophysiology, Tensilon test, result of thoracic computer tomography; for genetic muscle disease - creatine kinase (CK), neurophysiology, muscle biopsy and where

available genetic tests. In cases where the diagnosis from different sources did not match (often this occurred when a diagnosis given years ago was later changed as a result of more recent diagnostic tests), the most recent diagnosis was used. Data from all perused sources was crosschecked to eliminate duplicates. In cases where one of the variables was missing (e.g., date of birth), other available variables such as patient name, diagnosis and address were used for linking in order to prevent duplicates.

All patients enrolled, at some stage in their illness, had to be seen and diagnosed with NMD by a neurologist. Furthermore, in every case - in order to be included in the study - there had to be at least one abnormal investigation (e.g., laboratory, neurophysiology or histopathology). Where patients were labelled as "possible" myopathy or neuropathy or the diagnosis was otherwise unclear, these patients were not included in the study. Similarly, where patients were undergoing investigation and a diagnosis had not yet been reached, these cases were not included.

All cases with an undefined glycogen or lipid storage myopathy and their muscle biopsies were discussed with the consultant neuropathologist to ensure a correct diagnosis.

2.7 Statistical analysis

Descriptive statistical analysis were performed using IBM SPSS Statistics v20 (© SPSS 2010 Inc.) and Microsoft Excel (© 2010 Microsoft Inc.).

2.8 Ethics approval

As this study had to access data from multiple sites, it required multiple ethics application submissions to different institutions. Ethics approval was first obtained from Cork University Hospital and Beaumont Hospital. Certain institutions then required separate ethics applications such as: St. Vincent's University Hospital, Dublin; The Adelaide and Meath Hospital incorporating the National Children's Hospital, Dublin; Mater Misericordiae University Hospital, Dublin; Sligo General Hospital, Sligo and Letterkenny General Hospital, Letterkenny. Written confirmation of ethics approval, including permission to visit patient's homes, was obtained from the ethics committee of each participating institution.

Chapter 3

Results

3.1 Included cases

Identified individuals were classified according to the ascertained source into 6 groups (Table 25). Potential NMD cases were further subdivided according to whether they were found uniquely in one source or were identified in multiple overlapping sources (Figure 13). A total number of 3724 potential cases from 6 sources were identified. Out of these 3724 cases, 869 cases were also identified in another source / sources (i.e., duplicates, triplicates), and these were excluded from the study. HIPE analysis was carried out in 4 hospitals: 884 cases were identified and their medical charts were retrieved for diagnosis crosscheck and review of supporting investigations. After chart review, 133 were found to have been coded incorrectly and these were excluded; 121 (91%) of these 133 cases were coded in one hospital where the vast majority - 115 cases (95%) - were coded erroneously as hereditary sensory neuropathy (ICD 9: 3562). The correct diagnoses ranged from idiopathic, diabetic, uraemic to other acquired neuropathies. Furthermore, 74 patients were deceased and 7 patients had moved out of the country; these were also excluded. This resulted in 2641 as the actual number of cases recruited for inclusion in this study.

Table 25 Number of cases identified in each source

Source	*Number of cases (%)*	*Unique to source*
Neurology/Neurophysiology	1724 (46.3)	1008
Neuromuscular clinics	434 (11.6)	92
Neuropathology	269 (7.2)	130
HIPE	884 (23.7)	441
MDI	406 (10.9)	126
GBS society	7 (0.2)	5

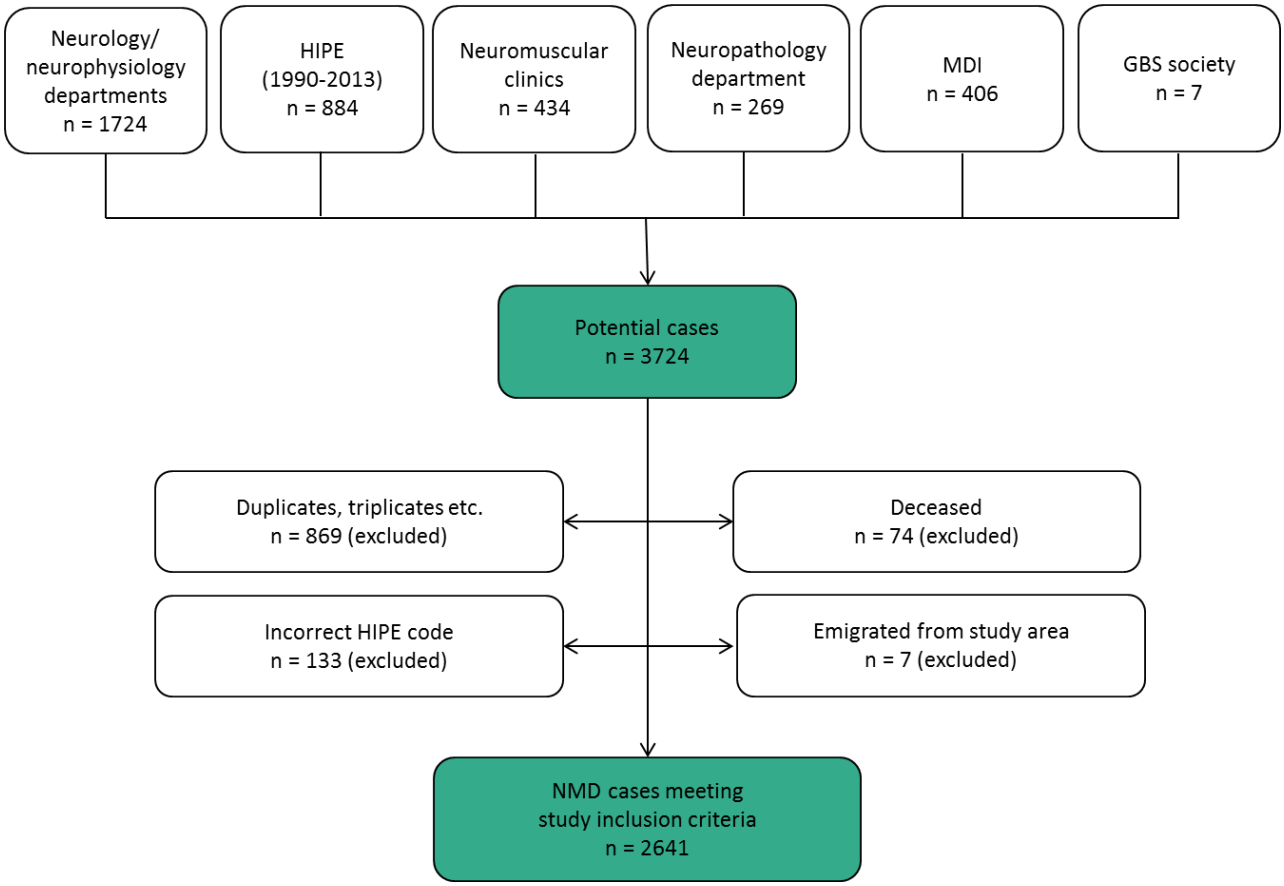


Figure 13 Flow diagram of identification of potential cases of NMDs in ROI

The highest number of total cases and 'unique to source' cases were identified in neurology departments and HIPE (Table 25). A Venn diagram illustrating the sources overlap is seen in Figure 14; 307 cases were identified in HIPE and neurology departments only, 123 in both neurology departments and neuromuscular clinics only, 85 in neurology departments and MDI only, 48 in MDI and neuromuscular clinics. Figure 15 illustrates the number of cases included in the study from each site. As described above, I visited each of these sites individually in order to ascertain cases. The higher numbers of cases in Cork University Hospital (CUH) (530 cases) and Beaumont Hospital (490 cases) reflect the larger catchment area but also the availability of neuromuscular clinics and neuropathology departments in these 2 national neuroscience centres.

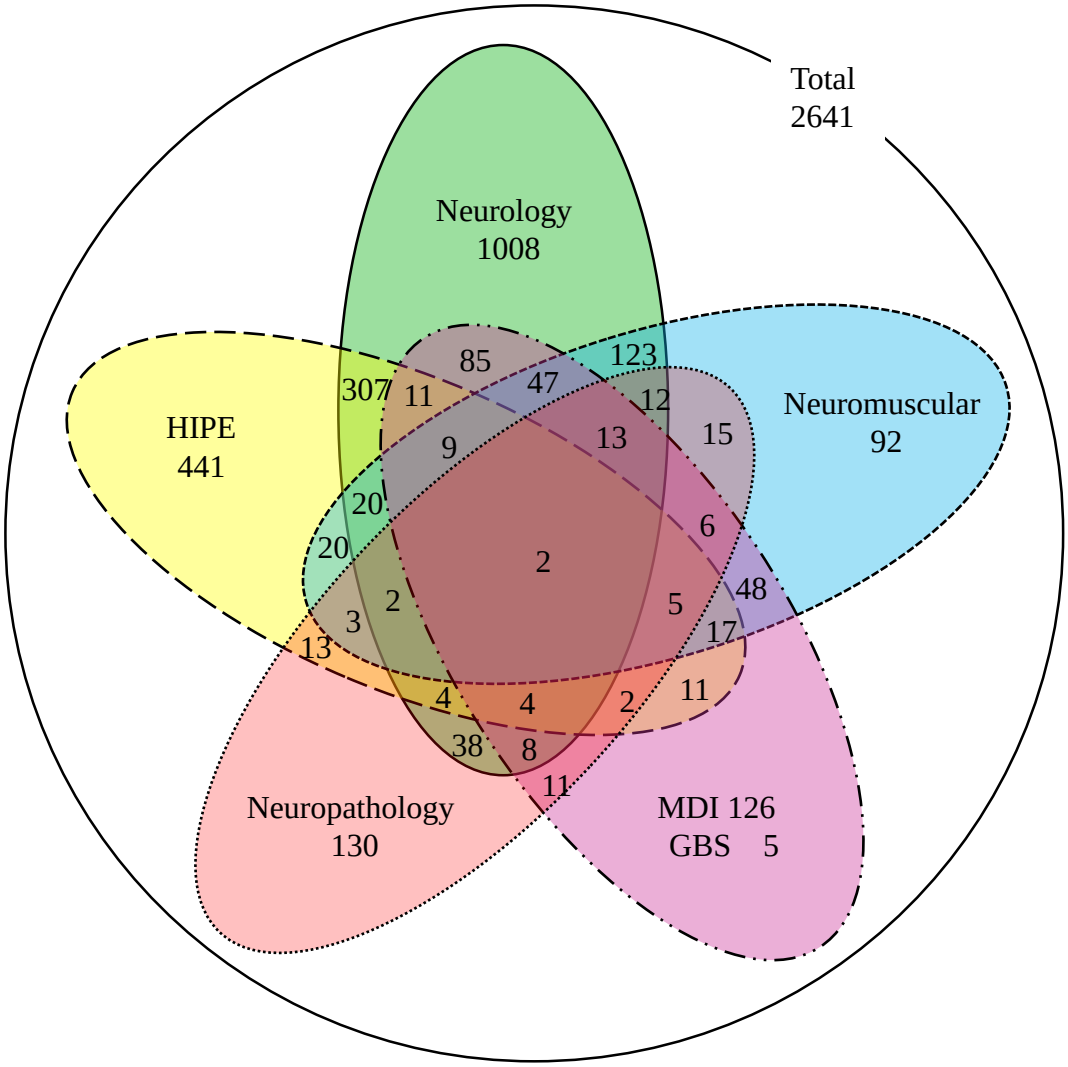


Figure 14 Venn diagram demonstrating sources overlap

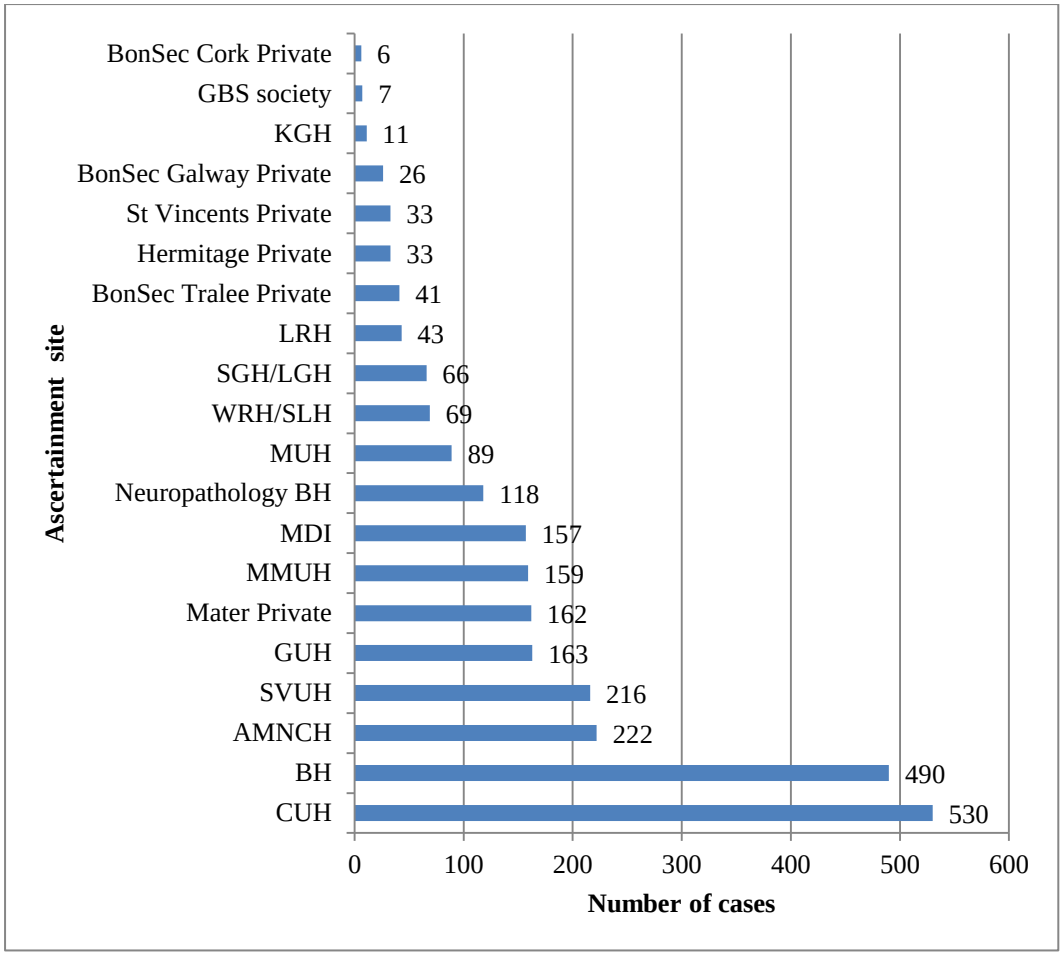


Figure 15 Number of cases from each ascertainment site

Abbreviations: BonSec = Bon Secours Private Hospital, GBS = Guillain-Barré syndrome (GBS Society), KGH = Kerry General Hospital, LRH = Limerick Regional Hospital, SGH/LGH = Sligo General Hospital/Letterkenny General Hospital, WRH/SLH = Waterford Regional Hospital/Saint Lukes Hospital, MUH = Mercy University Hospital, BH = Beaumont Hospital, MDI = Muscular Dystrophy Ireland, MMUH = Mater Misericordiae University Hospital, GUH = Galway University Hospital, SVUH - St. Vincent's University Hospital, AMNCH = The Adelaide and Meath Hospital, Dublin, incorporating the National Children's Hospital, CUH = Cork University Hospital

3.2 General description of the cohort

A total of 2641 individuals fulfilling the inclusion criteria were identified; 1481 (56.1%) were males and 1160 (43.9%) females. Male: female ratio was 1.28: 1. Age was calculated as per 31st January 2013. The age was missing in 150 cases (81 males and 69 females). The overall age range was 18-93 years; mean age of 54.05 (SD 18.75). Mean age in males was 54.12 (18.89) and 53.96 (SD 18.57) in females. Distribution of cases, stratified by age group and gender is shown in Table 26.

Table 26 Distribution of cases, stratified by age group and gender

Age, years	Men, n (%)	Women, n (%)	Total, n (%)
18-27	136 (9.2)	77 (6.6)	213 (8.1)
28-37	189 (12.8)	176 (15.2)	365 (13.8)
38-47	206 (13.9)	177 (15.3)	383 (14.5)
48-57	207 (14.0)	168 (14.5)	375 (14.2)
58-67	253 (17.1)	195 (16.8)	448 (17.0)
68-77	242 (16.3)	161 (13.9)	403 (15.3)
78-87	146 (9.9)	110 (9.5)	256 (9.7)
≥88	21 (1.4)	27 (2.3)	48 (1.8)
Missing age	81 (5.5)	69 (5.9)	150 (5.7)
Total	1481 (100)	1160 (100)	2641 (100)

Of the total number of 2641 cases identified, 1149 (43.5%) were neuropathies, 539 (20.4%) neuromuscular junction disorders and 953 (36.1%) myopathies (Figure 16). A total of 1380 (52.3%) cases represented acquired NMD which were more common in over 58 year old groups; 1261 (47.7%) were inherited NMD which were more common in 18–47 years old groups. Age-specific distribution of both acquired and inherited NMD is shown in Figure 17. Genetic confirmation was found in 46% of all inherited NMDs cases and in 52% of all GMD cases.

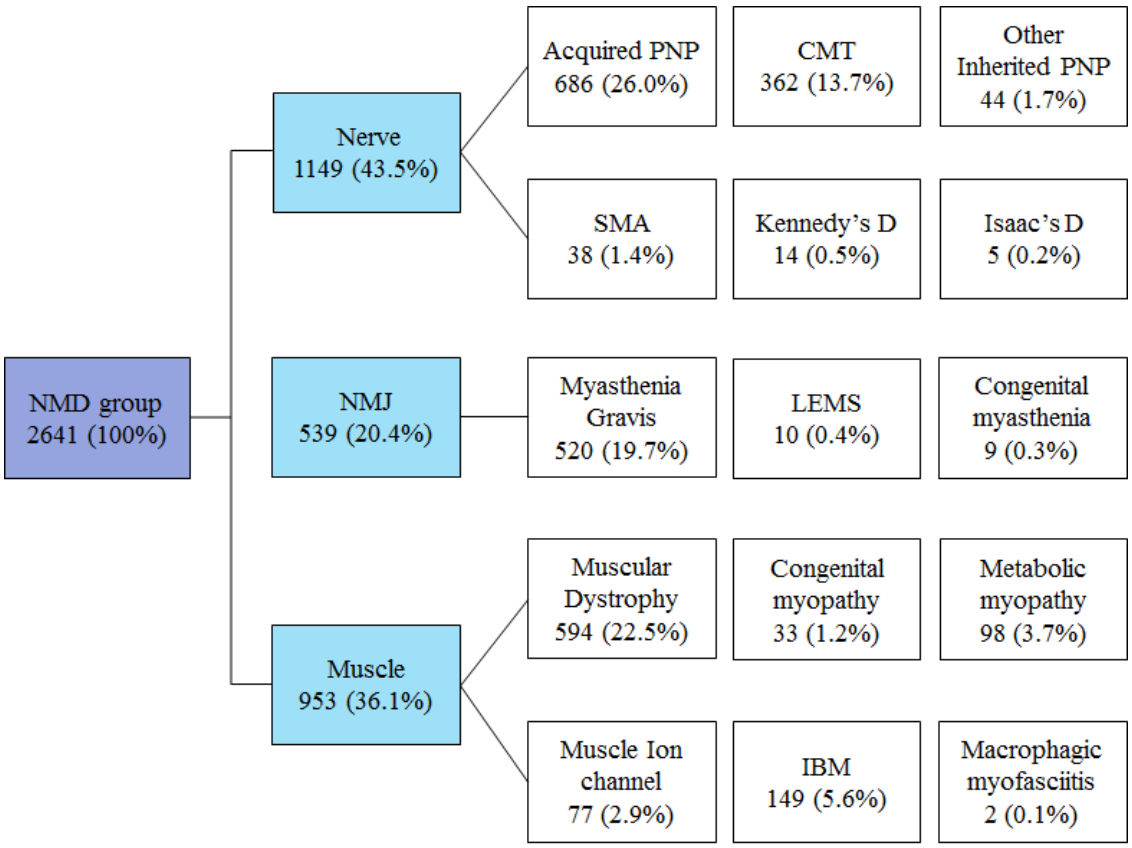


Figure 16 Number of cases of individual disorders

Abbreviations: NMD = neuromuscular disorder, PNP = polyneuropathy, CMT = Charcot-Marie-Tooth disease, SMA = spinal muscular atrophy, IBM = inclusion body myositis, NMJ = neuromuscular junction

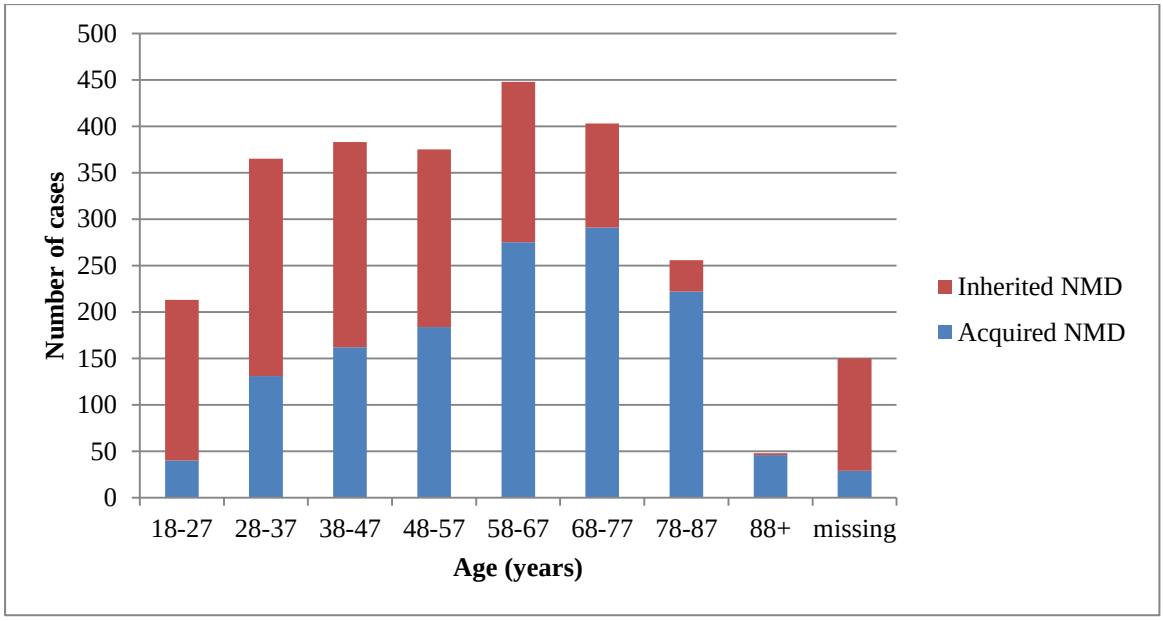


Figure 17 Age distribution of cases with acquired and inherited NMD

In the remaining sections of this chapter 3, a detailed description of the epidemiological figures from this work will be presented. For many of these conditions, the data from this study will be illustrated in tables together with international figures. However, the discussion comparing this study figures with those from international studies will be made in Chapter 4 (Discussion).

In the following chapters, IR and PR are expressed as cases per 100,000 of the population at risk, i.e., adult population (≥ 18 years) living in ROI at the time of data analysis (31st December 2013). For X linked conditions, PR was calculated per 100,000 male population. In addition, for sporadic inclusion body myositis (sIBM), the PR was calculated per 100,000 population at risk for this condition (≥ 50 years).

3.3 Incidence study

3.3.1 Guillain-Barre syndrome

From all sources, in the 20 year period (1992 to 2012), a total number of 488 cases with GBS were identified, of which 289 (59.2%) were male and 199 (40.8%) were female. Incidence (IR) for GBS was estimated for each year from 1992 to 2012. Per 100,000, IR varied from 0.3 in early 1990s to a maximum of 1.3 in 2010 (Figure 18). Of the total number of 488 cases with GBS (which occurred during the 20 year period), AIDP was the most common subtype (87% cases), followed by less common subtypes such as MFS (8%), AMSAN (3%) and AMAN (2%) (Figure 19).

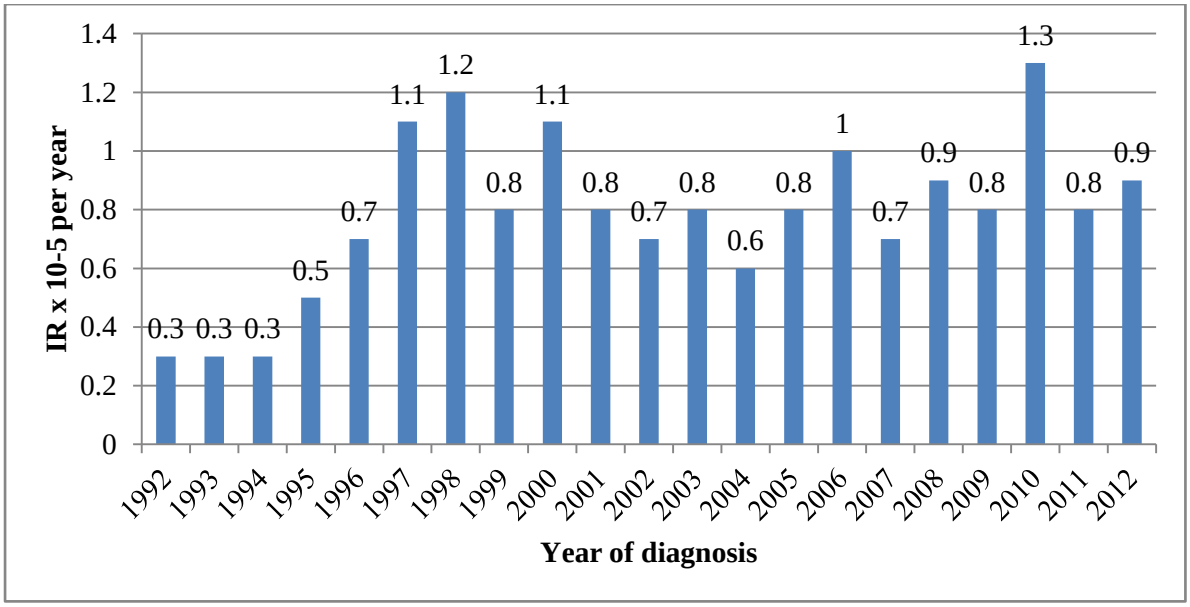


Figure 18 Incidence of GBS over 20 years (1992 - 2012)

3.3.1.1 Guillain-Barre syndrome subtypes

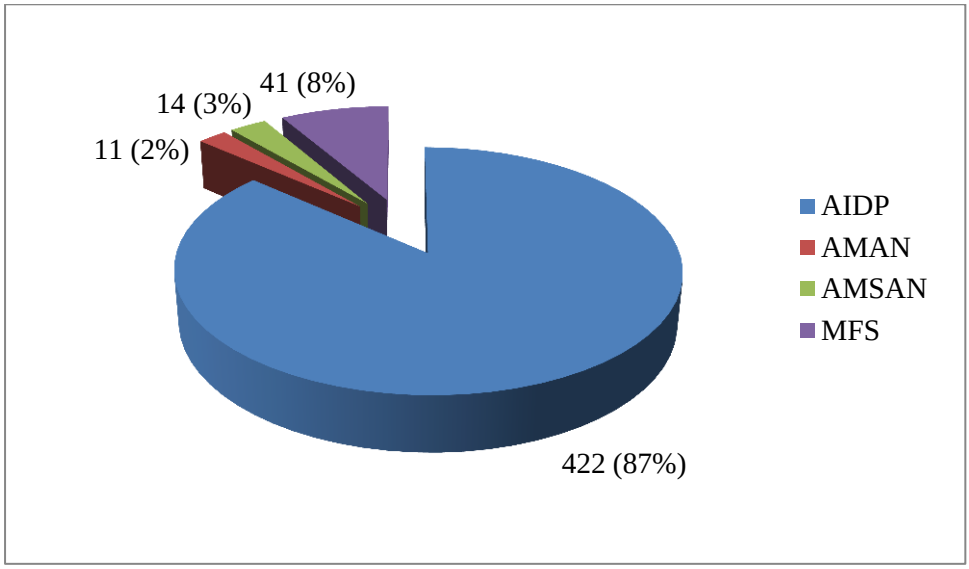


Figure 19 Guillain-Barre syndrome subtypes

3.4 Prevalence study

3.4.1 Chronic immune-mediated neuropathies

A total number of 230 cases of chronic immune-mediated neuropathies were found producing a country PR of 6.69 (Table 27). CIDP was the most common subtype, 202 cases, giving an overall PR of 5.87. Per county, the highest unadjusted PR (8 – 14), was encountered in north-eastern counties Carlow, Kildare, Wicklow, Dublin and Galway (APPENDIX 6). No cases of CIDP were found in counties Cavan and Longford. The estimated PR figures for the rarer forms such as MMN and IgM PDN (MAG+) were much lower: 0.70 and 0.06 respectively.

Table 27 Prevalence for chronic immune-mediated neuropathies in ROI

Condition	No. of cases	PR x 10^{-5} (95% CI)
CIDP		
CIDP, typical	189	5.49 (4.71-6.28)
CIDP, atypical	2	0.06 (0-0.14)
MADSAM	1	0.03 (0-0.09)
DADS	1	0.03 (0-0.09)
CIDP with paraproteinaemia	11	0.32 (0.13-0.51)
Ig G PDN	3	0.09 (0-0.19)
Ig M PDN	8	0.23 (0.07-0.39)
Total CIDP	202	5.87 (5.06-6.68)
Ig M PDN (MAG+)	2	0.06 (0-0.14)
MMN	24	0.70 (0.42-0.98)
POEMS	1	0.03 (0-0.09)
CANOMAD	1	0.03 (0-0.09)
Total	**230**	**6.69 (5.82-7.55)**

Abbreviations: CIDP = chronic inflammatory demyelinating polyradiculoneuropathy, MAG = myelin-associated glycoprotein, MADSAM - multifocal acquired demyelinating sensory and motor neuropathy, MMN - multifocal motor neuropathy, PDN = paraproteinaemic demyelinating neuropathy, POEMS - polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy and skin changes, CANOMAD = Chronic Ataxic Neuropathy Ophthalmoplegia IgM paraprotein Cold Agglutinins Disialosyl antibodies

3.4.2 Inherited neuropathies

3.4.2.1 CMT and HNPP

A total number of 362 CMT cases were identified, resulting in an overall PR of 10.52 in ROI (Table 28). Ninety-four cases with CMT were diagnosed by a neurologist at some stage but electrophysiology / genetic tests results were not possible to review and therefore this group was assigned as "unclassified". If we exclude these 94 unclassified CMT cases from the total number of 362 cases with CMT, then the estimated overall PR for CMT is 7.76 (based on a total number of 268 cases). Of the total number of 268 (100%) cases, CMT 1 accounted for 148 (40.8%) cases, CMT 2 accounted for 99 (27.3%) cases and CMT intermediate – for 21 (5.8%) cases, giving a PR of 4.30, 2.88 and 0.61 respectively. Per county, the highest estimated unadjusted PR for CMT was in county Longford (20 – 25 per 100,000) followed by counties Cork, Limerick and Clare (15 – 20 per 100,000) (APPENDIX 6). County Leitrim had no CMT cases identified. Of the total number of 268 (100%) cases with CMT, 88 (32.8%) cases were genetically confirmed. From the total number of 88 (100%) genetically confirmed cases, 68 (77.3%) cases had CMT 1, two (17.6%) cases had CMT 2 and 18 (20.45%) cases had CMT intermediate. *PMP 22* was the most common mutation, 64 (72.7%) cases, then *GJB1,* 18 (20.45%) cases, *MFN2*, 4 (4.5%) cases and *MPZ* with 2 (2.3%) cases (Table 28).

Based on the total number of 29 cases with HNPP, the overall estimated PR for this condition was 0.84. All 29 (100%) cases of HNPP were genetically confirmed. HNPP cases were only found in 10 counties and the highest PRs (2.5 – 4) were encountered in the south-western counties of Kerry and Cork (APPENDIX 6).

3.4.2.2 Other inherited neuropathies

Eight cases of 2 much rarer forms of hereditary neuropathies were identified: dHMN and HMSN 5 giving a PR of 0.12 for each. Neither of these rare inherited neuropathies were genetically confirmed. Seven cases of familial amyloid polyneuropathy (FAP) were found giving an overall PR of 0.2. All 7 (100%) cases of FAP were genetically confirmed.

Table 28 Prevalence of Inherited Neuropathies in ROI

Condition	No. of cases based on clinical diagnosis & electrophysiology type	No. of cases genetically confirmed	PR x 10^5 (95% CI)
CMT			
CMT 1 (demyelinating)	148	68 64 *(PMP22)* 4 *(MFN2)*	4.30 (3.61-5.00)
CMT 2 (axonal)	99	2 *(MPZ)*	2.88 (2.31-3.45)
CMT intermediate	21	18 *(GJB1)*	0.61 (0.35-0.87)
CMT unclassified	94	NA	NA
Total CMT	362	88	10.52 (9.44-11.61)
HNPP	29	29 *(PMP22)*	0.84 (0.54-1.15)
dHMN	4	0	0.12 (0-0.23)
HMSN 5	4	0	0.12 (0-0.23)
FAP	7	7 *(TTR)* c.328C>G;p.His110Asp c.238A>G;p.Thr80Ala	0.20 (0.05-0.35)
All inherited neuropathies	406		11.80 (10.66-12.95)

3.4.3 Kennedy disease

A total number of 14 cases with KD were identified making up a PR of 0.83 (95% CI 0.40-1.27). All cases with KD were genetically confirmed. Per county, the unadjusted PR distribution is illustrated in APPENDIX 7.

3.4.4 Neuromyotonia

For the 5 cases with a diagnosis of neuromyotonia the PR was 0.15 (95% CI 0.02-0.27).

3.4.5 Neuromuscular Junction Disorders

Ten cases of LEMS were identified, 5 cases in each form (with and without associated cancer) giving an overall PR of 0.29 (Table 29). Based on 520 cases, the estimated PR for myasthenia gravis was 15.12. Congenital myasthenic syndrome will be discussed in the next section.

Table 29 Prevalence of neuromuscular junction disorders in ROI

Condition	No cases	ROI study PR x 10^5 (95% CI)
LEMS	10	0.29 (0.11-0.47)
MG	520	15.12 (13.82-16.42)
Total	539	15.67 (14.35-16.99)

3.4.6 Genetic muscle diseases

A total number of 827 cases with GMD were ascertained. These included muscular dystrophies, congenital myopathies, spinal muscular atrophies, metabolic myopathies, skeletal muscle ion channel disorders and congenital myasthenic syndromes. Over two-thirds of these 827 patients fell into six major diagnostic groups: myotonic dystrophy type 1 (DM 1), 232 cases; limb girdle muscular dystrophies (LGMD), 99 cases; dystrophinopathies and facioscapulohumeral muscular dystrophy (FSHD), 89 cases in each group; mitochondrial myopathies (MM), 75 cases; periodic paralysis (PP), 58 cases (Tables 30 - 32).

3.4.6.1 Myotonic dystrophy type I

DM 1 group represented the largest group of GMD cohort representing more than a quarter (28%) of the cohort giving a PR of 6.75. Per county, the highest unadjusted PR (8.4 - 14) was noted in the south-west, counties Cork, Kerry and Clare (APPENDIX 6). Of the total number of 232 (100%) cases, 152 (65.5%) cases had expansion in the *DMPK* gene. For the remaining 80 (34.5%) cases, the diagnosis of DM 1 was based on clinical / electrophysiological features and family history of genetically confirmed DM 1. We did not attempt to do any genotype/phenotype correlation on the individual cases, analyse the size of *DMPK* deletion or look for familial clustering.

3.4.6.2 Limb girdle muscular dystrophies

LGMDs were the second major group of GMD comprising 11 % of the cohort with a combined PR of 2.88. A definite diagnosis was attained in 35 (35.4%) cases of the LGMD group. This leaves quite a large number of 64 patients (64.6%) with as yet undiagnosed LGMD, who clinically showed limb girdle weakness and dystrophic features on muscle biopsy. These patients either tested negative for various protein abnormalities on immunohistochemical analysis/gene mutations or had never been tested for such. Considering only those with a definite diagnosis of LGMDs, 35 cases, LGMD2B (dysferlinopathy) was the most common type, 10 (28.6%) cases, giving a PR of 0.29 for LGMD2B. To date, 6 patients were confirmed with detection of mutations in dysferlin gene and 4 cases have a diagnosis of LGMD2B based on a clinical picture and loss of dysferlin expression in biopsy samples. The next largest group represented laminopathy cases, combining LGMD1B (5 cases) and Emery–Dreifuss MD, autosomal dominant form (EDMD, AD) (5 cases) (listed together in Table 30); both conditions made up a combined PR of 0.29. All laminopathy cases were genetically confirmed.

The other LGMD subgroups were smaller. Four patients with LGMD2A (calpainopathy) and four patients with LGMD2C (gamma-sarcoglycanopathy) gave a PR of 0.12 for each condition. Three patients belonging to one family had a confirmed mutation in the fukutin-related protein *(FKRP)* gene and gave a PR of 0.09 for LGMD2I. Two patients with LGMD1C (caveolinopathy), one patient with LGMD2E (beta-sarcoglycanopathy) and one patient with LGMD2M gave a PR of 0.06, 0.03 and 0.03 respectively. Per county, the PR for LGMDs is

higher in the south-east part of the country with the highest PR (5.56 - 6.94) in counties Cork and Laois (APPENDIX 6).

3.4.6.3 Dystrophinopathies

Dystrophinopathies were the third major group, 89 cases, accounting for 10.8% of the whole GMD cohort, and giving a PR of 2.59. For males only, the PR for DMD and BMD were 3.0 and 2.2, respectively. All dystrophinopathy cases were proven to be in keeping with diagnostic standard by having a deletion, duplication or point mutation in the dystrophin gene.

3.4.6.4 Facioscapulohumeral muscular dystrophy

The cohort of FSHD represented a similar number of cases to dystrophinopathy group (89 cases), giving a PR of 2.59. All cases exhibited signs and symptoms consistent with either a confirmed molecular genetic diagnosis of FSHD or consistent with a pathogenic mutation confirmed within the pedigree. Of the 89 cases, 48 were known to have been genetically confirmed with the presence of a reduction of the microsatellite repeat *D4Z4* on chromosome 4q and one patient had hypomethylation at DR1 domain of *D4Z4* (FSHD2). It is possible, that in many genetically unconfirmed cases the diagnosis was made prior to the genetic era. Per county, the geographical distribution of the PR for muscular dystrophy group and separately for DM 1, FSHD, DMD and BMD is shown in APPENDIX 7.

Other more rare muscular dystrophies

In the oculopharyngeal muscular dystrophy (OPMD) group, there were 10 genetically confirmed cases, giving an overall PR of 0.29. Per county, geographical distribution of OPMD PR figures is illustrated in APPENDIX 7. Only 2 patients have been identified to have congenital muscular dystrophies giving an overall PR of 0.06. Four cases with Bethlem myopathy, the only identified cases belonging to collagen VI-related disorders, gave a PR of 0.12. Three patients from one pedigree with genetically confirmed Emery-Dreifuss muscular dystrophy, X-linked form gave a PR of 0.09.

PR figures for distal myopathies and myofibrillar myopathies are illustrated in Table 30. One pedigree with Laing distal myopathy, diagnosed within the current study period with a novel mutation in *MYH7* gene, gave an overall PR of 0.12 [273]. Three patients with genetically

confirmed desmin-related myofibrillar myopathy gave a PR of 0.03. Seven cases with pure distal myopathy (diagnosis based on clinical symptoms, serum CK, muscle biopsy, neurophysiological examinations +/- muscle MRI) and 16 cases with myofibrillar myopathy (diagnosis based on muscle biopsy findings) lack genetic diagnosis. Diagnostic work-up on many patients/families from the latter 2 groups is ongoing. *TTN, MYOT, ZASP, DES, CRYAB* and *FHL1* gene mutations have been excluded in one pedigree (12 cases) of genetically undetermined cases with myofibrillar myopathy. Genetic tests for the remaining 4 cases with myofibrillar myopathy and 6 cases with distal myopathy, either were not performed or information was not available.

Fourteen patients had an unclassified muscular dystrophy giving a PR of 0.41.

3.4.6.5 Congenital myopathies

Of the CM group (33 cases), nemaline myopathy was the most common form with 0.26. Of the 9 patients with nemaline myopathy, 3 had mutation confirmed within *ACTA1* gene and 1 – in *TPM2* gene. Central core disease was the next common CM, with 8 patients of which 6 patients had mutation confirmed within the *RYR1* gene. One patient with centronuclear myopathy and 2 patients with fibre type disproportion were identified giving a PR of 0.03 and 0.06 respectively (Table 30). Genetic tests for the genetically unconfirmed cases either were not performed or information was not available.

3.4.6.6 Spinal muscular atrophy

SMA group comprised 38 patients giving a combined PR of 1.1 in ROI. Of the 38 cases, only 2 cases (5.3%) were genetically diagnosed with a mutation in the *SMN1* gene; both belonged to the SMA III subgroup. Based on clinical, neurophysiological and histopathology features: 12 patients were diagnosed with SMA III and 3 patients were diagnosed with SMA IV; for the remaining 23 cases (in whom there was incomplete clinical data) a diagnosis of SMA was assigned.

3.4.6.7 Congenital myasthenic syndrome

Nine cases of CMS cases, of which 6 were genetically confirmed (*DOK7* – 3 cases, *CHRNE* – 3 cases), estimated an overall country PR of 0.26. For the 3 genetically unconfirmed cases (probable CMS) in which the diagnosis of CMS was based on clinical and neurophysiology tests, genetic tests were either in progress or results were not available.

3.4.6.8 Mitochondrial disorders with muscle involvement

MM, 75 cases, represented the fifth major group of the GMD cohort. Of the 75 cases, 23 cases were genetically confirmed, giving an overall PR of 2.18. Seventeen cases were found to have pathogenic mtDNA mutations: m.3243A>G (7 cases), m.3243A>G + mtDNA deletion (1 case), multiple mtDNA deletions/rearrangements (9 cases). Six cases had nuclear DNA mutations: *POLG1* (4 cases), *POLG* (1 case) and *PEO/Twinkle* (1 case) (Table 31). Per county, distribution of the PR figures is illustrated in APPENDIX 7.

3.4.6.9 Glycogen storage myopathies

GSM, 17 cases, gave a PR of 0.49. The most frequent was glycogen storage disorder V (GSD V) or McArdle's disease (12 cases) giving an overall PR of 0.35. Eight cases with McArdle's disease were genetically confirmed; the remaining 4 cases were diagnosed based on typical clinical presentation and muscle histology with reduced / absent myophosphorylase reaction. Per county, distribution of the PR for McArdle's disease is illustrated in APPENDIX 7. Myopathies associated with glycogen storage disorder II (GSD II) or late-onset Pompe's disease, glycogen storage disorder IIIB (GSD IIIB) or Forbe's disease and glycogen storage disorder VII (GSD VII) or Tarui disease were identified in 3 patients (1 patient with each condition) giving a PR of 0.03 for each condition. Two cases have been given a diagnosis of undefined GSM according to clinical phenotype, high CK and muscle biopsy findings reported by a consultant neuropathologist (myopathic features with pronounced vacuolar appearance, PAS staining showed large deposits of glycogen, without biochemical evidence of myophosphorlase, phosphofructokinase, myoadenylate deaminase and acid maltase enzymes absence/deficiency).

3.4.6.10 Lipid storage myopathies

Carnitine palmitoyltransferase type II deficiency (CPT II), diagnosed on skin biopsy fibroblast culture, was identified in 1 case, giving a PR of 0.03. Three cases were classified

as undefined lipid storage myopathy (LSM) based on clinical phenotype, high CK and muscle biopsy findings reported by a consultant neuropathologist (vacuolar myopathy filled with lipid droplets on oil red O staining). Further information on non-ischaemic forearm testing, carnitine/acylcarnitine profile and genetic tests either were not performed or were not available.

One genetically confirmed case with Myoadenylate Deaminase (MAD) deficiency was found giving a PR of 0.03.

Table 30 Analysis and prevalence of genetic muscle diseases in ROI and UK

Condition	Northern Ireland 1994[158] 2009[218] PR x 10^5	Northern England 2007[153] PR x 10^5 (95%CI)	ROI 2013 N cases	No cases confirmed by diagnostic standards[153]	ROI 2013 PR x 10^5 (95% CI)
Dystrophinopathies					
Duchenne MD	8.2	8.29 (6.8–9.8)	50	50 *(DMD)*	3.0* (2.33-3.70)
Becker MD	3.2	7.29 (5.9-8.7)	37	37 *(DMD)*	2.20* (1.64-2.88)
Manifesting carrier	0.1	0.43 (0.2-0.7)	2	2 *(DMD)*	0.06 (0-0.14)
Total		8.46 (7.4-9.5)	89	89	2.59 (2.05-3.13)
FSHD	3.1	3.95 (3.2-4.7)	89	48 *(D4Z4)* 1 (hypomethylation at DR1) 13 unconfirmed 27 unknown	2.59 (2.05-3.13)
DM 1	8.4	10.4 (9.3-11.6)	232	152 *(DMPK)*	6.75 (5.88-7.61)
Oculopharyngeal MD		0.13 (0-0.3)	10	10 *(PABPN1)*	0.29 (0.11-0.47)
Limb Girdle MD					
LGMD 1B (+EDMD, AD)		0.20 (0–0.4)	10	10 *(LMNA)*	0.29 (0.11-0.47)
LGMD 1C			2	2 *(CAV3)*	0.06 (0-0.14)
LGMD 2A		0.60 (0.3–0.9)	4	4 *(CAPN3)*	0.12 (0-0.23)
LGMD 2B		0.13 (0–0.3)	10	10 *(DYSF)*	0.29 (0.11-0.47)
LGMD 2C		0.13 (0–0.3)	4	4 *(SGCG)*	0.12 (0-0.23)
LGMD 2E		0.07 (0–0.2)	1	1	0.03 (0-0.09)

LGMD 2M			1	1- *POMGnT1* homoz. miss. mutation c. 1666G>A (Asp556Asn)	0.03 (0-0.09)
LGMD 2I		0.43 (0.2–0.7)	3	3 *(FKRP)*	0.09 (0-0.19)
LGMD unconfirmed		0.64 (0.4–0.9)	64	NA	1.86 (1.40-2.32)
LGMD total	1.1	2.27 (1.7-2.8)	99	35	2.88 (2.31-3.45)
Emery Dreifuss MD, X		0.13 (0-0.3)	3	3 *(EMD)*	0.09 (0-0.19)
Congenital MD					
Muscle-eye-brain			1	1	0.03 (0-0.09)
Merosin deficiency/MDC1A		0.60 (0.3–0.9)	1	1	0.03 (0-0.09)
Bethlem myopathy		0.77 (0.5–1.1)	4	NA	0.12 (0-0.23)
Congenital myopathy					
Nemaline		0.20 (0–0.4)	9	4	0.26 (0.09-0.43)
Central core disease		0.40 (0.2–0.6)	8	3 (*ACTA1)* 1 (*TPM2)* 6 *(RYR1)*	0.23 (0.07-0.39)
Centronuclear myopathy			1	0	0.03 (0-0.09)
Fibre type disproportion			2	0	0.06 (0-0.14)
Unclassified			13	NA	0.38 (0.17-0.58)
Total			33	10	0.96 (0.63-1.29)
Distal myopathy					
Miyoshi		0.1	1	1 *(DYSF)*	0.03 (0-0.09)
Laing			4	4 *(MYH7)*	0.12 (0-0.23)
hIBM/GNE			1	1 *(GNE)*	0.03 (0-0.09)

Unclassified		0.33	7	NA	0.20 (0.05-0.35)
Myofibrillar myopathy					
Desmin		0.17 (0–0.3)	3	3 *(DES)*	0.09 (0-0.19)
Unclassified			16	NA	0.47 (0.24-0.69)
Muscular dystrophy unclassified			14	NA	0.41 (0.19-0.62)
Spinal muscular atrophies (SMA)					
SMA type III		0.64 (0.4–0.9)	12	2 *(SMN1)*	0.35 (0.15-0.55)
SMA type IV			3	0	0.09 (0-0.19)
SMA			23	NA	0.67 (0.40-0.94)
SMA total	1.1	1.87 (1.4–2.4)	38	2	1.10 (0.75-1.46)
CMS	0.6	NA	9	6 *3 (DOK7)* 3 *(CHRNE)*	0.26 (0.09-0.43)

*Males only; NA = unknown or not performed; N = number

Table 31 Prevalence of metabolic myopathies in ROI and internationally

Condition	Spain 2003[246] Australia 1999[242] Spain 2012[152] PR x 10^5	ROI 2013 No cases (diagnosis based on clinical and histopathology features)	ROI 2013 No cases genetically confirmed	ROI 2013 Genetic mutation (no. cases) / biochemical analysis of a muscle biopsy	ROI 2013 PR x 10^5 (95% CI)
Mitochondrial disorders with muscle involvement[246]					
Mitochondrial myopathy	2.7	44	8	• m.3243A>G (4) • m.3243A>G and mtDNA del (1) • *POLG1* c.1760C>T(p.Pro587Leu) and c.752C>T(p.Thr251Ile) (1) • *POLG1* homoz W748S on exon 13 and E1143G on exon 21 (1) • *POLG1* homoz A467T and mtDNA del (1)	1.28 (0.90-1.66)
Mitochondrial myopathy + CPEO	NA	13	5	• m.3243A>G (3) • multiple mtDNA rearrangements (1) • *POLG1* homoz A467T (1)	0.38 (0.17-0.58)
CPEO	2.5	10	5	• mtDNA del (1) • 4977bp mtDNA del (1) • 4408bp mtDNA del (1) • mtDNA rearrangement (1) • *PEO1* (Twinkle) heteroz R 357P (1)	0.29 (0.11-0.47)
CPEO +	0.31	5	2	• mtDNA del (1) • *POLG* compound heteroz p.Ala467Thr (c.1399G>A) and p.Trp748Ser (c.2243G>C) (1)	0.15 (0.02-0.27)
KSS	0.15	3	3	• mtDNA del (2) • 4977bp mtDNA del (1)	0.09 (0-0.19)
Total MM	NA	75	23		2.18 (1.69-2.67)

	Glycogen storage myopathies (GSM)				
GSD II / Pompe's, late onset[242]	0.68	1	NA	NA	0.03 (0-0.09)
GSD IIIB / Forbe's		1	1	NA	0.03 (0-0.09)
GSD V / McArdle's[152]	0.6	12	8	PYGM (8)	0.35 (0.15-0.55)
GSD VII / Tarui's		1	1	NA	0.03 (0-0.09)
GSM undefined		2	NA	NA	0.06 (0-0.14)
Total GSM		17	10		0.49 (0.26-0.73)
	Lipid storage myopathy (LSM)				
CPT II		1	NA	Fibroblast cultures: CPT II deficiency (1)	0.03 (0-0.09)
Neutral LSM		1	NA	NA	0.03 (0-0.09)
LSM undefined		3	NA	NA	0.09 (0-0.19)
MAD deficiency		1	1	AMPD1 homoz mut (1)	0.03 (0-0.09)
Total		98	33		2.85 (2.29-3.41)

Abbreviations: GSD = glycogen storage disorder, MAD = Myoadenylate Deaminase Deficiency, Carnitine Palmitoyl Transferase 2 = CPT II, NA = unknown or not performed

3.4.6.11 Skeletal muscle ion channelopathies

In total, 75 cases with a skeletal muscle ion channel disorder were found giving an overall PR of 2.18. The sixth major group from GMD cohort was periodic paralysis (59 cases) with an overall PR of 1.72 (Table 32). Forty two cases (6 pedigrees and 2 sporadic cases) were identified with Hyper PP giving a PR of 1.25. Two different mutations in *SCN4A* gene were present in 19 cases with Hyper PP (p.Met1592Val - in 5 pedigrees and 1 sporadic case and p.Thr704Met – in 1 pedigree). Twenty-two as yet genetically unconfirmed Hyper PP cases (family members of the 18 genetically confirmed cases) were included in the study based on similar clinical symptoms and family history. One patient with typical Hyper PP presentation and positive family history tested negative for 3 most common *SCN4A* gene mutations and is awaiting sequencing of the entire coding region of *SCN4A* gene.

Hypo PP was identified in 16 cases (2 pedigrees and 6 sporadic cases) giving a PR of 0.44. Two different mutations in *CACNA1S* gene were present in 7 cases (p.Arg528His – in 2 pedigrees and 2 sporadic cases and p.Arg1239His – in 1sporadic case). One sporadic case with Type 2 Hypo PP had p.Arg672His mutation in *SCN4A* gene. Eight genetically unconfirmed Hypo PP patients were included in the study based on similar clinical symptoms and family history of genetically confirmed Hypo PP. One patient with Andersen-Tawil syndrome, diagnosed and genetically confirmed with *KCNJ2* mutation during the present study period, gave a PR of 0.03 [274].

Eleven patients with MC were identified giving an overall PR of 0.32; six had a positive family history. Based on the inheritance pattern and genotype, 3 patients were classified as dominant form (Thomsen's disease), 4 patients were classified as recessive form (Becker's disease) and 4 cases were sporadic. All but one patient with MC from our study have confirmed mutation in *CLCN1* gene. A total of 11 different *CLCN1* gene mutations were detected. Type and frequency of *CLCN1* mutations are illustrated in Table 30. One patient with typical clinical and electrophysiological features of MC, in whom sequencing of exon 4 of *CLCN1* gene was negative, is awaiting results of entire *CLCN1* gene sequencing. Five patients (2 pedigrees and 1 sporadic case) with PMC have been identified giving a PR of 0.15. Two patients belonging to one family have c.3917G>T, p.Gly1306Val mutation in *SCN4A* gene. The remaining 3 patients were labelled as probable PMC by an experienced neurologist, based on clinical phenotype and neurophysiology tests, but were genetically unconfirmed.

Table 32 Prevalence of Skeletal Ion Muscle Channelopathies in ROI and England

Condition	England 2013 PR x 10^5 [151]	ROI 2013 No. cases (pedigrees)	ROI 2013 No. cases genetically confirmed	ROI 2013 Gene mutation (no. cases)		ROI 2013 PR x 10^5 (95% CI)
Periodic paralysis	0.37	59 (9)	28	NA		1.72 (1.28-2.15)
Hypo PP	0.17	16 (2)	8	*CACNA1S*	p.Arg528His (6) p.Arg1239His (1)	0.44 (0.27-0.71)
				SCN4A	p.Arg672His (1)	
Hyper PP	0.13	42 (6)	19	*SCN4A*	p.Met1592Val (17) p.Thr704Met (2)	1.25 (0.94-1.64)
ATS	0.08	1 (1)	1	*KCNJ2*	p.Arg218Trp (1)	0.03 (0-0.15)
Myotonia congenita	0.52	11 (2)	10	*CLCN1*	c.577G>A, p.Glu193Lys (1) c.871G>A, p. Glu291Lys (1) c.1437_1450del (1) p. Arg894X (1) c.811T>C p.C.271R (2) c.562+1G>C (1) c.979G>A (1) c.920T>C, P307S (2) c.1013G>A, p.Arg338Gln (1) c.817G>A, p.Val273Met (1)	0.32 (0.18-0.56)
AD MC		3	NA			
AR MC		4	NA			
Sporadic cases		4	NA			
PMC	0.17	5 (2)	2	*SCN4A*	c.3917G>T, p.Gly1306Val (2)	0.15 (0.06-0.34)
Total	1.12	75 (21)	43			2.18 (1.78-2.65)

3.4.7 Acquired muscle disease

3.4.7.1 Sporadic Inclusion Body Myositis

A total number of 149 cases with sIBM were identified. The PR for sIBM was 11.7 (≥50 year of age). Table 33 illustrates the sIBM PR in ROI and other countries. Per county, the unadjusted PR distribution of sIBM is illustrated in APPENDIX 7 and the age-adjusted PR is illustrated in APPENDIX 3.

Table 33 Prevalence of sIBM in ROI and internationally

Study date [Ref]	Country	Cases	PR X 10^5 (all age) (CI)	PR X 10^5 (> 50 yrs) (CI)
Oflazer et al. 2010 [260]	Turkey	9	0.07	0.4
Badrising et al. 2000 [262]	Netherlands	76	0.5	1.6
Phillips et al. 2000 [263]	Western Australia	17	0.9	3.5
Needham et al. 2008 [264]	Western Australia	31	1.5	5.1
Felice et al. 2001 [265]	USA, Connecticut	35	1.1	2.9 (>45 years)
Wilson et al. 2008 [266]	USA, Minnesota	9	7	nd
Suzuki et al. 2003 [267]	Japan	1255	1	nd
Lefter et al. 2013 (current study)	Ireland	149	4.3 (3.64-5.03) (≥18 years)	11.7 (9.82-13.58)

3.4.7.2 Macrophagic myofasciitis

Two cases with macrophagic myofasciitis gave a PR of 0.06 (95% CI 0-0.14).

3.4.8 All neuromuscular diseases as a group

Based on the total number of both inherited and acquired NMD in our study (excluding GBS cases), the overall PR for the NMD group in the ROI is 62.6 per 100,000 adult population (Table 34). Per county, the geographical distribution of the unadjusted PR for the NMD

group is shown in APPENDIX 7. The highest PR is noted in county Cork (77-87) followed by counties Roscommon and Sligo (67-77) and counties Dublin, Wicklow, Galway and Clare (57-67). For the inherited conditions alone the PR is 36.7.

Table 34 Prevalence of NMDs in the ROI and Northern Ireland

Study (population)	**Inherited PR x 10^5 (95% CI)**	**Inherited & acquired PR x 10^5 (95% CI)**
Current study, ROI (≥ 18 years)	36.7 (34.64 – 38.68)	62.6 (59.95-65.24)
Northern Ireland (all population)[158]	35 (32 – 37)	NA

Chapter 4

Discussion

This 2-year study was the first large, comprehensive, epidemiological study in the ROI investigating both acquired and inherited NMDs in an adult population (≥18 years). Previously, several population based studies have been carried out to investigate epidemiology of a single NMD in all age groups including children; a few looked at both acquired and inherited NMDs but only in children. A comprehensive population-based study involving capture of cases over such a wide geographical area necessitated a thorough approach for case ascertainment.

4.1 Study methodology

In this body of work, care was taken to utilise a number of multiple overlapping sources to achieve as complete as possible case ascertainment in order to accurately estimate the country-wide prevalence of NMD (as described in Methodology). This involved travelling to 24 different institutions/sites in order to optimise case ascertainment.

An obstacle in this study was the non-searchable new patient databases in 2 major hospitals which impeded case identification for the last 3 years at these sites. However, HIPE data crosschecked with medical charts for diagnosis verification and disease classification purposes allowed comprehensive case ascertainment in these 2 hospitals.

High potential for miscoding in HIPE exists highlighting the necessity, albeit laborious, to crosscheck the discharge diagnosis in the medical charts. In all 4 HIPE departments analysed, the majority of cases were coded correctly apart from significant coding errors found in one institution. It was not possible to collect data from one neurology department in a public hospital and one private clinic; however, a substantial number of cases from these sources were identified through other sources such as MDI and neuropathology. Neurology databases and HIPE were the two sources with the highest number of cases identified. Despite the big number overlap between these 2 sources (307), there was still a significant number of unique cases identified in these 2 sources (1008 and 441 respectively) indicating that searching these 2 sources separately was worthwhile.

Another challenge in this study was the need for separate ethics application submission to each hospital/site. Each institution had different requirements and timeframe for ethics approval which rendered the process cumbersome and time consuming. The existence of a unified national ethics committee in the ROI would have circumvented these issues.

Nevertheless, despite the difficulties encountered, the detailed methodology and source data employed in this study, suggests that our data is robust. Moreover, the PR figures from this study are comparable with UK and other international studies suggesting comprehensive case ascertainment.

4.2 Comparison of results with published international studies

4.2.1 Guillain-Barre syndrome

During the last 40 years, most population studies found that GBS is evenly distributed throughout the world, with an annual IR of approximately 1–2 per 100.000 person-years [23]. However, some studies reported a wide variation of IR range between 0.2 and 4.0 thought to be influenced by methodological differences such as small sample size, incomplete retrospective reviews and an underestimation of mild cases not referred to the hospital [29]. The IR for GBS in our study, ranged from 0.3 in early 1990s to a maximum of 1.3 in 2010. This is comparable with a meta-analysis of 13 articles from North America and Europe from 1966–2009 which estimated a crude IR ranging from 0.81 to 1.89 (median, 1.11)[159]. The annual IR remained more or less stable over the 20 year period in the ROI apart from a low IR of 0.3 in 1992 to 1994 and a high IR of 1.3 in 2010. Similar to our study, stable annual IR was found in a large Swedish study [163]. Interestingly, a large study from Netherlands even found a declining IR from 1987 to 1996 [164]. In our study, AIDP was the most common subtype (87% cases). This compares well with data from other Western countries where AIDP accounts for 85–90% of GBS cases [160]. Italian population-based studies found that MFS accounts for 6–7% of total cases of GBS which is very similar to our study (8%) [23]. In our study, like in other previous studies, males were more often affected than females (1.5:1).

4.2.2 Chronic immune-mediated neuropathies

CIDP

Epidemiologic data on CIDP is limited and very little is known about the frequencies of different CIDP subtypes. Previous epidemiological studies have shown variable results which may be attributed to the use of different diagnostic criteria. Using 2006 EFNS/PNS diagnostic criteria, the last published European study (2008) from Leicestershire and Rutland, UK found

a PR of 4.77 which is slightly lower in comparison with the PR from ROI, 5.87 [33]. The results from our study and from above UK study are in-between the extremes of 1 and 7.1 found previously in the south-eastern UK [180] and northern Norway, respectively [181]. Per 100,000, similar PR figures for CIDP associated with paraproteinaemia were found in our study, 0.32 (based on 11 patients), compared with Leicestershire and Rutland, UK study, 0.31 (based on 3 patients). On the other hand, there are some differences in our study findings from the study from Leicestershire and Rutland, UK study. In contrast to our study, where only one case with MADSAM was identified, MADSAM accounted for 15.2% of CIDP patients in UK study giving a PR of 0.73. Also, there were no cases with CIDP associated with malignancy identified in our study whereas 2 patients from this subgroup were identified in UK study.

MMN

Our PR figure for MMN is higher (0.7) in comparison with a recent study from Japan which reported a PR of 0.3. However, detailed epidemiological studies of MMN in other populations have not been performed [184].

4.2.3 Inherited neuropathies

Charcot-Marie-Tooth disease

The overall PR for CMT in our study is 10.52. If we exclude the 94 unclassified CMT cases from the total number of 362 cases with CMT, then the estimated overall PR for CMT is 7.76. Our PR rate is comparable with PR of 9.8 in Northern England but is lower than PR of 15.2 found in in Newcastle upon Tyne [149]. In 1994, the Northern Ireland study estimated a much lower PR of 3.1. The highest PR in Europe was reported in 2011 in Norway: 82.3 [186, 189]. The high PR in Norway may be explained by the relatively isolated genetic population, although figures from Iceland, a neighboring country, shows much lower PR rates. Another explanation could be the use of various methods of ascertainment and selection criteria, and it is believed that family members of index cases were intensively investigated in the Norwegian study [149]. In addition, some of the differences may also be explained by ethnicity where point mutations are probably unevenly spread and some areas may have founder effects. Foley considers that a more realistic minimal PR for CMT in Europe is likely to be 10-28 [149].

In comparison with Northern England study in which a diagnosis of CMT 1, CMT 2 and CMT intermediate was found in 56.7%, 17.6% and 8.7% of cases respectively, in our study, the percentages were 40.8%, 27.3% and 5.8% cases respectively. The CMT 1 frequency in our study is lower and the CMT 2 frequency is higher. From the same Northern England study, where the figures were taken from the inherited neuropathy clinic, Centre for Neuromuscular Disease at the National Hospital for Neurology and Neurosurgery, London, molecular diagnosis was achieved in 62.6% of cases in contrast to our figure of 32.8%. This highlights the need to genetically define this Irish population. Furthermore, only 46% of CMT 1 and 2% of CMT 2 cases achieved genetic diagnosis in our study versus 80.4% and 25.2% respectively from the same inherited neuropathy clinic.

Hereditary neuropathy with liability to pressure palsies

For HNPP, the overall estimated PR of 0.84 in our study is lower than previously reported in Northern England (2.0), Newcastle upon Tyne (7.3) or South West Finland (16).

4.2.4 Kennedy disease

The PR of KD in our study was 0.83 per 100,000 male which is comparable with the PR of 0.6 from Northern Ireland but is lower than the reported PR in Italy, 3.3 per 100,000 male. Suggesting a founder effect, a much higher PR of 15.3 per 100,000 male was reported in Western Finland [196].

4.2.5 Neuromyotonia

For the rare cases of conditions such as neuromyotonia, the PR is not known. Based on 5 cases of of neuromyotonia from our study the estimated PR was 0.15.

4.2.6 Neuromuscular Junction Disorders

LEMS

Ten cases of LEMS gave an overall PR of 0.29 in ROI which was much lower in comparison with previously reported PR of 2.5 in Netherlands [199].

MG

The estimated PR of 15.12 for MG in our study is lower compared with the PR of 20.24 from a comprehensive study from Northern Ireland in 2009 [218]. The Northern Ireland study reported the second highest PR after a study from Serbia which reported the highest yet PR for MG – 31.7 per 100,000 population over 16 years of age. On the other hand, our PR figures are comparable with other countries such as Australia, Italy and Norway which reported a PR ranging between 11.7 and 13.1.

4.2.7 Genetic muscle disease

DM1

DM1 was the most common GMD group in our study. Surprisingly, DM1 PR was lower in our study, 6.75, in comparison with Northern Ireland and Northern England's studies, 8.4 and 10.4 respectively. The high PR figure from Northern England's study reflects rigorous proband's family tracing in an attempt to ascertain all family members potentially at risk of having inherited the condition [153]. The PR in other studies varied widely according to geography ranging from 2 in Japan to 28 in Iceland (Table 20). The highest PR was reported in Quebec, 159; however this high prevalence is due to founder effects.

FSHD

The PR for FSHD in our study was 2.59 (based on 89 cases) which was lower than in Northern Ireland (3.1), Northern England (3.95) and Italy (4.4), based on 50, 118 and 40 cases respectively. In Emery's review from 1991, the PR figures ranged from 0.22 to 6.69.

Dystrophinopathies

Not surprisingly, in comparison to our study which reported a PR of 3 for DMD, both Northern Ireland's and Northern England's studies which included children as well, reported a much higher PR of 8.2 and 8.29 per 100 000 males respectively. For BMD, in the 2 UK studies, the PR was higher, 3.2 and 7.2, versus 2.2 in our study.

The study from Western Sweden reported PR figures of 16.8 for DMD and 1.6 for BMD per 100 000 males under 16 years. The higher PR for DMD in the paediatric population in the past is probably a more accurate illustration for this group although rising life expectancy will have increased the PR in our current population.

LGMD

Of the total number of 827 patients with GMD in our study, 99 were found to be LGMDs giving a PR of 2.88. Several studies reported frequencies of various LGMD subtypes in their patient populations while others concentrated on a specific subtype. In Northern England study, using immunohistochemical analysis and genetic analysis, Norwood and colleagues analyzed 68 LGMD patients and were able to classify 72% of cases [153]. In their study, calpainopathy (LGMD2A) was the most frequent LGMD type (26.5 % of the total) followed by LGMD2I (19.1% of the total). In our study, dysferlynopathy was the most common type (28.6% of the total LGMD with a definite diagnosis) followed by laminopathy. A study from Netherlands was able to classify 51% of LGMDs into a definite subtypes of which like in the UK study calpainopathy was the most frequent diagnosis affecting 21% of the families [226]. On the other hand, a low PR of LGMD2A was reported in Denmark where the authors estimate to be 5- to 6-fold lower in ethnic Danes compared with other European countries [275]. Conversely, a Danish study showed a high proportion of LGMD2I (38% of LGMD2-classified patients) [225]. The PR of LGMD2I in UK was close to the Danish study perhaps indicating previous migration from Denmark to Northern England [153]. An Italian study reporting 181 LGMD patients (155 families) was able to confirm a diagnosis in 72.9% of cases [276]. In their cohort, calpainopathy was the most common group (28.4% of families) followed by dysferlinopathy (18.7% of families) and the combined sarcoglycanopathies (18.1% of families). The reported frequency of dysferlinopathy varied among the study populations. In Norwood study, these represented only 5.9% of LGMD cases in keeping with the similar low frequency in the Dutch LGMD population [226] whereas higher frequencies, 18.7% and 18%, were reported in the Italian and USA population respectively [276, 277]. Although these studies had different results when compared with our study, a true comparison is not possible due to the high proportion of unclassified cases in our study (64.6%). This is to be contrasted with a proportion of 27.9% – 51% of patients with unclassified LGMD in the above mentioned international studies. However, of importance is the fact that the above studies were performed in specialized neuromuscular centres with easy and direct access to immunohistochemistry and genetic laboratory testing. Potential other reasons for a high proportion of unclassified LGMDs were: lack of access to neurologists as until recently the ROI had a small number of neurologists (i.e., long waiting lists) and lack of easy access to a specialised neuromuscular clinics. Moreover, in recent years, the available diagnostic methods for LGMDs have changed dramatically. These points highlight the fact that there is much work to be done in order to

accurately classify these patients. With future work-up, it is probable that many of the currently unclassified LGMD cases in the current study will achieve a definite diagnosis.

Other more rare muscular dystrophies

Epidemiological data for many of the rarer GMD is scarce. Only 3 cases of X-linked Emery–Derifuss muscular dystrophy were identified in our study giving a PR of 0.09 which is lower than in Northern England study, 0.13. The PR of myofibrillar and distal myopathies is largely unknown. Of the GMD group (827 cases) in our study, only 1.6% patients were found to have a distal myopathy and 2.3% a myofibrillar myopathy. Ten cases with OPMD were ascertained in our study giving a PR of 0.29 which is higher than in Northern England study, 0.13 but lower than in France, 1 and French-Canadians from Quebec, 10.

Congenital myopathies

In our study, CM PR was 0.96 and NM was the most frequent type followed by CCD. Higher PR was reported in Northern Ireland (1994) and Northern England (2007), 3.5 and 1.37 respectively. Not surprisingly, two paediatric studies from Western Sweden (2000) and Michigan, US (2011) reported higher PR of 5 and 3.8 respectively [228]. In both studies from Northern England and Michigan, CCD was the most common type whereas in study from Western Sweden, NM was the most common.

Glycogen storage myopathies

The most common GSM in our study was McArdle disease with an estimated PR of 0.35. The PR estimate of McArdle disease is generally not well known. A recent Spanish study, the only study reporting PR figures based on a well-defined cohort, reported a higher PR of 0.6 [152].

Myopathies associated with a treatable GSD such as (GSD II) or late-onset Pompe's disease (by definition, presenting after 1 year of age) were identified only in one patient in our study. Precise numbers on the frequency of Pompe disease in the general population are not available and frequency estimates vary between different clinical forms and different ethnic groups. For example, in 1999, based on the calculated carrier frequencies of the 3 common mutations in Dutch neonates, the predicted frequency of LOPD was 1 per 57, 000 [242]. A much lower PR of 1 per 146,000 was estimated for LOPD in Australian population [241, 242]. However, data from population based studies on the PR of LOPD is not available. The

low PR in our study could be explained by the possibility that this condition is extremely rare in our ethnic group or by the fact that we excluded the paediatric population.

Mitochondrial disorders with muscle involvement

Even though once believed to be rare, increasing evidence suggests that mitochondrial disorders are rather common disorders. In our study, mitochondrial myopathies (MM) represented the fifth major group of the GMD cohort comprising 75 cases giving an overall PR of 2.18 per 100,000 adult population. The Finnish study estimated a PR of 16.3 per 100,000 adult population of the A3243G mtDNA mutation encompassing the entire clinical spectrum of mitochondrial disorders [244]. In comparison, a study from Northern England (which included mitochondrial DNA disease only) found a PR of 9.2 per 100,000 adults of working age (16-60 years) but no specific figures for myopathy were reported [245]. However, the aim of our study was to capture only cases with muscle involvement as part of a mitochondrial disorder. Therefore, the Spanish study from 2003 (the only study identified to report on PR of certain phenotypes such as mitochondrial myopathies and CPEO), was used for comparison of figures with our study. PR figures for MM and CPEO were lower in our study (1.28 and 0.29 respectively) when compared with figures found in Spanish population over 14 years of age (2.7 and 2.5 respectively) [246].

There are no published epidemiological data for the rarer metabolic myopathies such as Tarui and Forbe's diseases, CPT II and myoadenylate deaminase deficiency.

Skeletal muscle ion channelopathies

An overall PR of 2.18 was estimated for SMIC group. This figure is higher than in the recent English study which reported a PR of 1.12 [151]. Interestingly, based on the 58 cases (8 pedigrees) found in this work, the overall PR for periodic paralysis (PP) only in the ROI is nearly five times higher in comparison with the PR from England: 1.69 vs 0.37. Of the PP cohort in this study, the Hyper PP group (71.2% cases) was larger than Hypo PP group (27.1% cases). These findings differ from English study where Hypo PP was the largest group of the PP cohort (44% - Hypo PP cases and 35.4% - Hyper PP cases). However, it is fair to mention that the high PR figures in our study are based on large families with Hyper PP probably reflecting a founder effect.

Forty two cases (6 pedigrees) with Hyper PP were found giving a PR of 1.25 for ROI which again was higher than the PR of 0.13 from England [151]. Two different mutations in *SCN4A*

gene were present in 19 cases with Hyper PP (p.Met1592Val and p.Thr704Met) in comparison with six different SCN4A mutations found in the larger English cohort (77 cases). The PR for Hypo PP was 0.44 which is similar to the PR from 1992 in Finland but higher in comparison with English PR of 0.17 from 2012. High PR of 1 and 1.7 were previously reported in Japan and Spain; however, these predate the genetic testing era. Two different mutations in *CACNA1S* gene (p.Arg528His and p.Arg1239His) and one in *SCN4A* gene (p.Arg672His) were found in our study whereas a total of 5 different CACNA1S and 9 SCN4A mutations were detected in the English cohort. The small variety of mutations in our study reflects the small cohort size where large families harboured similar mutations; this could suggest a founder effect. One patient with ATS, harbouring a *de novo* mutation, gave a PR of 0.03 for the ROI. Based on 40 cases, the English study (the first study reporting the PR for ATS) reported a higher PR of 0.08.

In comparison to the English study, we estimated a lower PR for non-dystrophic myotonia: 0.75 vs 0.47. A higher PR of 1.1 was reported in Northern Ireland in 1994. The paediatric study from Western Sweden reported a PR of 2.2. If we included paediatric population in our study, the PR rates would be higher. In our study, based on a total number of 11 patients with MC identified, in which 11 different *CLCN1* gene mutations were detected, the overall PR for ROI is 0.32. The study from England analysed 277 cases, in which 15 different *CLCN1* gene mutations were detected, giving a higher PR of 0.52. Studies from Northern Finland and Northern Scandinavia, reported even higher PR rates, 7.3 and 9.0; however, these areas were found to have an unusually high population frequency of mutations due to founder effects [247, 248, 278]. In our study, autosomal recessive cases outnumbered the dominant ones just by one case. This is similar to other 2 previous studies in Northern Scandinavia where autosomal recessive cases were predominant [247, 248]; however, equal numbers of both types of MC were noted in the English study. Five patients with PMC from our study gave a PR of 0.15. The findings from the present study are consistent with those from England (0.17) but are much lower in comparison with Swedish paediatric cohort (1.1). However, the findings from England would be more accurate as the estimation was based on a big cohort of 88 cases whereas those from Sweden were based on 4 patients only.

It is noteworthy that while undertaking this study, we attained genetic confirmation for families with rare genetic muscle conditions, previously unreported in ROI, including Laing distal myopathy *(MYH7),* Andersen Tawil syndrome *(KCNJ2)* and FSHD2 (hypomethylation of *D4Z4*, *DR1* domain) [273, 274]. Interestingly, this research project did not yield any patients

with other rare conditions such as DM2 / proximal myotonic myopathy (PROMM) and only one patient with late onset Pompe disease was found. It may be the case that the PR for these conditions varies geographically in different countries and they may be absent or extremely rare in Ireland.

4.2.8 Acquired muscle disease

Sporadic inclusion body myositis

In our study, for sIBM in those greater than 50 years of age, the PR was 11.7 which significantly exceeds the previously reported PR ranging between 0.4 to 5.1 per 100,000 in Turkey, Netherlands, USA and Australia (Table 31). The higher figures in our study probably reflects recent increased awareness of the disease, better diagnostic modalities and a more comprehensive case ascertainment.

Macrophagic myofasciitis

Based on 2 cases of macrophagic myofasciitis found in the present study the estimated PR was 0.06. A group from France reviewed the files of 457 adults with MMF collected over 17 years in the Neuromuscular Centre of Créteil; however its PR was never reported [147].

4.2.9 All neuromuscular diseases as a group

In this study, the PR figure for all inherited and acquired NMD groups was 62.6 and for inherited conditions alone 36.6. Our combined PR figure for inherited NMD compares well with previous population studies. In 1991, Emery estimated the inherited NMD PR as exceeding 33.3 [224]. In 1994, the figure for inherited NMDs from Northern Ireland study was 34.5. In 2009, the study Northern England reported a PR of 37 for GMDs only. The paediatric study from Western Sweden produced an inherited NMD PR figure of 53.1. The higher PR from this age population would be explained by the inclusion of conditions more prevalent in childhood such as DMD, CM and SMA. By analysing our study findings in the adult population together with findings from the Swedish study including children only, one could posit that if we were to include paediatric population in our study, our PR figures would exceed the rate of 110 per 100,000 all age population.

In this work, in 46% of all inherited NMDs cases and in 52% of all GMD cases, the clinical diagnosis was confirmed by diagnostic standard (histopathology/genetic) tests. In both

studies from Northern Ireland and Sweden, the number of cases definitely confirmed by genetic analysis is not stated. In the Northern England's study where they did not include GMDs such as skeletal ion muscle channel disease and metabolic myopathies in contrast to our study, a definite diagnosis was achieved in 75% of cases. The low figures from our study point to where we can do better and that future emphasis must be placed on improving awareness, resources and easy access to genetic testing to achieve a definite diagnosis. We would expect that the figures from our study will increase in the future with the increasing awareness and new genetic screening technologies.

4.2.10 Comparison of NMD with other chronic neurological conditions

There is a common misperception that NMD are rare which is not true based on findings in this research study. If we compare the combined PR of NMD from our study with PR of other chronic neurological diseases in Ireland such as multiple sclerosis and Parkinsons disease, our study findings demonstrate that NMD are a relatively common group of chronic diseases (Table 35). This information will be invaluable when advocating for increased recourses for patients with NMDs.

Table 35 Prevalence comparison of NMD with other chronic neurological conditions in ROI

Condition	PR x 10^5
Neuromuscular Diseases	62.6
Multiple Sclerosis[279]	128 - 290
Parkinson's disease	100 - 180

4.2.11 Geographical distribution of NMDs in ROI

Ireland is an island country in which about a quarter of the population lives in Dublin and the surrounding area followed by a further concentration in the cities of Cork, Galway and Limerick. Outside of these urban areas, the population density varies from county to county depending on the extent of the rural economy.

The main purpose of the PR mapping was to show the burden of various NMDs in ROI and thus was unadjusted for age.

Looking at the geographical spread illustrated in the maps, there was an even spread for majority of the acquired NMDs conditions such as CIDP and myasthenia gravis. For many inherited conditions, the PR was patchy across the country for a number of reasons such as probable uneven spread of mutations and founder effects in some areas. For example, the PR for periodic paralysis was higher in the South which may be due to the founder effect of a large family with Hyper PP originally described by Kelly et all [280]. For some rare conditions such as OPMD, Kennedy disease and McArdle disease, due to small numbers, the spread of the data was not possible to analyse. Interestingly, for DM 1 and CMT, there was a higher PR found on the western seaboard and southwest of the country respectively. On the other hand, in some counties DM 1 cases were not identified which may reflect familial clustering. In order to further investigate the differences in spread of these conditions, further research is needed with regard to detailed pedigree tracing and looking for founder mutation.

For sIBM, the PR was calculated focusing on the population at risk for this condition, i.e. ≥ 50 years. In addition, age-adjusted PR was calculated for all counties (APPENDIX 3). For most counties the age adjusted rate is not much different from the crude rate. There are a few exceptions, for example the rate for Sligo, Cavan and Mayo is 12%, 12% and 10% lower, respectively, after being standardised whereas the rate for Kildare, Meath and Wicklow is 20%, 18% and 16% higher after standardisation, respectively. This probably reflects the possibility that Sligo, Cavan and Mayo have a relatively old population whereas Meath, Kildare and Wicklow, all satellite counties around Dublin, have relatively younger populations. However, in view of the small numbers of sIBM cases and widespread variation in the rate across the counties, drawing firm conclusions from this inter-county age adjustment analysis in population greater than 50 years is difficult.

With regard to the spread of all NMDs as a group, there was no dramatic difference in the PR in different counties. There was a higher PR in certain counties in the South of ROI which could be explained by the effect of family grouping for some conditions as discussed above.

For all NMDs as a group in ROI, there was a higher PR in county Cork as compared with Dublin. One would consider whether referral bias plays a role here reflecting the proximity to the specialised neuromuscular centres in the cities of Cork and Dublin. If one was invoking referral bias as a significant confounder, one would expect the PR figures to be higher in Dublin (greater population of 1.5 million) but this was not the case in our study.
As another example, after county Cork, counties Sligo and Roscommon had the second highest PR of NMDs as a group. Both Sligo and Roscommon are remote from neuromuscular clinics and are rural counties relatively sparsely populated, again arguing against referral bias as a major player resulting in the differences in PR.

4.3 Strengths and limitations

This is the first and only study revealing the prevalence of adult NMDs not only in ROI but internationally. In contrast to previous studies which either focused on individual conditions or groups of conditions, this is the first study estimating the combined PR of a broad spectrum of both acquired and inherited NMDs. In addition, many previous studies focused on their clinic population whereas this was a population-based study focusing both on the neuromuscular/neurology clinic population and the general population. One of the main strengths of this population-based epidemiologic study is it's prospective and retrospective design. Another important strength was usage of multiple overlapping case ascertainment sources in order to capture fully all the cases existing in the adult Irish population. Also, the input of the patients support group, Muscular Dystrophy Ireland, was very useful in sourcing cases which are currently not attending neurology services and might otherwise have been missed.

As this was an adult study, paediatric cases were not included. Indeed, the way the service is provided in the ROI is that there is a division between paediatric and adult services with a resultant division in the neurologists (paediatric versus adult) who look after these cases. This study aimed to estimate the burden of cases that adult neurologists encounter in their practice in the ROI. This factor (studying adults only) might cause underestimation of the

frequency and distribution of some NMDs groups especially for paediatric prevalent conditions such as DMD and BMD. However, as none of the previous studies analysed the PR of these conditions in an adult population, our study information contributes very meaningfully to the literature in this area and will be an invaluable resource when planning adult neuromuscular care services in ROI.

This study was not designed to include all of the mitochondrial cytopathy cases. Only patients who had muscle involvement as a feature of mitochondrial disease were included. Therefore, this is a limitation of this study as is it was not designed to accurately estimate the PR of all mitochondrial disorders but rather focused on clinical mitochondrial involvement of the muscle. In addition, case ascertainment in many cases relied on clinic letters and the precise DNA diagnosis was not available. Furthermore, detailed pedigree tracing was not undertaken and no attempt to define those at risk was made. The purpose of this study was to estimate the PR and burden of various NMDs in ROI which would serve as a starting point for more targeted studies in the future.

As the main purpose of the PR mapping per each county was to show the burden of these conditions across the country and apart from sIBM, no attempt was made to correct for differences in the age spectrum to look for inter-county variation. Inter-county age adjusted PR analysis for many separate conditions in this study is not feasible as the number of cases is very small. Furthermore, as many conditions occur at different ages, an analysis like this cannot be performed for all NMDs as a group. This would be possible for other conditions with sufficient number of cases such as MG or CIDP but, in our study, because of missing data for some cases (age and county patient lives in) this was not possible.

Finally, new non-searchable patient databases in some hospitals and inability to collect data in one major hospital might have caused an underestimation of the true numbers. However, I believe that this underestimation to be minimal as these cases were likely captured through other sources such as HIPE, Neurophysiology and Neuropathology departments and Muscular Dystrophy Ireland. This study methodology and source data, together with its comparable figures with international figures, suggest that our data is robust and is as close as we could get to the true figures reflecting comprehensive case ascertainment.

4.4 Current relevance and future directions

Current relevance

This study reveals for the first time the prevalence of adult NMDs reflecting the burden of these conditions in ROI and allows comparison with the results from international studies. It demonstrates that NMDs are not as rare as previously thought and raises the awareness of these conditions. The number of undefined genetic cases identified highlights the work that needs to be done in the future. Undoubtedly, the data from this study will aid in advocating for resources for NMD patients in ROI.

Future directions

The data obtained in this study will serve as a starting point for future research studies, e.g., obtaining genetic confirmation of currently undefined cases. It will serve as a basis for setting up future disease registries for NMDs in ROI and will help in planning special care programs for these patients.

Chapter 5

Conclusion

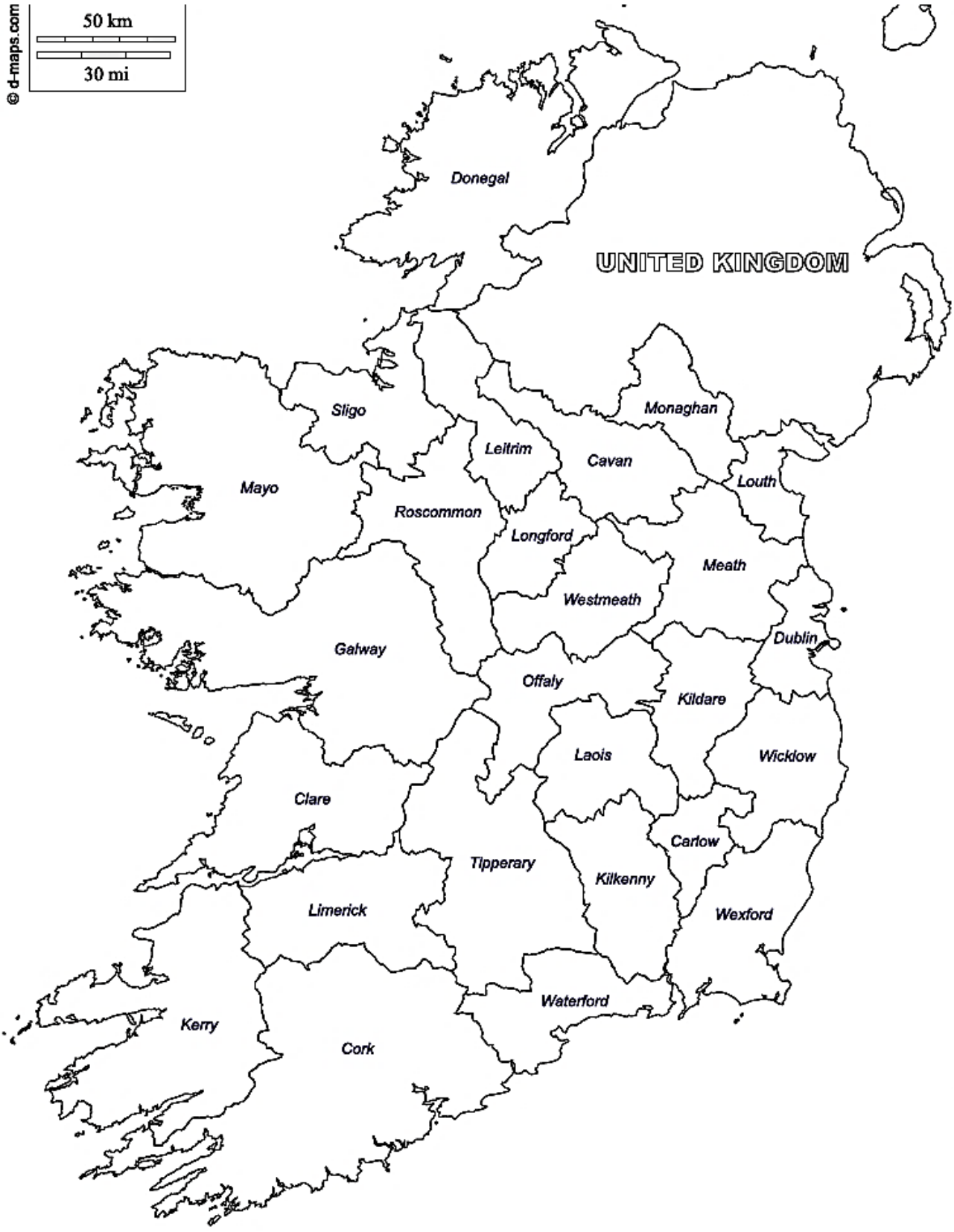
This body of work reveals for the first time the prevalence (PR) of adult NMDs in the ROI. This is the first reported epidemiological study investigating both acquired and inherited NMD in adults in ROI. PR data was calculated for conditions such as CIDP, sIBM, Kennedy disease and genetic metabolic myopathies such as mitochondrial myopathies and McArdle's disease, rare NMDs for which heretofore limited or no data was available. Furthermore, for the first time, PR figures are reported for rare conditions such as neuromyotonia and macrophagic myofasciitis (world-wide) and for MMN (in European population).

Interestingly, it was found that there was no significant difference between the proportions of acquired and inherited NMD cases, 52.3% versus 47.7%. In the paediatric population, these figures would be skewed towards inherited cases highlighting the importance of conducting such a study in an adult population only. Overall the data showed that the PR figures from this work compare favourably with international studies with similar rates for GBS and in many cases similar PR rates for most of the inherited and acquired NMDs. Some of the interesting differences identified in this study included higher PR rates for CIDP, sIBM and periodic paralysis. The proportion of unclassifiable LGMD and unclassified CMT cases is quite high emphasizing that more work needs to be done in this regard.

This comprehensive population-based study capturing country-wide cases resulted in invaluable data previously unavailable in the ROI. Despite the common belief that NMD are rare, the results of this study demonstrated a high PR for all NMD group of 62.6 per 100,000 adult population in the ROI. If we compare the combined PR of NMD from our study with the PR of other chronic neurological diseases, it is clear that NMD is a relatively common group of disorders. The results of this study will be instrumental when advocating for increased resources for NMD patients in the future as well as serving as a starting point for future research studies.

APPENDICES

APPENDIX 1 Map of Republic of Ireland (26 counties)



APPENDIX 2 Per county, number of adult population in ROI

(CSO, Census 2011)

County	No. male (≥18 years)	No. female (≥18 years)	All population (≥18 years)	All population (≥50 years)
Carlow	20187	20286	40473	14954
Cavan	26628	26361	52989	20768
Clare	42796	43734	86530	35099
Cork	191741	198843	390584	146697
Donegal	58065	59340	117405	48386
Dublin	473030	512781	985811	329815
Galway	93428	96031	189459	69163
Kerry	54976	55586	110562	48123
Kildare	74035	76828	150863	47735
Kilkenny	34918	35486	70404	27915
Laois	29005	28622	57627	20036
Leitrim	11980	11767	23747	10606
Limerick	72153	73589	145742	55334
Longford	14177	14230	28407	11557
Louth	43843	45762	89605	32262
Mayo	48802	49322	98124	44269
Meath	64429	66306	130735	43133
Monaghan	22176	22276	44452	17546
Offaly	27547	27991	55538	21351
Roscommon	24219	23770	47989	21226
Sligo	24361	25491	49852	20933
Tipperary	58723	59271	117994	48965
Waterford	41674	43213	84887	33807
Westmeath	31067	32045	63112	23408
Wexford	52093	54385	106478	42624
Wicklow	48864	51332	100196	37375
Total	1684917	1754648	3439565	1273087

APPENDIX 3 Per county, sIBM age adjusted PR in population ≥50 years

Per county, sIBM age adjusted PR calculation in population ≥50 years of age in ten year age bands																					
Number of population ≥50 years of age						Number of sIBM cases					Non-adjusted PR					Age-adjusted PR				Total age-adjusted PR	Difference between adjusted & non-adjusted PR
County	50-59	60-69	70-79	80+	Total	50-59	60-69	70-79	80+	Total	50-59	60-69	70-79	80+	PR	50-59	60-69	70-79	80+		
Carlow	6163	4616	2711	1464	14954	0	0	1	1	2	0.0	0.0	368.9	683.1	133.74	0.00	0.00	67.58	68.96	136.54	-2.79
Cavan	8378	6238	3765	2387	20768	0	0	0	1	1	0.0	0.0	0.0	418.9	48.15	0.00	0.00	0.00	42.30	42.30	5.86
Clare	14164	11357	6147	3431	35099	1	0	0	1	2	70.6	0.0	0.0	291.5	56.98	28.78	0.00	0.00	29.43	58.20	-1.22
Cork	59370	44945	27478	14904	146697	8	4	8	2	22	134.7	89.0	291.1	134.2	149.97	54.92	27.43	53.34	13.55	149.24	0.73
Donegal	18471	15442	9195	5278	48386	0	1	1	2	4	0.0	64.8	108.8	378.9	82.67	0.00	19.96	19.92	38.26	78.14	4.53
Dublin	134821	99365	62247	33382	329815	4	6	20	17	47	29.7	60.4	321.3	509.3	142.50	12.09	18.61	58.86	51.41	140.98	1.52
Galway	28377	21111	12385	7290	69163	0	2	4	0	6	0.0	94.7	323.0	0.0	86.75	0.00	29.20	59.17	0.00	88.37	-1.62
Kerry	18673	15373	9024	5053	48123	0	2	2	1	5	0.0	130.1	221.6	197.9	103.90	0.00	40.10	40.60	19.98	100.68	3.22
Kildare	22395	15020	6757	3563	47735	1	0	2	1	4	44.7	0.0	296.0	280.7	83.80	18.20	0.00	54.22	28.34	100.76	-16.96
Kilkenny	11503	8567	4977	2868	27915	1	2	1	1	5	86.9	233.5	200.9	348.7	179.12	35.43	71.96	36.81	35.20	179.41	-0.29
Laois	8603	5997	3502	1934	20036	0	0	0	0	0	0.0	0.0	0.0	0.0	0.00	0.00	0.00	0.00	0.00	0.00	0.00
Leitrim	4167	3139	2034	1266	10606	0	0	1	0	1	0.0	0.0	491.6	0.0	94.29	0.00	0.00	90.07	0.00	90.07	4.22
Limerick	22339	17375	10300	5320	55334	0	4	0	1	5	0.0	230.2	0.0	188.0	90.36	0.00	70.96	0.00	18.98	89.94	0.42
Longford	4616	3691	2084	1166	11557	0	0	0	0	0	0.0	0.0	0.0	0.0	0.00	0.00	0.00	0.00	0.00	0.00	0.00
Louth	13264	10009	5835	3154	32262	0	0	1	1	2	0.0	0.0	171.4	317.1	61.99	0.00	0.00	31.40	32.01	63.41	-1.41
Mayo	16990	13777	8368	5134	44269	0	0	1	2	3	0.0	0.0	119.5	389.6	67.77	0.00	0.00	21.89	39.33	61.22	6.55
Meath	19199	13526	6877	3531	43133	0	0	4	2	6	0.0	0.0	581.6	566.4	139.10	0.00	0.00	106.56	57.18	163.74	-24.64
Monaghan	7046	5371	3215	1914	17546	0	0	1	0	1	0.0	0.0	311.0	0.0	56.99	0.00	0.00	56.98	0.00	56.98	0.01
Offaly	8775	6537	3892	2147	21351	0	1	0	1	2	0.0	153.0	0.0	465.8	93.67	0.00	47.15	0.00	47.02	94.18	-0.50

Roscommon	8299	6388	3953	2586	21226	0	0	2	0	2	0.0	0.0	505.9	0.0	94.22	0.00	0.00	92.69	0.00	92.69	1.54
Sligo	8262	6448	3823	2400	20933	0	0	0	2	2	0.0	0.0	0.0	833.3	95.54	0.00	0.00	0.00	84.13	84.13	11.41
Tipperary	19364	15065	9229	5307	48965	0	1	0	1	2	0.0	66.4	0.0	188.4	40.85	0.00	20.46	0.00	19.02	39.48	1.36
Waterford	13301	10550	6554	3402	33807	1	4	3	1	9	75.2	379.1	457.7	293.9	266.22	30.64	116.87	83.86	29.68	261.05	5.17
Westmeath	9722	6988	4229	2469	23408	0	1	0	0	1	0.0	143.1	0.0	0.0	42.72	0.00	44.11	0.00	0.00	44.11	-1.39
Wexford	16911	13518	8255	3940	42624	1	0	2	0	3	59.1	0.0	242.3	0.0	70.38	24.10	0.00	44.38	0.00	68.49	1.90
Wicklow	15735	12011	6390	3239	37375	0	0	0	3	3	0.0	0.0	0.0	926.2	80.27	0.00	0.00	0.00	93.51	93.51	-13.24
Total	518908	392424	233226	128529	1273087	17	28	54	41	140	32.8	71.4	231.5	319.0	109.97	13.35	21.99	42.42	32.21	109.97	0.00

APPENDIX 4 Per county, number of Irish population in ten year age bands

(CSO, Census 2011)

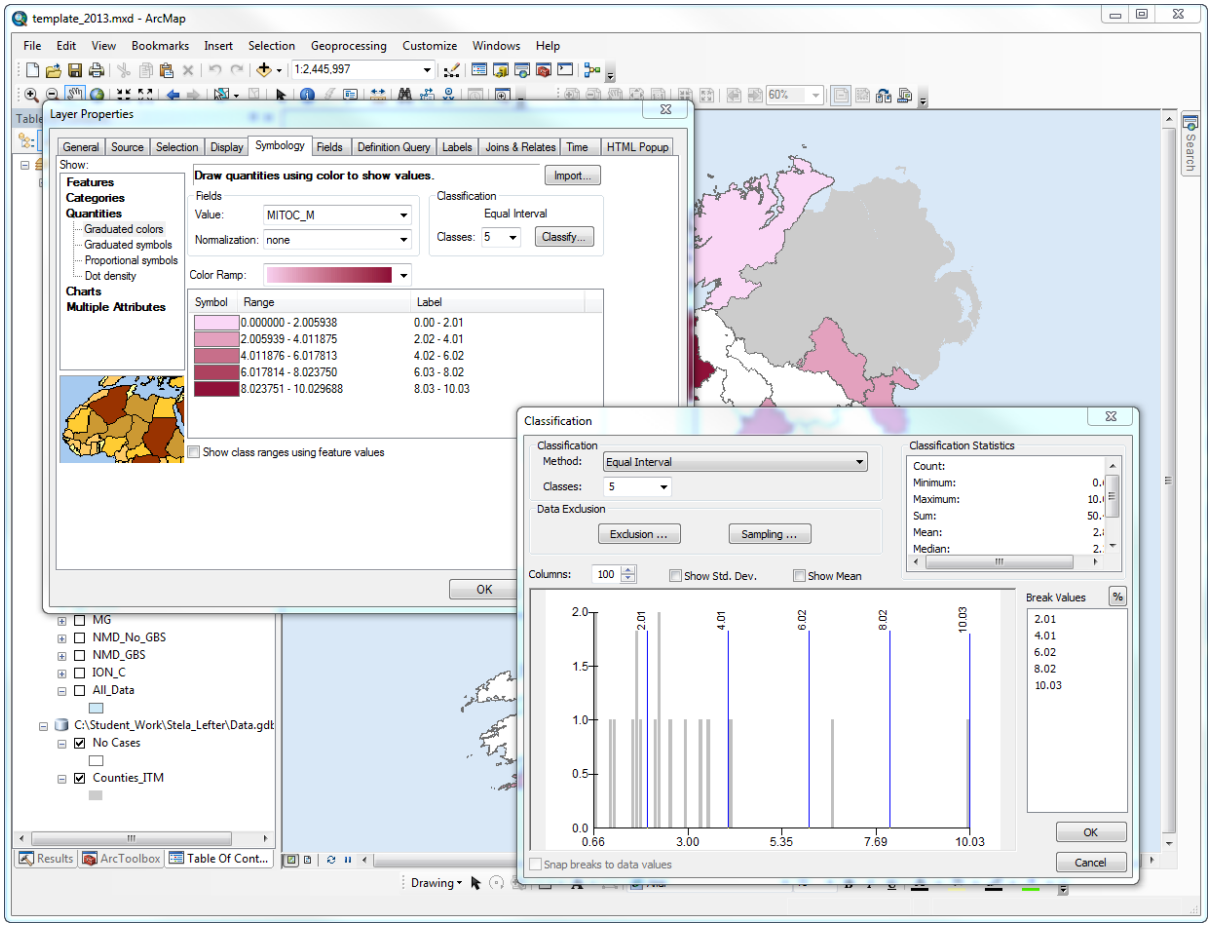
County	0-9	10-19	20-29	30-39	40-49	50-59	60-69	70-79	80+	Total
Carlow	8446	7093	7715	8874	7530	6163	4616	2711	1464	54612
Cavan	11706	10109	9239	11211	10150	8378	6238	3765	2387	73183
Clare	17629	15760	13772	17823	17113	14164	11357	6147	3431	117196
Cork	75724	65756	72837	84934	73084	59370	44945	27478	14904	519032
Donegal	24943	22544	19400	23573	22291	18471	15442	9195	5278	161137
Dublin	172049	148425	223010	231474	168296	134821	99365	62247	33382	1273069
Galway	36316	31793	37143	42015	34223	28377	21111	12385	7290	250653
Kerry	19639	18444	17211	21559	20526	18673	15373	9024	5053	145502
Kildare	36254	28532	29290	37648	30853	22395	15020	6757	3563	210312
Kilkenny	14426	12854	11581	15196	13447	11503	8567	4977	2868	95419
Laois	14146	10433	11023	13664	11257	8603	5997	3502	1934	80559
Leitrim	4750	3907	3456	4698	4381	4167	3139	2034	1266	31798
Limerick	26720	25277	28906	30137	25435	22339	17375	10300	5320	191809
Longford	6315	5101	4875	5865	5287	4616	3691	2084	1166	39000
Louth	19918	16325	16892	19929	17571	13264	10009	5835	3154	122897
Mayo	18302	17181	14998	17915	17973	16990	13777	8368	5134	130638
Meath	32997	24533	22949	33026	27497	19199	13526	6877	3531	184135
Monaghan	9260	8195	7964	9256	8262	7046	5371	3215	1914	60483
Offaly	12169	10740	9843	11791	10793	8775	6537	3892	2147	76687
Roscommon	9175	8186	7384	9132	8962	8299	6388	3953	2586	64065
Sligo	8790	8698	8738	9364	8870	8262	6448	3823	2400	65393
Tipperary	23159	21218	19285	23667	22460	19364	15065	9229	5307	158754
Waterford	16778	14878	14665	17492	16175	13301	10550	6554	3402	113795
Westmeath	13271	11901	11834	13572	12178	9722	6988	4229	2469	86164
Wexford	22564	19526	17428	22261	20917	16911	13518	8255	3940	145320
Wicklow	21653	18101	16915	22130	20466	15735	12011	6390	3239	136640
Total	677099	585510	658353	758206	635997	518908	392424	233226	128529	4588252

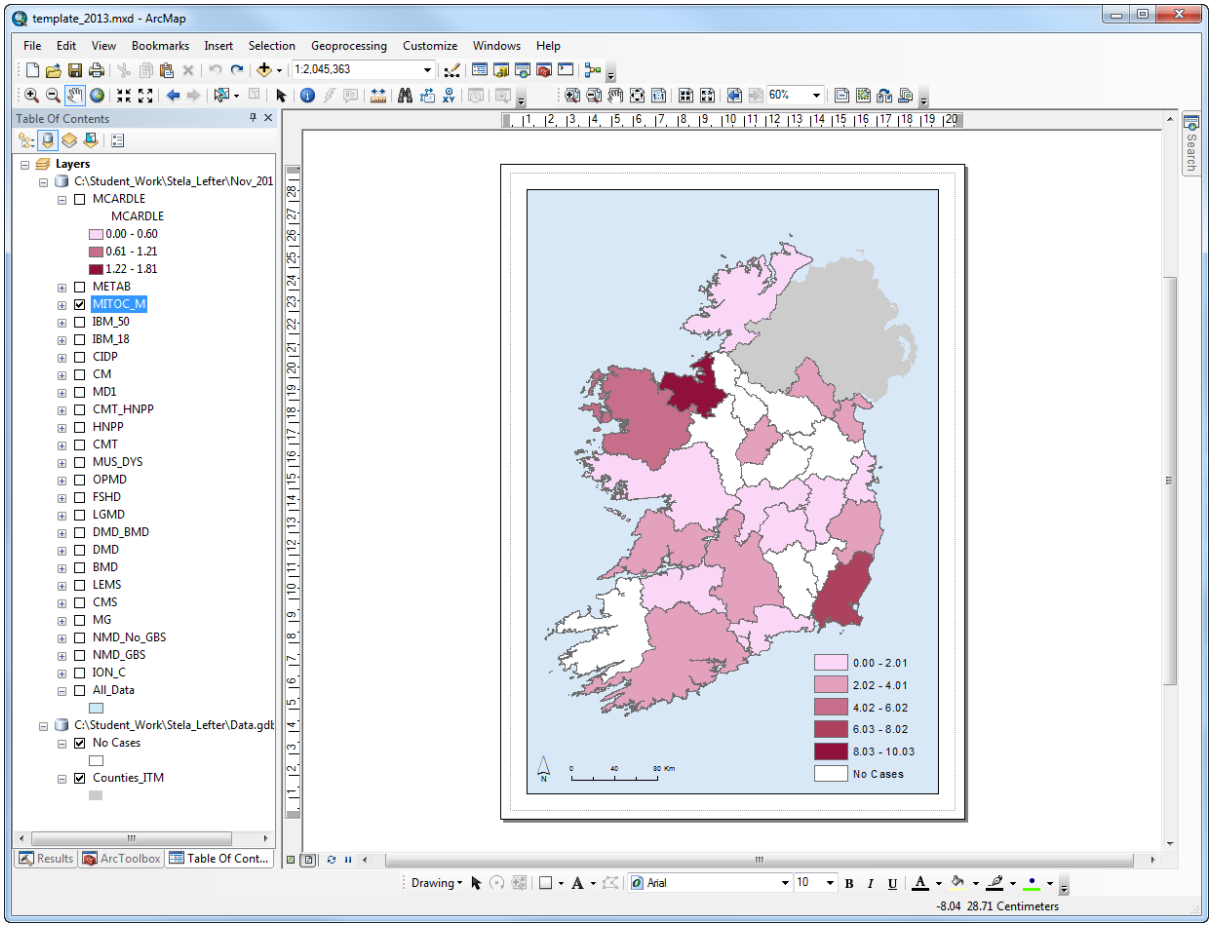
APPENDIX 5 Per county, percentage of Irish population in ten year age bands

(CSO, Census 2011)

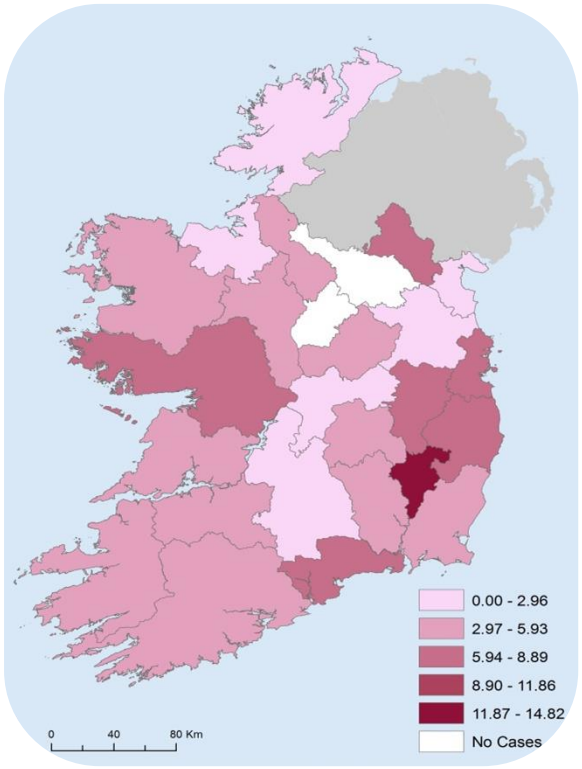
County	0- 9	10-19	20-29	30-39	40-49	50-59	60-69	70-79	80+	Total
Carlow	15.5	13.0	14.1	16.2	13.8	11.3	8.5	5.0	2.7	100.0
Cavan	16.0	13.8	12.6	15.3	13.9	11.4	8.5	5.1	3.3	100.0
Clare	15.0	13.4	11.8	15.2	14.6	12.1	9.7	5.2	2.9	100.0
Cork	14.6	12.7	14.0	16.4	14.1	11.4	8.7	5.3	2.9	100.0
Donegal	15.5	14.0	12.0	14.6	13.8	11.5	9.6	5.7	3.3	100.0
Dublin	13.5	11.7	17.5	18.2	13.2	10.6	7.8	4.9	2.6	100.0
Galway	14.5	12.7	14.8	16.8	13.7	11.3	8.4	4.9	2.9	100.0
Kerry	13.5	12.7	11.8	14.8	14.1	12.8	10.6	6.2	3.5	100.0
Kildare	17.2	13.6	13.9	17.9	14.7	10.6	7.1	3.2	1.7	100.0
Kilkenny	15.1	13.5	12.1	15.9	14.1	12.1	9.0	5.2	3.0	100.0
Laois	17.6	13.0	13.7	17.0	14.0	10.7	7.4	4.3	2.4	100.0
Leitrim	14.9	12.3	10.9	14.8	13.8	13.1	9.9	6.4	4.0	100.0
Limerick	13.9	13.2	15.1	15.7	13.3	11.6	9.1	5.4	2.8	100.0
Longford	16.2	13.1	12.5	15.0	13.6	11.8	9.5	5.3	3.0	100.0
Louth	16.2	13.3	13.7	16.2	14.3	10.8	8.1	4.7	2.6	100.0
Mayo	14.0	13.2	11.5	13.7	13.8	13.0	10.5	6.4	3.9	100.0
Meath	17.9	13.3	12.5	17.9	14.9	10.4	7.3	3.7	1.9	100.0
Monaghan	15.3	13.5	13.2	15.3	13.7	11.6	8.9	5.3	3.2	100.0
Offaly	15.9	14.0	12.8	15.4	14.1	11.4	8.5	5.1	2.8	100.0
Roscommon	14.3	12.8	11.5	14.3	14.0	13.0	10.0	6.2	4.0	100.0
Sligo	13.4	13.3	13.4	14.3	13.6	12.6	9.9	5.8	3.7	100.0
Tipperary	14.6	13.4	12.1	14.9	14.1	12.2	9.5	5.8	3.3	100.0
Waterford	14.7	13.1	12.9	15.4	14.2	11.7	9.3	5.8	3.0	100.0
Westmeath	15.4	13.8	13.7	15.8	14.1	11.3	8.1	4.9	2.9	100.0
Wexford	15.5	13.4	12.0	15.3	14.4	11.6	9.3	5.7	2.7	100.0
Wicklow	15.8	13.2	12.4	16.2	15.0	11.5	8.8	4.7	2.4	100.0
Total	14.8	12.8	14.3	16.5	13.9	11.3	8.6	5.1	2.8	100.0

APPENDIX 6 The process of mapping using Geographical Information Systems

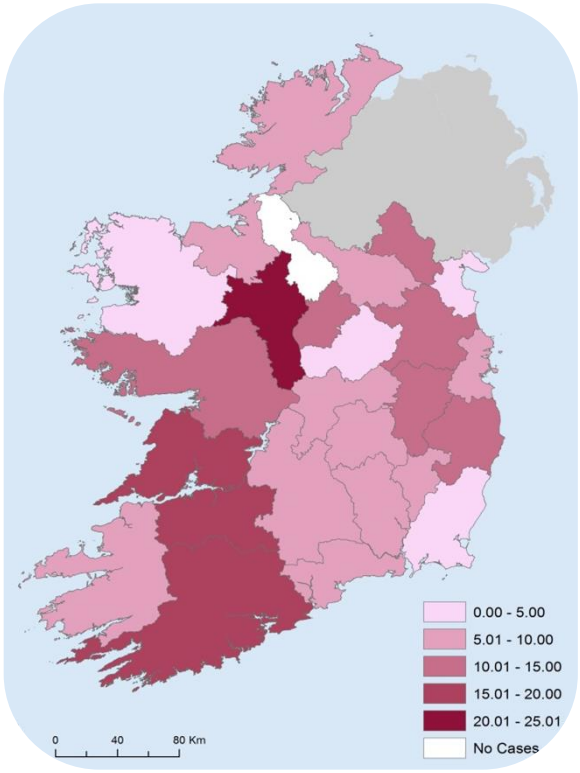




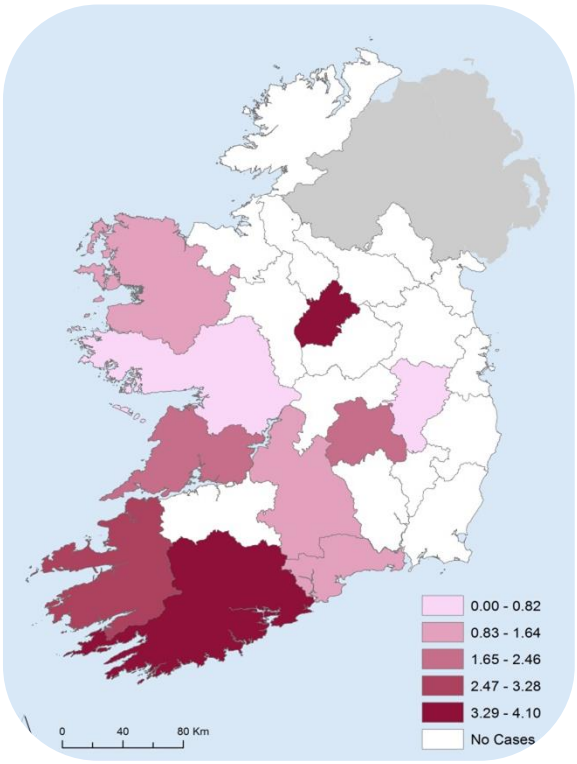
APPENDIX 7 Unadjusted PR rates maps for various NMDs in ROI



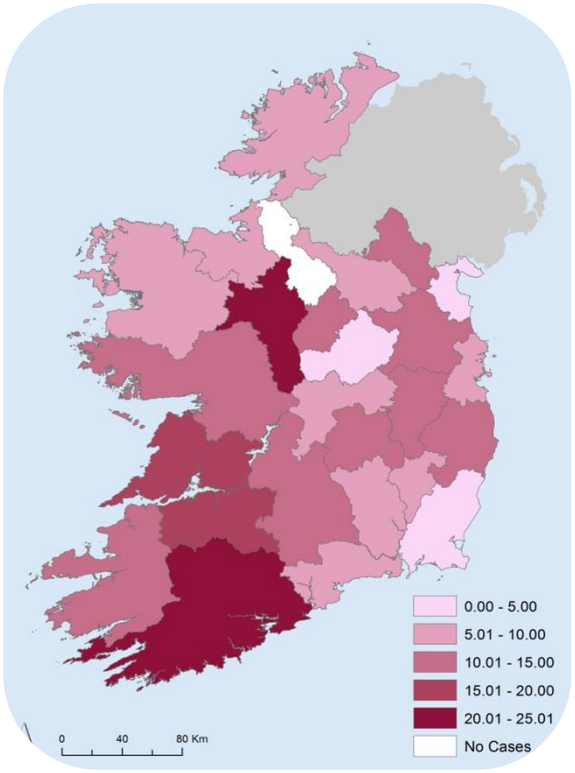
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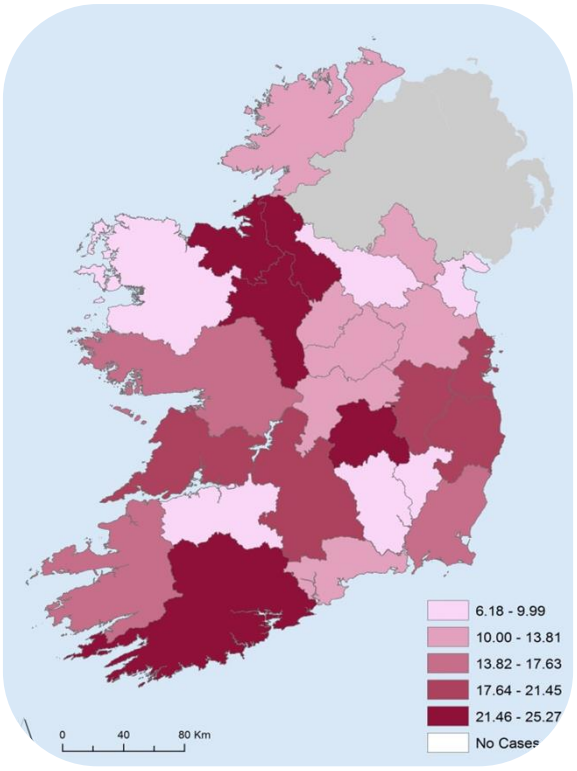
CMT



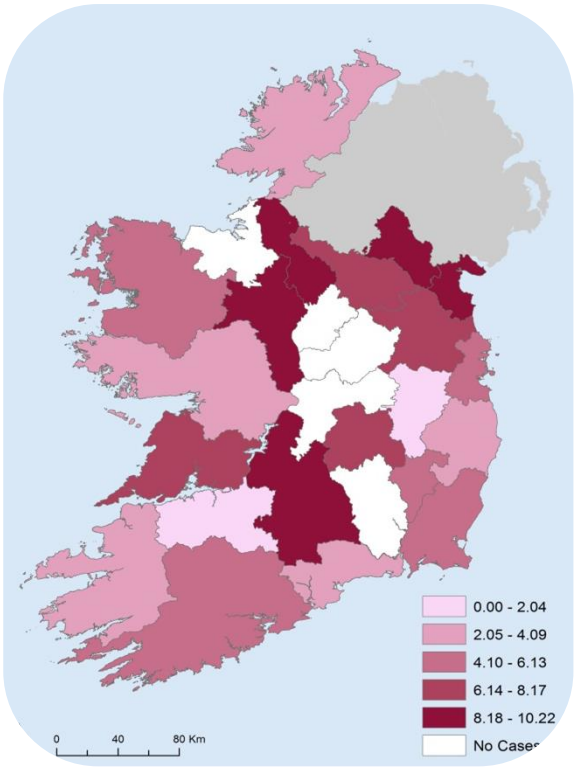
HNPP



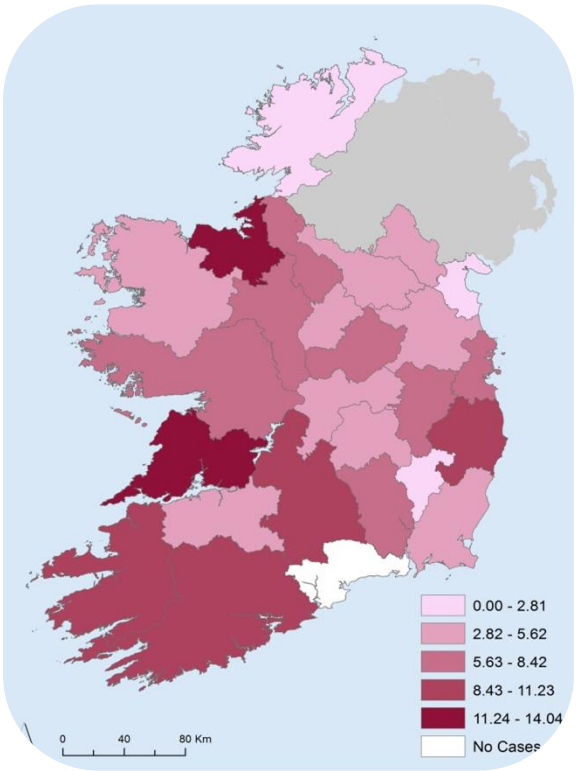
CMT and HNPP



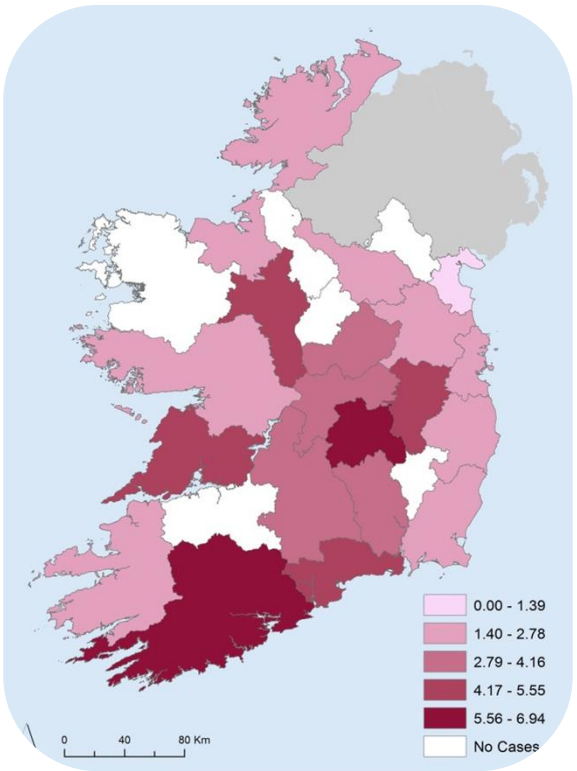
Muscular dystrophy group



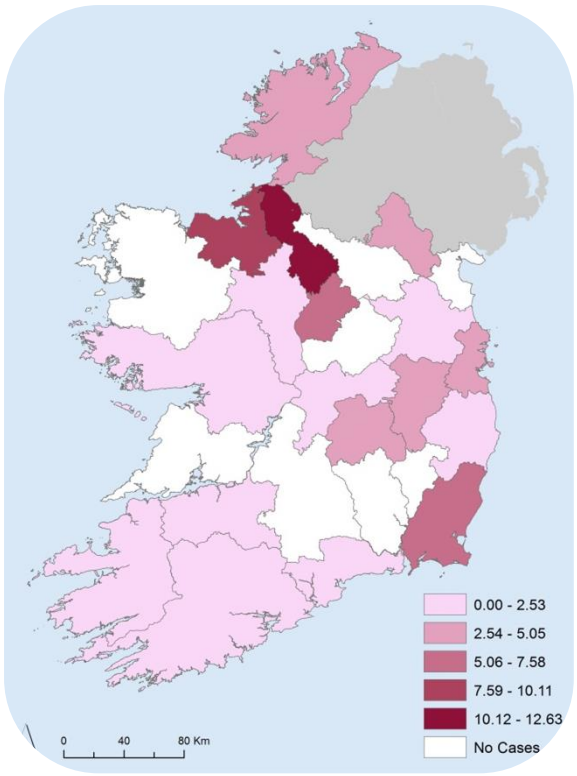
Dystrophynopathies



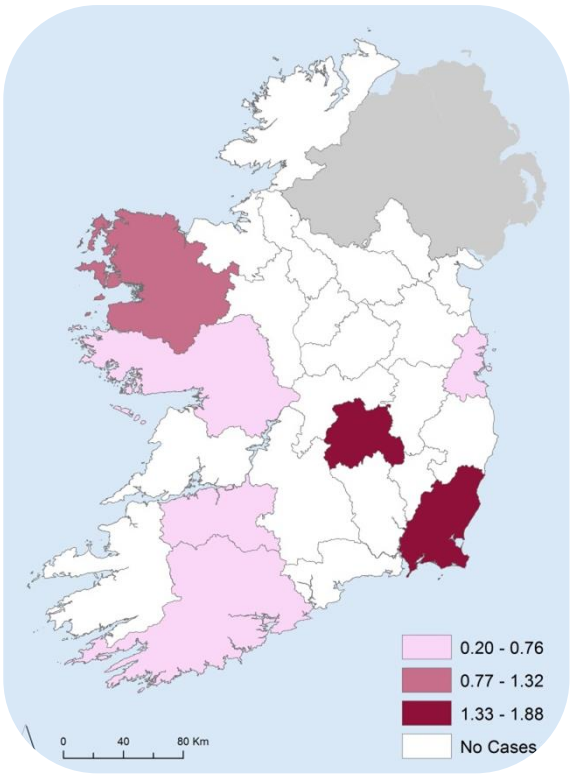
DM 1



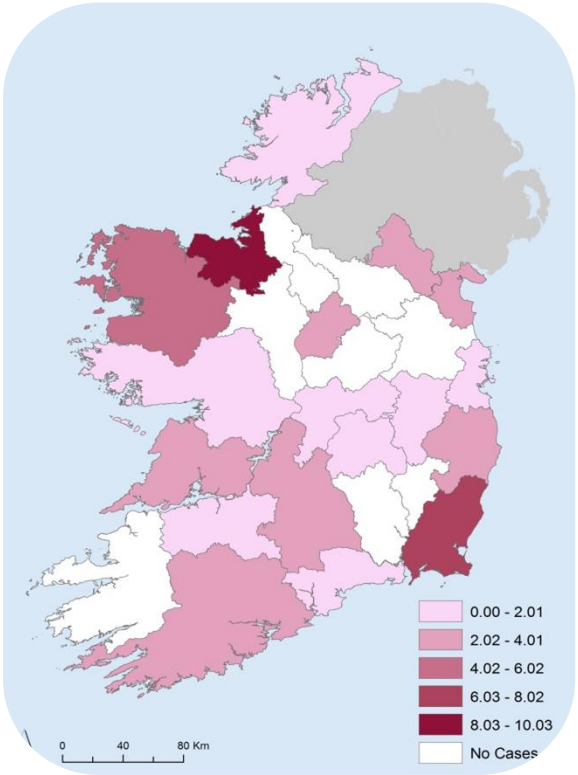
LGMD



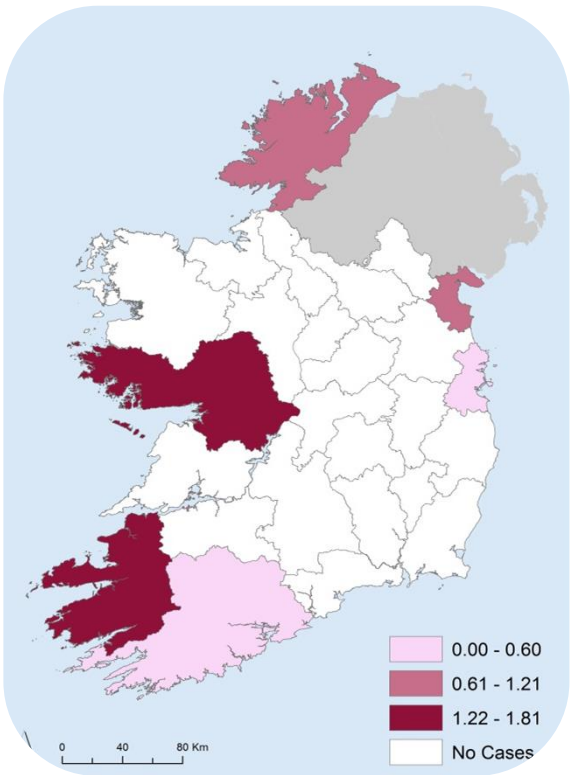
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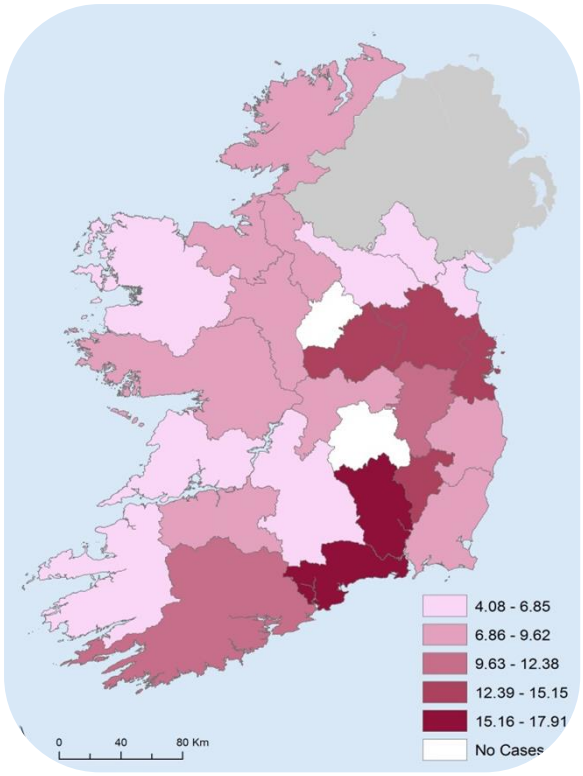
OPMD



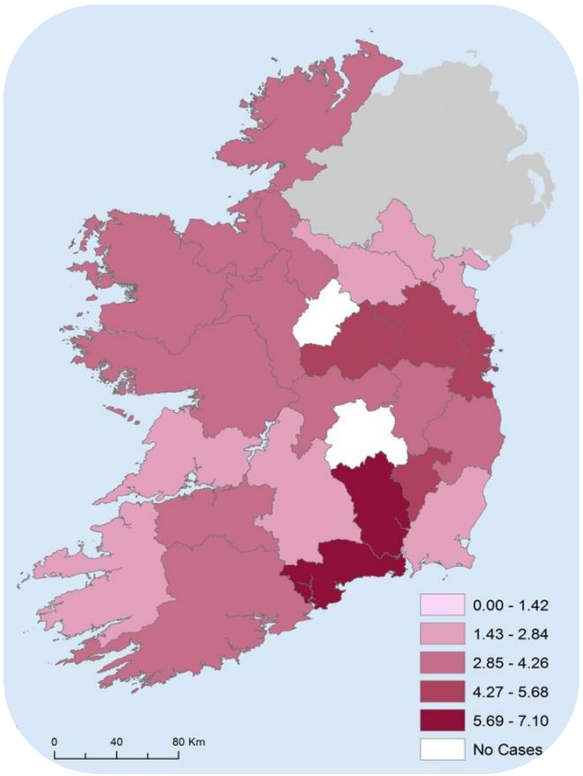
Mitochondrial myopathy



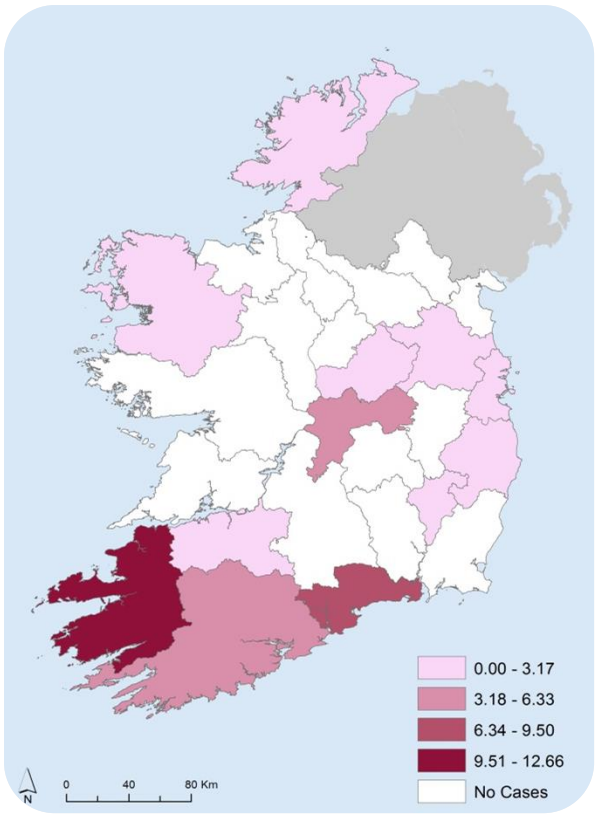
McArdle disease



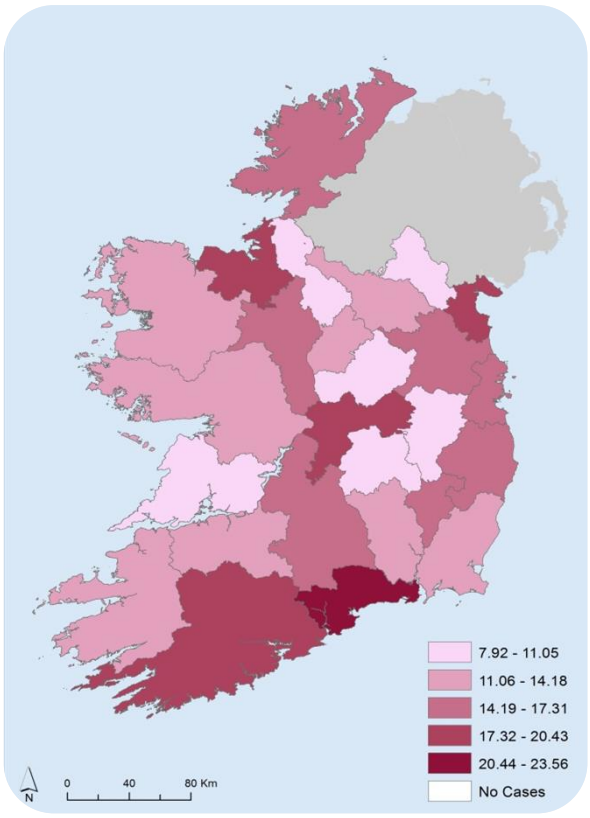
IBM (≥50 years)



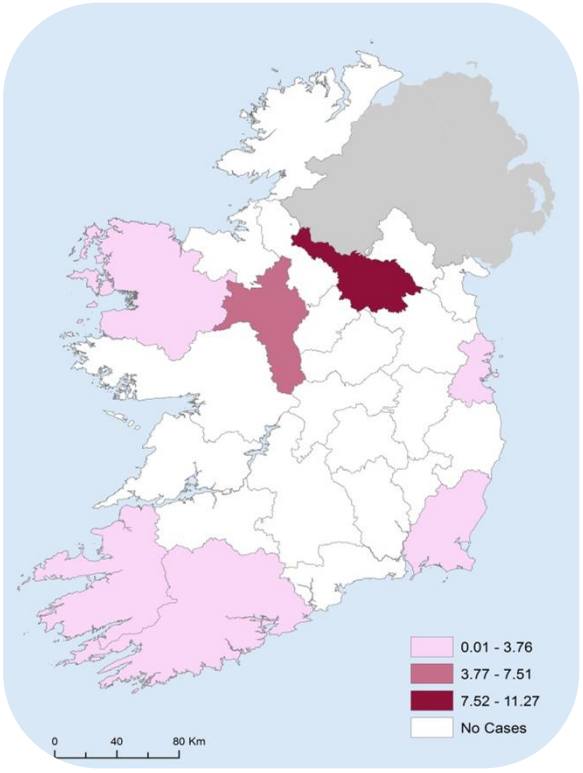
IBM (≥18 years)



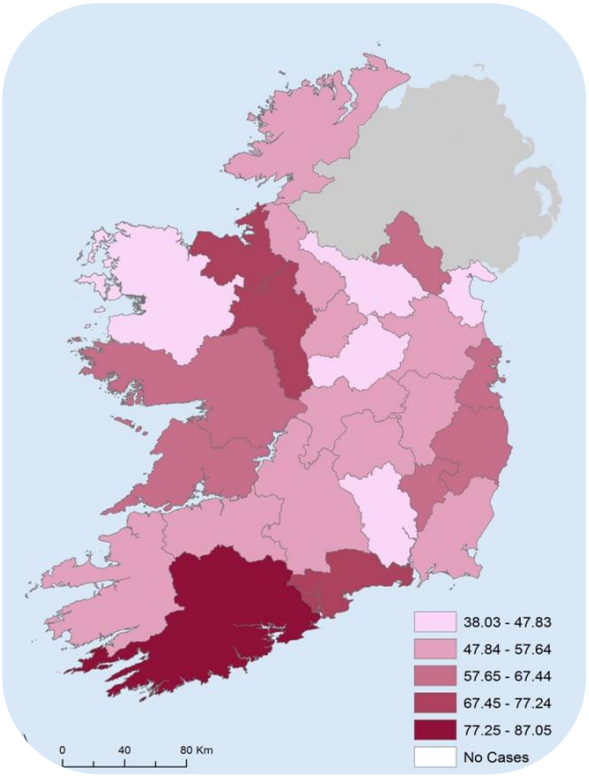
Periodic Paralysis



Myasthenia Gravis



Kennedy disease



All NMD group

APPENDIX 8 Publications published from this thesis

1. Lefter S, Hardiman O, Ryan AM. **Methodology and design of a national epidemiological study on adult neuromuscular disease.** Neuroepidemiology 2014;43:123-30

2. S. Lefter, O. Hardiman, R. L. McLaughlin, S.M. Murphy, M. Farrell, A.M. Ryan. **A novel MYH7 L1453P mutation resulting in Laing distal myopathy in an Irish family.** Neuromuscular disorders. Published Online: September 24, 2014.

3. S. Lefter, O. Hardiman, D. Costigan, B. Lynch, J. McConville, C.K. Hand, A.M. Ryan. **Andersen-Tawil syndrome with early fixed myopathy.** J Clin Neuromuscul Dis 2014;16:79-82.

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