Journal of Neuromuscular Diseases 2 (2015) 73–85
DOI 10.3233/JND-140045
IOS Press

Research Report

The Epidemiology of Neuromuscular Disorders: A Comprehensive Overview of the Literature

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Abstract.
Background: In 1991, the first world survey of neuromuscular disorders (NMDs) was published in the peer reviewed literature. Since then, diagnostics have been greatly improved through genetic confirmation and consensus on criteria. This prompted us to search the scientific literature since 1990 for the epidemiology of NMDs.
Objectives: To study occurrence rates, gender and age distribution.
Methods: Pubmed was searched for 'epidemiology', 'incidence' and 'prevalence' regarding thirty NMDs for peer reviewed literature from 1990–2014.
Results: We found incidence rates for ten disorders, ranging from 0.05 to 9 per 100,000/yr. Most NMDs showed prevalence rates between 1 and 10 per 100,000 population, except for multifocal motor neuropathy, Lambert-Eaton myasthenic syndrome, Emery-Dreifuss dystrophy, oculopharyngeal muscular dystrophy, and congenital muscular dystrophies, which were <1/100,000. Post-polio syndrome and Charcot-Marie-Tooth disease revealed prevalences >10/100,000. Information regarding incidence, prevalence, age distribution and gender was complete for eight disorders. No data were found for chronic inflammatory demyelinating polyneuropathy, neuralgic amyotrophy, progressive spinal muscular atrophy, McArdle's and Pompe's disease. For the 17 remaining disorders, information was partially available.
Conclusions: Compared to 1991, prevalence rates of Becker muscular dystrophy, facioscapulohumeral dystrophy, myotonic dystrophy and Charcot-Marie-Tooth disease showed increase, yet with highly overlapping ranges with the exception of myotonic dystrophy. The sum of the available prevalence rates comprises only the tip of the iceberg, but is already in range with the prevalence of Parkinson's disease. Although individual NMDs are rare, as a group they are not.

Keywords: Neuromuscular diseases, epidemiology, incidence, prevalence

INTRODUCTION

Knowledge on disease mechanisms of neuromuscular disorders is growing fast, facilitating identification of potential therapeutic targets [1, 2]. As clinical studies on interventions can be expected in the near future, reliable information regarding disease epidemiology is needed for trial readiness and will help to identify gaps in the knowledge on the epidemiology of neuromuscular disorders.

In 1991, the first world survey of mostly inheritable neuromuscular disorders was published in the peer reviewed literature [3, 4]. In addition, Great Britain's patient association Muscular Dystrophy Campaign presented a report in 2010 that included thirteen groups of neuromuscular diseases [5]. Three years later, Orphanet reported on the prevalence of rare diseases, including neuromuscular disorders as those are almost invariably rare [6].

Since the 1991 survey, genetic confirmation of various neuromuscular disorders has become common

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ISSN 2214-3599/15/$35.00

practice. Also, consensus on diagnostic criteria was reached for a number of diseases [7]. Therefore, we expanded the scope of the first world survey by investigating the epidemiology of thirty disorders, that are either relatively frequent, or have a particular distinguishable phenotype. We searched published peer reviewed literature for available incidence and prevalence rates and for information regarding the distribution of age and gender within the diseases. With this overview, we aim to give useful estimates of prevalence, incidence and age and gender distribution based on the recent world literature.

MATERIALS AND METHODS

Search terms, period and inclusion criteria

We searched Pubmed for thirty neuromuscular disorders frequently seen or clearly distinguishable in the neuromuscular clinic, using the mentioned disease names as search term (Table 1). Symptomatic disorders such as neuropathies secondary to HIV or diabetes mellitus were excluded. We additionally searched for articles using the terms neuromuscular disorder, neuromuscular disease, neurological disorder, or muscle disease in the title. We combined all search terms with the keywords epidemiology, incidence, and prevalence in the title and as MeSH term. We studied the peer reviewed literature published between January 1990 up until July 2014. Inclusion criteria were: published in English, research concerning humans, looking into one of the 30 scrutinised neuromuscular disorders, in case of multiple publications of the same or overlapping data: inclusion of the most recently reported data only, concerning the general population and not specific subgroup(s), findings for the overall disorder, no specific disease type(s), containing information regarding incidence or prevalence rates, original data therefore

Table 1
The considered thirty neuromuscular disorders, arranged by anatomical origin

Disorder	Common abbreviation	Referenced articles
Anterior horn cells		
spinal muscular atrophy	SMA	[8–13]
progressive spinal muscular atrophy	PSMA	–
amyotrophic lateral sclerosis	ALS	[14–63]
post-polio syndrome	PPS	[9, 64]
Peripheral nerve		
Charcot-Marie-Tooth disease	CMT	[8, 10, 65–72]
chronic inflammatory demyelinating polyneuropathy	CIDP	[73–79]
Friedreich ataxia	FA	[80–84]
hereditary neuropathy with liability to pressure palsies	HNPP	[72, 85]
Guillain-Barré syndrome	GBS	[73, 86–113]
idiopathic neuralgic amyotrophy	INA	–
multifocal motor neuropathy	MMN	[79]
neuropathy with monoclonal gammopathy of unknown significance	MGUS	[75, 79]
chronic idiopathic axonal polyneuropathy	CIAP	–
Neuromuscular junction		
myasthenia gravis	MG	[9, 114–144]
Lambert-Eaton myasthenic syndrome	LEMS	[9, 115, 145]
Muscle		
Duchenne muscular dystrophy	DMD	[8–10, 13, 146–149]
Becker muscular dystrophy	BMD	[8, 10, 13, 146, 148, 150–153]
facioscapulohumeral dystrophy	FSHD	[8, 10, 13, 146, 154, 155]
limb-girdle muscular dystrophies	LGMD	[10, 13, 146, 156, 157]
Emery-Dreifuss dystrophy	EDD	[10, 13]
oculopharyngeal muscular dystrophy	OPMD	[13]
myotonic dystrophy	MD	[8–10, 13, 146, 158–161]
congenital muscular dystrophies	CMD	[10, 13, 146, 162, 163]
non-dystrophic myotonia	–	[9, 10]
chronic progressive external ophthalmoplegia	CPEO	[164]
Pompe's disease	–	–
McArdle's disease	–	–
polymyositis	PM	[9, 165–170]
dermatomyositis	–	[9, 165, 167–171]
inclusion body myositis	IBM	[166, 170, 172–176]

Table 2A
Occurrence rates for 30 neuromuscular disorders arranged by anatomical origin

Anatomical location	Incidence rate				Prevalence rate			
Disorder	mean (per 100,000 PY)	median (per 100,000 PY)	range (per 100,000 PY)	based on # studies	mean (per 100,000)	median (per 100,000)	range (per 100,000)	based on # studies
Anterior horn cells								
SMA	9	9	5.1–13.7	2	2	2	1.3–3.2	4
PSMA	–	–	–	–	–	–	–	–
ALS	2	2	0.42–5.3	45	5	4	1.07–11.31	26
PPS	–	–	–	–	60	60	18–92	2
Peripheral nerves								
CMT	–	–	–	–	20	10	3.1–82.3	10
CIDP	0.9	0.8	0.35–1.6	4	4	3	0.67–8.9	6
Friedreich Ataxia	4	4	2.7–6.19	2	2	1	0.6–3.98	5
GBS	1	1	0.4–3.0	30	–	–	–	–
INA	–	–	–	–	–	–	–	–
HNPP	–	–	–	–	9	9	2.0–16	2
MMN	–	–	–	–	0.5	0.5	–	1
MGUS with neuropathy	–	–	–	–	3	3	1.04–5.1	2
CIAP	–	–	–	–	–	–	–	–
Neuromuscular junction								
MG	1	0.8	0.3–2.8	24	10	10	5.35–35	24
LEMS	0.05	0.05	–	1	0.3	0.3	0.23–0.40	3
Muscle								
DMD	–	–	–	–	3	3	0.70–4.7	8
BMD	–	–	–	–	2	2	0.07–3.65	9
FSHD	–	–	–	–	4	4	2.03–6.8	6
LGMD	0.7	0.7	–	1	3	2	0.81–6.9	5
Emery Dreifuss dystrophy	–	–	–	–	0.3	0.3	0.13–0.4	2
OPMD	–	–	–	–	0.1	0.1	–	1
MD	–	–	–	–	10	10	7.1–26.5	9
CMD	–	–	–	–	1	0.8	0.6–3.90	5
Non-dystrophic myotonia	–	–	–	–	1	1	1.1–1.1	2
CPEO	–	–	–	–	3	3	–	1
Pompe's disease	–	–	–	–	–	–	–	–
McArdle's disease	–	–	–	–	–	–	–	–
Polymyositis	2	0.6	0.27–3.80	8	7	7	3.45 – 9.7	6
Dermatomyositis	0.9	0.8	0.08–1.78	8	8	5	1.97–21.42	6
IBM	0.4	0.3	0.09–0.79	3	2	1	0.07–7.06	6

excluding reviews, and finally, methods of ascertainment and calculation of disease frequency needed to be mentioned in the article.

Frequency measures

Selected articles were scrutinised for incidence and prevalence rates. To facilitate comparison, estimates that used the number of live births as the denominator (birth prevalences) were excluded. In addition, all prevalence rates were standardised into units of 100,000 persons and all incidence rates into units of 100,000 persons per year. Next, the articles containing data regarding incidence or prevalence were searched for information about gender and age distribution. We classified the age at diagnosis of each disorder as early, uniform or late, depending on the highest frequency of the occurrence rates and their range. For gender, we reported the percentage of males within the total group of patients per disease.

Summarising the findings

We presented the range of the identified rates, the number of estimates and we calculated the mean and median of the findings. Means and medians were rounded to one significant digit, thus reporting on the general order of magnitude rather than seemingly exact numbers. We did not perform significance tests or determine confidence intervals for comparisons, as these would imply a level of precision that does not match the methods applied or our aim to present the general order of magnitude of the rates rather than exact numbers.

RESULTS

We identified 169 articles containing relevant information on one or more of the 30 specified disorders (Table 1). Incidence and prevalence rates and

Table 2B
Age distribution and gender for 30 neuromuscular disorders arranged by anatomical origin

Anatomical location	Age distribution		Gender, male		
Disorder	early, uniform, late (number of studies)	number of studies	mean %	range	number of studies
Anterior horn cells					
SMA	–	–	53	40–67	2
PSMA	–	–	–	–	–
ALS	late	47	57	45–69	48
PPS	late	2	–	–	–
Peripheral nerves					
CMT	uniform	4	51	44–62	5
CIDP	uniform (3) late (1)	4	68	57–80	7
Friedreich Ataxia	early	3	55	46–68	3
GBS	uniform (19) late (6)	25	57	38–68	25
INA	–	–	–	–	–
HNPP	–	–	52	–	1
MMN	–	–	–	–	–
MGUS with neuropathy	–	–	–	–	–
CIAP	–	–	–	–	–
Neuromuscular junction					
MG	uniform (20) late (1) ♂late/♀uniform (5)	26	38	20–48	30
LEMS	late	3	59	58–60	2
Muscle					
DMD	early	3	97	91–100	6
BMD	early (2) uniform (1)	3	100	100–100	7
FSHD	uniform	1	63	–	1
LGMD	–	–	39	–	1
Emery Dreifuss dystrophy	–	–	–	–	–
OPMD	–	–	–	–	–
MD	uniform	3	54	43–61	3
CMD	early	1	45	–	1
Non–dystrophic myotonia	uniform	1	33	–	1
CPEO	–	–	–	–	–
Pompe's disease	–	–	–	–	–
McArdle's disease	–	–	–	–	–
Polymyositis	uniform	4	36	17–50	5
Dermatomyositis	uniform	3	35	27–42	5
IBM	late	4	51	33–66	4

data about gender and age were found for eight of the thirty neuromuscular disorders: amyotrophic lateral sclerosis, chronic inflammatory demyelinating polyneuropathy, Friedreich ataxia, myasthenia gravis, Lambert-Eaton myasthenic syndrome, polymyositis, dermatomyositis and inclusion body myositis (Table 2). We were able to identify incidence rates for 11 disorders. Rates ranged from 0.05/100,000 population per year for Lambert-Eaton myasthenic syndrome to 9/100,000 in spinal muscular atrophy.

We found prevalence data for 24 of the 30 disorders. The rates ranged from 0.1/100,000 population for oculopharyngeal muscular dystrophy to 60/100,000 population for post-polio syndrome. Twenty-three disorders had prevalences lower than 50/100,000 and thus are considered to be rare diseases [177]. When we added up the 24 obtained prevalence rates, we found a total of 160/100,000 population.

Age distribution was available for 17 disorders, the majority presenting a uniform age distribution. Friedreich ataxia, Duchenne muscular dystrophy and congenital muscular dystrophies occurred early in life, whereas amyotrophic lateral sclerosis, post-polio syndrome, Lambert-Eaton myasthenic syndrome and inclusion body myositis are revealed later in life. In five disorders, the age distribution was ambiguous.

Gender data for 19 disorders could be retrieved. For the most part, disorders were equally distributed among men and women. Seven disorders showed male predominance, including amyotrophic lateral sclerosis, chronic inflammatory demyelinating polyneuropathy, Guillain-Barré syndrome, Lambert-Eaton myasthenic syndrome, Duchenne and Becker muscular dystrophies and facioscapulohumeral dystrophy. Myasthenia gravis, non-dystrophic myotonia, polymyositis and dermatomyositis occurred up to twice as often in women.

Table 3
Surveys regarding the prevalence of neuromuscular disorders per 100,000 population

Anatomical origin Disorder	*Our median findings regarding thirty NMDs*	*Emery inherited NMDs 1991 [3, 4]*	*Muscular Dystrophy Campaign NMDs 2010 [5]*	*Orphanet rare diseases 2013 [6]*
Methods	Pubmed search for available peer reviewed literature 1990-2014	No search methods described, likely all available estimates in 1991 including unpublished info; reported finding followed by calculated median in parentheses	Mix of a number of articles (British as well as European), unpublished data, expert opinions and fact sheets MDC	Systematic survey of literature incl websites, registries, Medline, medical books, grey literature and expert opinions; outcome = mean of lowest and highest finding
Peer reviewed?	yes	yes	no	no
Anterior horn cells				
SMA[1]	2	1.2 (1.2)	2.0	3.45[2]
PSMA	-			
ALS	4*	4.16 (3,5*)		5.2
PPS	60			
Peripheral nerve				
CMT	10*	10 (6.1*)	38.0	23.6[3]
CIDP	3			3.7
Friedreich ataxia	1			2
HNPP	9		10.6	
GBS	-			6.75[4]
CIAP	-			
INA	-			3.3
MMN	0.5			1.5
MGUS with neurop.[5]	3			
Neuromuscular junction				
MG	10	-[6]	-[7]	20
LEMS	0.3			1
Muscle				
DMD	3*	3.2 (3,4*)	14.9	5
BMD	2*	0.7 (0.7*)		
FSHD	4*	2 (0.8*)		4
LGMD	2*	4 (2,5*)		3.43[8]
CMD	0.8			5.46[9]
Emery-Dreifuss dystr.	0.3			0.3
OPMD	0.1			1
MD	10*	5 (3.5*)	15.7	5.5[10]
Non-dystr myotonia	1[11]	1 (0.44)		5[12]
CPEO	3		5.8[13]	2[14]
Pompe's disease	-		1.2[15]	
McArdle's disease	-			
Polymyositis	7		9.1	6.5
Dermatomyositis	5			17
IBM	1			0.49

*depicted in Fig. 1. [1]Each report includes different combination of disease types, thus outcomes are incomparable. [2]Includes childhood- and adult-onset autosomal dominant proximal spinal muscular atrophy, proximal spinal muscular atrophy type 1, 2, 3, 4 and Kennedy disease. [3]Includes Charcot-Marie-Tooth disease and X-linked Charcot-Marie-Tooth disease. [4]Includes acute inflammatory demyelinating polyradiculoneuropathy, Guillain-Barré syndrome, acute motor axonal neuropathy, acute motor-sensory axonal neuropathy. [5]Neuropathy associated with paraproteinaemia/monoclonal gammopathy of unknown significance (MGUS). [6]Estimate combined with 'familial motor neurone disease'. [7]Estimate combined with myasthenic syndrome. [8]Includes limb girdle muscular dystrophy, autosomal dominant limb girdle muscular dystrophy type 1B, autosomal recessive limb girdle muscular dystrophy type 2A, 2B, 2C, 2F, 2I. [9]Includes congenital muscular dystrophy, congenital muscular dystrophy type 1A, congenital muscular dystrophy with integrin deficiency and congenital muscular dystrophy, Ullrich type. [10]Includes Steinert myotonic dystrophy and proximal myotonic myopathy. [11]Not included in Fig. 1 our survey rendered only one observation. [12]Includes Thomsen and Becker disease, hyperkalemic and hypokalemic periodic paralysis. [13]Referred to as mitochondrial myopathies. [14]Includes Kearns-Sayre syndrome. [15]Referred to as metabolic myopathies.

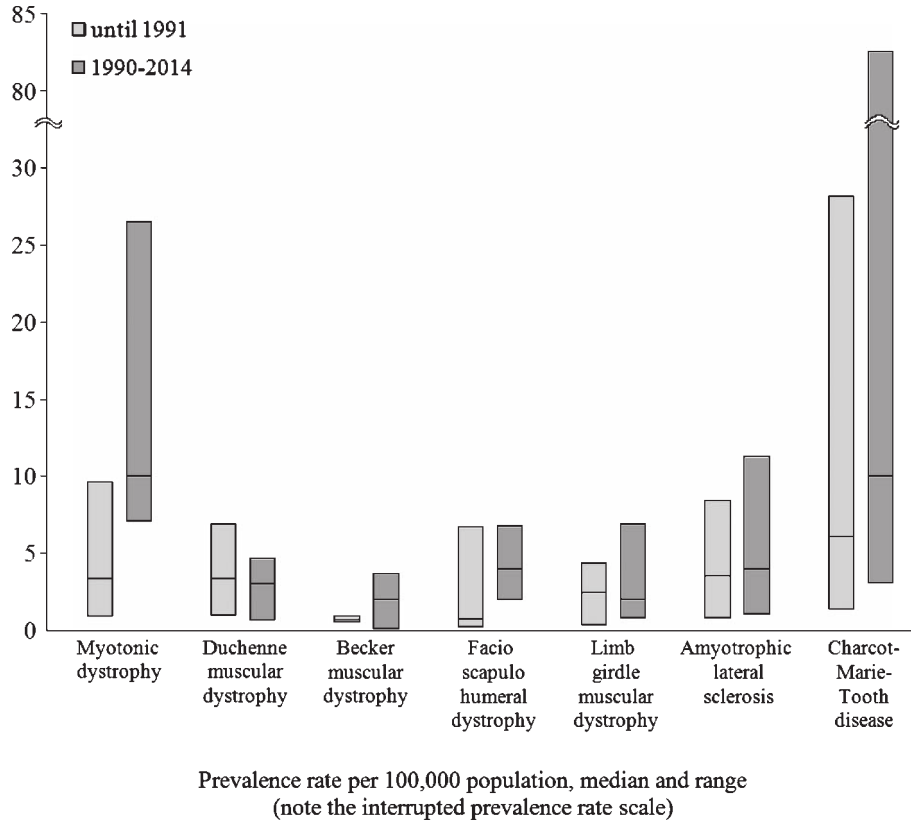

Fig. 1. Median prevalence rates for seven neuromuscular disorders until 1991 and 1990–2014 [3, 4].

We found no information on five disorders: progressive spinal muscular atrophy, idiopathic neuralgic amyotrophy, chronic idiopathic axonal polyneuropathy, Pompe's disease and McArdle's disease.

We compared the collected data with two peer reviewed articles dating from 1991 and two reports (Table 3, Fig. 1) [3–6].

DISCUSSION

This study presents epidemiologic data from the recent literature for thirty individual neuromuscular disorders, to serve as a reference for both clinicians, researchers and policymakers. The added value lies in the grouped epidemiology that is made available, enabling comparisons in the order of magnitude as well as the identification of lacunas in the body of knowledge.

When we compared our findings to the earlier peer reviewed survey, data on nine of thirty disorders were available in this survey and only seven were comparable (Table 3, Fig. 1). Amyotrophic lateral sclerosis, Duchenne muscular dystrophy and limb-girdle muscular dystrophy showed stable prevalence estimates over time. Becker muscular dystrophy, facioscapulohumeral dystrophy, myotonic dystrophy and Charcot-Marie-Tooth disease prevalences seemed to have increased considerably. However, in most disorders also the overlap of the ranges of both observations overlapped considerable, except for myotonic dystrophy [3, 4]. The prevalence estimate of myotonic dystrophy, in contrast, appeared to be at least twice as high compared to the 1991 estimate and it displayed less overlapping ranges. The current estimate was based on nine separate observations with prevalence rates ranging from 7.1 to 26.5/100,000 and therefore can hardly be contributed to chance alone. Genetic testing may be one of the contributing factors, as the genetic origin of myotonic dystrophy was identified in 1993, in addition to reaching consensus on diagnostic criteria. The increased prevalence rate in myotonic dystrophy could also be due to improved levels of ascertainment in the included studies compared to the studies reported in the 1991 survey.

We added up the 24 available prevalence estimates,, to enable comparison with other diseases. As such, the

prevalence of neuromuscular disorders as a group is at least similar to that of Parkinson's disease worldwide (100 - 300/100.000) and twice that of multiple sclerosis in Europe (80/100.000). [178, 179].

As our methods, although systematic, were not designed to capture all studies, the general order of magnitude rather than seemingly exact numbers were presented. For future research it would be interesting to present these data, as well as data on disease subgroups. In our experience however, specific information for subgroups was limited, and data on several subgroups were often combined in changing combinations.

In conclusion, prevalence rates of Becker muscular dystrophy, facioscapulohumeral dystrophy, Charcot-Marie-Tooth disease and in particular myotonic dystrophy showed increase, with highly overlapping ranges except for myotonic dystrophy. The summed estimate for neuromuscular disorders as a group represents only the tip of the iceberg. Although neuromuscular disorders are rare as individual disease entities, as a group they are not.

ACKNOWLEDGMENTS INCLUDING SOURCES OF SUPPORT

The authors would like to thank Dr AE Emery (Oxford, United Kingdom) for his contributions to our study. This work was supported by *Prinses Beatrix Spierfonds* (W.OR09-21).

CONFLICT OF INTEREST

Ms Deenen reports no disclosures.

Dr Horlings reports no disclosures.

Dr Verschuuren reports involvement in Duchenne trials that are sponsored by Prosensa, GSK, Santhera or Lilly, in a FP7-sponsored project with Curavac on myasthenia gravis, and consultancy services for BioMarin (2009-2010). All reimbursements were received by the LUMC, Dr Verschuuren did not personally benefit financially from these activities.

Dr Verbeek is non-profit full professor in Clinical Epidemiology at Radboud university medical center, Nijmegen, the Netherlands and reports no personal compensations and other supports.

Dr van Engelen receives institutional support from the Radboud university medical center, Nijmegen, the Netherlands, grant support from the Global FSH, Netherlands Organization for Scientific Research, Prinses Beatrix Spierfonds, and the Dutch FSHD Foundation.

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