Pediatric Neuromuscular Diseases Prevalence in Siriraj Hospital, Thailand's Largest Tertiary Referral Hospital

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ABSTRACT

Objective: There are no epidemiological data on childhood neuromuscular diseases in Thailand. We aimed to estimate the proportion of NMDs among pediatric neurology patients in Siriraj Hospital and determine the specific diagnosis.

Methods: A retrospective study was conducted in the pediatric neuromuscular clinic at Siriraj Hospital between 2014 and 2016.

Results: Of 1,994 patients aged < 21 years with neurological diseases, 217 (10.88 %) had received a diagnosis. Diagnostic clarity can be achieved using clinical tools such as electromyography, serum creatinine kinase, muscle histo-immunology, and genetic analysis. Of the 217 patients, 143 (65.9 %) had inherited and 74 (34.1%) had acquired neuromuscular diseases. The most common inherited NMD were the Dystrophinopathies, including Duchenne / Becker muscular dystrophy (n = 58), while spinal muscular atrophy was the second most common (n = 25). Myasthenia Gravis was the most common acquired neuromuscular disease (n = 36).

Conclusion: We found 10.88 percent of patients with neurological diseases have NMD. NMD is a chronic disease with poor quality of life and so multidisciplinary clinical care is crucial for these patients. In order to improve the standard of care, collaboration with government and other tertiary hospitals is important and will help serve a growing population of NMD patients.

Keywords: Neuromuscular diseases; neurology; Duchenne Muscular Dystrophy; spinal muscular atrophy (Siriraj Med J 2020; 72: 125-131)

INTRODUCTION

Neuromuscular diseases (NMD) usually result in chronic long-term disabilities and pose a significant burden to society and the healthcare system. Most NMD patients will need multi-disciplinary care due to complications in multiple organ systems including joint contractures, respiratory failure and cardiomyopathy. NMD can be either inherited or acquired. It is important to precisely diagnose patients since most acquired NMD can be effectively treated. For inherited NMD, genetic counseling is crucial to prevent inheritance (transmission) to the next generation.

Neuromuscular disorders (NMD) can be broadly divided by the location of the pathological lesions into those affecting anterior horn cell (AHC), peripheral nerve, neuromuscular junction (NMJ) and muscle fibers.[1-3] Epidemiologic research that explores NMD types, frequency and their associated genotypic distribution among the

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http://dx.doi.org/10.33192/Smj.2020.17

population is important to prioritize healthcare resource allocation. Emery[2] conducted a comprehensive literature review and estimated the global prevalence of inherited neuromuscular diseases to be $28.6x10^{-5}$ or 1 in 3,500. Other studies have reported a higher prevalence. For example, in Northern Ireland the prevalence of inherited NMD in patients age 0-84 years was estimated to be $34.5x10^{-5}$ or 1 in 2,900.[4] A study of childhood neuromuscular diseases (age 0-15 years) in western Sweden[5] reported the prevalence to be $63.1x10^{-5}$ for all neuromuscular diseases and $53.1x10^{-5}$ for inherited neuromuscular diseases. This study also reported that in 227 children with NMDs, 191 (84%) had inherited NMDs. In contrast, a study of Chinese children with NMDs (age <19 years old) in Hong Kong[6] reported a prevalence of $21.4x10^{-5}$ or 1 in 4,669. In the Chinese study, the investigators found that (68%) of 332 children with NMD had inherited disease. For prevalence of inherited muscle diseases, a study from Northern England reports $37.0x10^{-5}$ According to these studies, the most common inherited NMD are muscular diseases, followed by anterior horn cell and peripheral nerve diseases.[4-8]

Few studies have examined the prevalence and proportion of inherited NMD in childhood and none were conducted in Thailand. Worldwide, the diagnosis of inherited NMD is improving, especially for those involving single genes. For the more complex diseases involving multiple genes, the diagnosis still largely depends on the technical capability of each institution. This, in turn, affects healthcare resource allocation. There is currently no cure for inheritable NMD. Therefore, genetic counseling is essential to achieve a disease-free state in at-risk individuals and their offspring who are disease carriers.

The Multidisciplinary Neuromuscular Clinic at Siriraj Hospital is the largest tertiary care referral center in Thailand. Each year, the clinic sees (diagnoses?) over 100 (new?) cases of pediatric NMD. An understanding of the proportion of inherited NMD can provide insight into the urgent need for genetic diagnosis, counseling and intervention in this vulnerable patient population. Epidemiologic research is important in all ethnic groups to gain understanding about genetic parameters, inform healthcare planning, and to enable interethnic group comparisons. This study will also contribute to the development of a registry that will prepare our hospital for future clinical trials of new therapeutic agents. The data will also support resource management decisions, policy planning, and the allocation of rehabilitation and social welfare program funds.[5,6,9,10] It is difficult to estimate the prevalence of neuromuscular diseases in Thailand since there are multiple academic hospitals treating these patients. Siriraj Hospital is Thailand's largest tertiary hospital with more than 2,000 beds. The distinct different from other hospital is that Siriraj has pediatric neuromuscular clinic which is considered the first one in Thailand. Our data represents the proportion of NMDs among other pediatric neurological diseases in Siriraj Hospital. Therefore, we conducted a retrospectivestudy of the clinical characteristics of NMD children that receive care at the neuromuscular clinic (NMC) at Siriraj Hospital, the largest academic medical center in Thailand.

MATERIALS AND METHODS

Objective

To report the number and specific diagnosis of NMD cases referred to Neuromuscular Clinic at Siriraj Hospital in Bangkok, Thailand, with a focus on the proportion of inherited NMDs found in this population.

Methods

This was a retrospective study of patients aged 0-21 years with pediatric neuromuscular disease and pediatric neurologic disease at Siriraj Hospital between July 2014 and December 2016. The institutional Review Board at Faculty of Medicine Siriraj Hospital Mahidol University approved the study (Si 724/2015). Patients were seen in the neurology clinic or neuromuscular clinic. The Neuromuscular clinic is a multi-disciplinary clinic that offers specialist care in Pediatric Neurology, Rehabilitation, Orthosis, Physical Therapy and social work. We used Emery's criteria and the classification of the World Federation of Neurology Research Committee Group on Neuromuscular Disease[2,11,12] to make the diagnosis. A pediatric neurologist specializing in neuromuscular disease examined all patients. Appropriate investigations including nerve conduct study (NCS), serum creatinine kinase (CK), electromyography (EMG), muscle biopsy and molecular genetic study were performed to establish the diagnosis. Approximately 90% of all patient received full investigations, the rest are diagnosed by clinical diagnosis for partial investigation. Demographic data, socioeconomic status, clinical manifestations, complications and treatment of the disease were collected.

Operational definitions: neuromuscular disorders affect the nerves that control motor or sensory functions and the muscle itself, other neurological disorders in this manuscript means that the neurological disorders that are not neuromuscular disorders, and inherited NMDs are neuromuscular disorders that cause by a broad group of genetic conditions.

RESULTS

There were 217 children with NMD who followed up at the Pediatric Neurology Clinic, representing 10.88% of all patients with neurologic disease who presented to the clinic during the study period. One hundred forty-three patients (65.9%) had inherited neuromuscular diseases. (Table 1). The most common inherited NMD is Dystrophinopathies (Duchenne Muscular Dystrophy (DMD)/Becker Muscular Dystrophy (BMD)) (n=58). (Table 2) The second most common is Spinal Muscular Atrophy (SMA) (n= 25), followed by Hereditary Motor Sensory Neuropathy (HMSN) (n= 16). The most common acquired NMD was Myasthenia Gravis (MG) (n=36), followed by Brachial Plexus Injury (n=9), and Acute Inflammatory Demyelinating Polyneuropathy (AIDP) (n=7), respectively. (Table 3) Thirty-five of these 143 patients (24%) also had a positive family history of a similar disorder in a first or second-degree relative. (Table 4)

Since the Dystrophinopathies are the most common inherited neuromuscular disease found in our NMC clinic, we also collected further clinical information from these patients (Table 5). Twenty-six (45%) DMD patients were ambulatory. Of the 58 DMD patients, 55 were sent for genetic study (54 sent for Multiplex Ligation-dependent Probe Amplification (MLPA) and 1 sent for Polymerase chain reaction (PCR). Twenty-nine (50%) were diagnosed by MLPA, while the test showed no abnormality in the remaining 26 patients. Seven DMD patients were not receiving steroids due to side effects including obesity. SMA was the second most common inherited neuromuscular disease (Table 6). All SMA patients received genetic study (PCR or Denaturing High Performance Liquid Chromatography (DHPLC)), however one patient result was missing because he was diagnosed at a different hospital. Overall, 76% of the patients had exon 7&8 deletion of the SMN1 gene. 60% of these patients were SMA type II.

DISCUSSION

The estimated prevalence of neuromuscular disease among patients with neurological diseases was 10%, similar to a previous report.[13] The majority of neuromuscular diseases in our pediatric patients are inherited in nature. Even with muscle biopsy however, it is sometimes difficult to conclude if the etiology is acquired or inherited. In these cases, next generation sequencing is a promising tool for patient care. Interestingly, with the arrival of detailed genetic testing and sophisticated histo-immunochemical staining methods, established diagnoses are sometimes changed.

We found that inherited NMDs constituted 65.9% of all NMDs, similar to a report from Hong Kong. That study also found that Dystrophinopathies followed by SMA, were the most common NMD.[6] A Swedish study,[5] reported a higher percentage of inherited NMDs (84%) and the most common diseases were Hereditary Motor Sensory Neuropathy (HMSN), Dystrophinopathies and SMA, respectively. However, when the dataset includes adult patients such as in studies from Northern Ireland[4] and Northern England,[8] the most common neuromuscular disease becomes Myotonic Dystrophy then followed by DMD. This may be due to pediatric patients with Myotonic Dystrophy normally having mild disease severity compare to other congenital neuromuscular diseases, so they don't seek medical attention. Since the most common inherited neuromuscular diseases in children are not different from previous studies, we can conclude that ethnicity is not an important etiological factor. The previous studies done in all age group show differently because the age different of population. Four patients were diagnosed with Nonspecific muscle disease, due to limited diagnostic resources, especially advance immunochemistry and next generation sequencing. A collaboration with an international neuro-genetic center would be helpful for these patients.

TABLE 1. A 217 patients with neuromuscular diseases classify by neuroanatomy and etiology.

Location	Inherited	Acquired
Anterior horn cell	25 (11.52%)	2 (0.92%)
Peripheral nerve	16 (7.37%)	28 (12.90%)
Neuromuscular junction	3 (1.38%)	36 (16.59%)
Muscle	99 (45.62%)	8 (3.69%)
Total	143 (65.9%)	74 (34.1%)

TABLE 2. Detail of specific neuromuscular diseases including acquired and inherited, categorize by anatomical origin.

	N
Anterior Horn Cell (AHC)	
Spinal Muscular Atrophy (SMA)	25
Monomelic Amyotrophy (MMA)	2
Peripheral Nerve (PNS)	
Hereditary Motor Sensory Neuropathy (HMSN)	16
Brachial Plexus Injury	9
Peroneal Nerve Injury	4
Sciatic Neuropathy	2
Left L2-4 Plexopathy	1
Acute Inflammatory Demyelinating Polyneuropathy (AIDP)	7
Chronic Inflammatory Demyelinating Polyneuropathy (CIDP)	3
Diabetic Polyneuropathy	1
Acute Motor Axonal Neuropathy (AMAN)	1
Neuromuscular Junction (NMJ)	
Congenital Myasthenic Syndrome (CMS)	3
Myasthenia Gravis	36
Muscle	
Muscular Dystrophy*	79
Congenital Myopathy*	10
HyperCKemia	1
Mitochondria/Metabolic Myopathy*	5
Polymyositis	4
Juvenile Dermatomyositis	2
Necrotizing Autoimmune myositis	2
Nonspecific muscle disease	4

*Please find more diagnosis detail for inherited muscular dystrophy, congenital myopathy and mitochondria/metabolic myopathy in Table 3.

TABLE 3. Detail of 99 patient with inherited muscular dystrophy, congenital myopathy and mitochondria/metabolic myopathy.

	N
Muscular Dystrophy	
Duchenne Muscular Dystrophy (DMD) /Becker Muscular Dystrophy (BMD)	58
Congenital Muscular Dystrophy (CMD)	6
Emery-Dreifuss Muscular Dystrophy (EDMD)	3
Ullrich Congenital Muscular Dystrophy (UCMD)	2
COL6A1 Congenital Muscular Dystrophy	2
Facioscapulohumeral muscular dystrophy (FSHD)	2
Limb-girdle muscular dystrophy (LGMD) type IIB	1
Non-specific Muscular Dystrophy	5
Congenital Myopathy	
Congenital Myopathy (Non-specific)	7
Congenital Myopathy Uniform type 1	1
Myofibrillar Myopathy	1
Congenital Myopathy (Titin)	
Mitochondria/Metabolic Myopathy	1
Glutaric aciduria type II with myopathy	3
Hypokalemia Periodic Paralysis (PP)	2
Nonspecific muscle disease	4

TABLE 4. The detail of 35 inherited neuromuscular disorders cases with positive family history.

Inherited neuromuscular disorders	Positive Family History Cases	Affected Family
DMD	16/58 (28%)	11/53 (21%)
CMT	4/16 (25%)	4/16 (25%)
SMA	1/25 (4%)	1/25 (4%)
Other	14/44 (32%)	9/39 (23%)
Total	**35/143 (24%)**	**25/133 (19%)**

TABLE 5. The characteristic of 58 DMD patients.

	Value
Clinical Stage	
Early ambulatory	17 (29.3%)*
Late ambulatory	9 (15.5%)*
Early non-ambulatory	19 (32.8%)*
Late non-ambulatory	13 (22.4%)*
CPK level (n=50)	22,182 ± 56,008 (3,517 - 405,418)**
Diagnosis by MLPA	29 (50%)*
Deletion	24 (41.1%)*
Duplication	5 (8.6%)*
Restrictive Lung	10 (17.2%)
Cardiomyopathy	8 (13.8%)
Steroid	51 (87.9%)

*n (%), **mean ± SD

TABLE 6. The characteristic of SMA patients (n=25).

	Value
Type	
Type I (0-6 mo.) Non-Sitter	2 (8%)*
Type II (7-18 mo.) Sitter	15 (60%)*
Type IIIA (>18 mo.) Walker and age onset < 3 years	4 (16%)*
Type IIIB (>18 mo.) Walker and age onset > 3 years	4 (16%)*
Exon 7&8 deletion	19 (76%)*
Exon 7 deletion	5 (20%)*

*n (%)

The second most common inherited NMD in our study was SMA, a disease that is often reported to be associated with SNM1 gene deletion in exon 7. In a separate study, we found deletions in both exon 7 and 8.[14] We also reported that SMA type II was the most common in our patient population, while another study reported Type I as most common.[15] This reflects our status as a provider of tertiary care neurologic consultation. Those with SMA type I whose disease is severe may not have been referred in time to receive our care. This difference could also be due to the fact that the diagnosis of SMA type I is typically made early in the course of disease by a geneticist, and these patients may die before being evaluated by neurologist or geneticist.

Despite representing only 10% of all patients, management of the pediatric neuromuscular disease population is challenging. These diseases are chronic, progressive and are associated with severe disability from joint contractures, respiratory failure, cardiomyopathy and scoliosis, while most patients have intact cognition. The goal of supportive care is to prevent complications and provide physical therapy to overcome limitations and improve quality of life. Hence, multidisciplinary management in an established neuromuscular clinic is crucial to improve quality of life for these patients. Prenatal diagnosis also plays important role since inherited NMDs often affect family members in different generations. Therefore, intervention to prevent the disease in offspring can decrease disease prevalence[3] as well as reduce social and healthcare costs. The limitation of the study also include that this study is single center study, thus we can't provide the information about the prevalence of neuromuscular disease in Thailand.

CONCLUSION

We found 10.88 percent of patients with neurological diseases have NMD. The majority of children with NMD who follow up at Siriraj Hospital had Duchenne Muscular Dystrophy, Hereditary Motor Sensory Neuropathy and Spinal Muscular Atrophy. Childhood NMD is a chronic disease with poor quality of life and so multidisciplinary clinical care is crucial for these patients. In order to improve the standard of care, collaboration with government and other tertiary hospitals is important and will help serve a growing population of NMD patients. Limited access to advanced diagnostic modalities prevents proper diagnosis in some patients. A future collaboration with an international genetics research center would be an important step forward to help establish a disease registry and improve genetic counseling in Thailand. National treatment guidelines and uniform implementation in pediatric neuromuscular disease clinics is needed for Thailand and other developing countries.

ACKNOWLEDGMENTS

The authors would like to deeply thank all parents, caregivers and patients with neuromuscular diseases for their kind participation. We gratefully acknowledge the staff of the Neurogenetic and Neuromuscular Research Network Faculty of Medicine Siriraj Hospital for their support of this study and for providing exceptional patient care. The authors would also like to thank Miss Chanapa Supachad for research coordination and support, and Dr. Chulathida Chomchai for assistance with English editing.

Funding: Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok, Thailand

Ethical approval: The Siriraj Hospital Institutional Review Board approved this study.

Competing interest: All authors declare that there is no conflict of interest.

REFERENCES

1. Dubowitz V. Muscle disorders in childhood / Victor Dubowitz. 2nd ed. England: London; Philadelphia: Saunders, c1995. 540 p.
2. Emery AEH. Population frequencies of inherited neuromuscular diseases—A world survey. Neuromuscul Disord 1991;1:19-29.
3. Deenen JC, Horlings CG, Verschuuren JJ, Verbeek AL, van Engelen BG. The Epidemiology of Neuromuscular Disorders: A Comprehensive Overview of the Literature. J Neuromuscul Dis 2015;2:73-85.
4. Hughes MI, Hicks EM, Nevin NC, Patterson VH. The prevalence of inherited neuromuscular disease in Northern Ireland. Neuromuscul Disord 1996;6:69-73.
5. Darin N, Tulinius M. Neuromuscular disorders in childhood: a descriptive epidemiological study from western Sweden. Neuromuscul Disord 2000;10:1-9.
6. Chung B, Wong V, Ip P. Prevalence of neuromuscular diseases in Chinese children: a study in southern China. J Child Neurol 2003;18:217-9.
7. Khedr EM, Fawi G, Abbas MA, Abo El-Fetoh N, Zaki AF, Gamea A, et al. Prevalence of neuromuscular disorders in Qena governorate/ Egypt: population-based survey. Neurol Res 2016;38:1056-63.
8. Norwood FL, Harling C, Chinnery PF, Eagle M, Bushby K, Straub V. Prevalence of genetic muscle disease in Northern England: in-depth analysis of a muscle clinic population. Brain 2009;132:3175-86.
9. Emery AE. Population frequencies of inherited neuromuscular diseases--a world survey. Neuromuscul Disord: NMD 1991;1: 19-29.

10. Lagergren J. Children with motor handicaps. Epidemiological, medical and socio-paediatric aspects of motor handicapped children in a Swedish county. Acta Paediatr Scand Suppl 1981; 289:1-71.
11. World Federation of Neurology Research Committee Research Group on Neuromuscular Diseases. J Neurol Sci 1988;86:333-60.
12. Emery AEH. Diagnostic Criteria for Neuromuscular Disorders: Royal Society of Medicine Press; 1997.
13. Kuntzer T, Lettry-Trouillat R, Bogousslavsky J. Epidemiology of adult neuromuscular disorders. Rev Med Suisse Romande 2000;120:725-31.
14. Darras BT. Spinal muscular atrophies. Pediatr Clin North Am 2015;62:743-66.
15. Arnold WD, Kassar D, Kissel JT. Spinal Muscular Atrophy: Diagnosis and Management in a New Therapeutic Era. Muscle Nerve 2015;51:157-67.