Challenges involved in performing an epidemiological survey of genetically determined myopathies

O desafio na realização do levantamento epidemiológico das miopatias geneticamente determinadas

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Abstract

Epidemiological surveys are costly and time consuming, requiring persistence on the part of the researchers. The decision to conduct such a survey should consider the basic characteristics of a good research question and involve a cost-benefit analysis. **Objective:** The aim of the present study was to describe the difficulties involved in conducting an epidemiological survey of myopathies in the Federal District. **Methods:** The entire process (three years) was described, including the first contact among colleagues in January 2011 until the identification of cases. **Results:** The following were the main obstacles encountered: limitations in the recruitment method based on signs and symptoms; the low degree of reliability regarding the data collected from hospital records; disbelief of the researchers and resistance encountered at the hospitals of the Federal District to the implantation of the project. Over the course of 3 years, 62 cases were identified. The main diagnoses were Duchenne and limb-girdle dystrophies. **Conclusion:** Whereas genetic myopathies are rare conditions difficult to diagnose, given the scenario of few technological resources, slowly progressive disorder and mostly untreatable, the low number of identified patients in this study is justified. The findings reveal the enormous difficulty clinics have in performing an epidemiological study on neuromuscular diseases in the capital of Brazil.

Key words: Muscle disorders, Epidemiological profiles, Genetic diseases, Hospital file, Descriptive study, Rare disease

Resumo:

Os levantamentos epidemiológicos são pesquisas de elevado custo que demandam tempo e persistência dos pesquisadores, especialmente quando são estudadas doenças raras. A decisão de realizá-los deve levar em consideração os quesitos de inovação, relevância, originalidade, mas essencialmente o custo-benefício. **Objetivos:** apresentar as dificuldades para se realizar um estudo epidemiológico das miopatias no Distrito Federal. **Métodos:** os autores relatam toda a trajetória de três anos, desde o primeiro contato entre os pares, em janeiro de 2011 até a detecção dos casos. **Resultados:** As dificuldades encontradas fo-

ram: as limitações no método de avaliação a partir de sinais e sintomas, a baixa confiabilidade de dados obtidos no sistema de registros hospitalares, o descrédito dos profissionais envolvidos na pesquisa com os inexpressivos índices obtidos e a resistência da rede de saúde para implantação do projeto. Em três anos de levantamento, foram detectados 62 casos, ressaltando: distrofia muscular de Duchenne e Distrofia de cinturas. **Conclusão:** Considerando as dificuldades de conclusão diagnóstica das miopatias, num cenário de poucos recursos tecnológicos, além do curso lentamente progressivo e, na maioria das vezes, intratável, justifica-se o baixo número de casos encontrados neste levantamento. Os resultados evidenciam a enorme dificuldade dos clínicos em realizar um estudo epidemiológico sobre doenças neuromusculares em plena capital federal.

Palavras-chave: Doenças musculares, Perfil epidemiológico, Doenças genéticas, Registros hospitalares, Estudo descritivo, Doenças raras

Introduction

Myopathy is any disease or syndrome in which the signs and symptoms can be attributed to pathological, biochemical or electrophysiological changes in muscle fibers or the interstitial tissue of striated muscle and for which there is no evidence that such signs and symptoms are secondary to abnormalities in the central or peripheral nervous system.[1] Together with adverse conditions of the neuromuscular junction and anterior horn of the spinal cord, myopathies account for approximately 5% of all neuromuscular conditions, which corresponds to 1 to 3% of all conditions detected in patients with neurological conditions.[2]

In a study[3] conducted in England, the combined prevalence of genetically determined muscle diseases was 37/100000, demonstrating that such disorders represent a significant proportion of patients with chronic diseases. A total of 1105 cases were identified, distributed among at least 30 different types of myopathy, the most common of which were myotonic dystrophies (30%), followed by dystrophinopathies (23%) and facioscapulohumeral muscular dystrophy (10%). The prevalence of myotonic dystrophies (10/100 000) was in agreement with rates reported in previous studies.[4,5]

Knowledge of epidemiological data on this group of diseases is limited, especially in Brazil[6]. In the last 20 years, studies have been mainly restricted to the description of case series and genetic evaluations of predefined groups.[7,8,9,10,11,12] The present study was undertaken in an attempt to fill this gap in knowledge, as epidemiological indicators assist in the determination of priorities in public health policies and the creation of reference centers for the diagnosis and follow up of patients with muscle disorders. However, upon accepting the task of outlining the epidemiological profile of genetically determined myopathies, the authors came up against a number of obstacles.

The aim of the present study was to describe the difficulties and limitations involved in conducting an epidemiological survey of myopathies in the Federal District of Brazil (FD) and the low indices detected.

Methods

A descriptive epidemiological study was conducted between January 2011 and January 2014. Patients were identified through multiple sources, such as hospital records, information systems, databanks on social security beneficiaries, a survey of electroneuromyography results and active search strategies, with the assistance of neurologists, pediatricians and physiotherapists.

Patients of either sex and any age group born and/or residing in the FD (city of Brasília and surrounding municipalities) with a clinical and/or laboratory condition compatible with genetically determined myopathy were included in the study. Individuals with inflammatory myopathy or myopathy stemming from non-neurological (rheumatic, endocrinologic, infectious or toxic) causes were excluded.

Adaptations were performed of the classification of myopathies proposed in 19681 and the classification of neuromuscular disorders proposed by Emery.[13] The following conditions were selected: muscular dystrophies (Duchenne, Becker, Emery-Dreifuss fascioscapulohumeral distrophy, Limb-girdle muscular dystrophies distal myopathy, oculopharyngeal); congenital myopathies (congenital muscular dystrophy, central core, nemalinic, mitochondrial, myotubular, myosclerosis); myotonic diseases (Myotonic

muscular dystrophy type 1 and 2, autosomal recessive, paramyotonia); glycogen storage diseases (Von Gierke's, Pompe's, McArdle's, familial periodic paralysis); progressive ossifying myositis; myopathy in homocystinuria; and familial myoglobinuria of unknown cause.

The following strategies were employed: 1) divulgation of signs and symptoms of muscle diseases for residents of the FD, with the drafting of a response letter for assistant physicians and posters designed for patients (Figure 1) and healthcare professionals (Figure 2);

2) Offer of care for spontaneous demand at screening centers (Sobradinho Hospital, Taguatinga Hospital, Brasília Children's Hospital and Brasília University Hospital) for the identification of cases of myopathies among patients with correlate complaints; 3) Structuring of reference clinics at the Asa Norte Regional Hospital and the Federal District Base Hospital (FDBH) for the reception of individuals identified as possible patients with myopathies; 4) Drafting of statement of confidentiality for authorization of the study of beneficiaries of the National Social Security Institute with G71 and similar codes of the

International Classification of Diseases; 5) Invitation to fields of pathology and genetics of the different hospitals of the FD and Sarah Network Rehabilitation Hospital; and 6) Continual study of hospital records (nursing and neurology clinics of different hospitals) and electromyography laboratory.

This project was partially funded by the Genzyme Laboratory of Brazil Ltd., which was responsible for divulgation through the production of posters, promotion of lectures directed at the scientific community and general public, facilitation of patient access to healthcare services and the provision of kits for the identification of individuals with Pompe's disease. Authorization was obtained from the administrative boards of the different institutions involved (collection of signatures), including approval from the FD Secretary of Health. This study also received approval from the local Human Research Ethics Committee under process number (CAAE) 12283213300005553.

Results

Data were collected in a three-year period spanning from January 2011 to January 2014, during which 62 patients with myopathies were identified. Table 1 displays the characteristics of the patients (sex and age) and most frequent diagnoses. Figure 3 shows the distribution of the cases according to residence in the different regions of the Federal District.

The entire divulgation strategy was followed to achieve the results. Posters directed at patients were put up at the different primary care units, such as health centers, without much resistance. Posters directed at healthcare professionals were distributed among the facilities of the FD Public Healthcare Network and hospitals that form the supplementary healthcare network. However, no adherence/authorization was obtained at the different private healthcare services, except in rare instances, which hampered the divulgation of the project at these locations. Documents were drafted and several attempts were made to publicize the project through broadcast media, but none of the stations manifested any interest.

Extra-official contacts were also made with professionals of the Sarah Hospital Network. This center in Brasília is a pioneering facility in Brazil focused on care for patients with neuromuscular diseases, with state-of-the-art technology that includes electronic patient charts, a transcription pool, highly organized statistical service and the only public molecular biology laboratory in the FD for the diagnosis of such conditions.14 Two official written invitations were made asking for the institution to participate and/or collaborate in the study. However, no interest was manifested, and no answer was given in the three years of development of the project.

A number of individuals sought the screening services with complaints similar to those divulged on the posters. After six months and the evaluation of numerous cases, the majority had complaints compatible with fibromyalgia, arthrosis, degenerative disc disease, etc. Among the hundreds of patients evaluated, only four were suspected of having myopathy and were sent to reference hospitals.

A survey was also conducted of the results of all elec-

Table 1. Epidemiological data according diagnosis of the patients.

Diagnosis	Sex(%)		Age (years)				
	Male	Female	0-6	7-19	>20	All	Mean ± SD
Duchenne muscular dystrophy	16(100)	0(0)	2	14	-	16	10,4 ± 3,7
Limb-Girdle muscular dystrophy	9(69)	4(31)	-	1	12	13	42,9 ± 16,2
Presumptive diagnosis of myopathy	5(42)	7(58)	-	4	8	12	27,4 ± 1,3
Other myopathies	5(71)	2(29)	-	2	5	7	36,6 ± 19,4
Facio scapulo humeral muscular dystrophy	3(50)	3(50)	-	1	5	6	30,2 ± 11,3

Diagnosis	Sex(%)		Age (years)				Mean ± SD
	Male	Female	0-6	7-19	>20	All	
Myotonic dystrophy pompe disease	5(83)	1(17)	-	1	5	6	29,5 ± 12,9
	0(0)	2(100)	2	-	-	2	0,5 ± 0,71
Total	43(69)	19(31)	4	23	35	62	27,3 ± 18,1

Graph I - Geographical distribution of the region at patients of Federal District and around

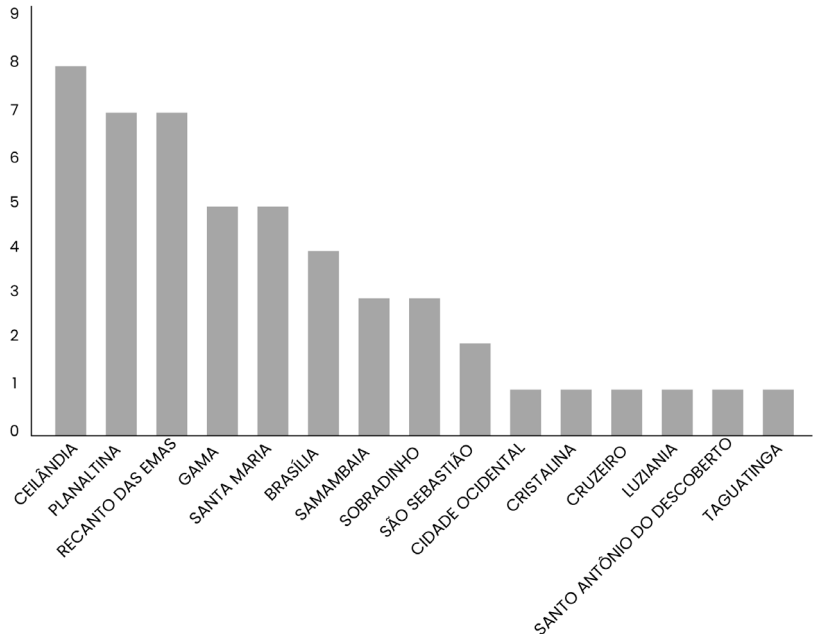

Figure 3. Geographical distribution of the region at patients of Federal District and around

troneuromyography exams conducted at the FDBH between 2006 and 2013. All patients who underwent electroneuromyography with suspected myopathy or an electrophysiological diagnosis of myopathy were included in the study (153 records). The continual attempts at communication with these patients have occurred slowly and flaws have been found in the filling out of information in a system that has not yet been automated.

Considering the impact of muscle disorders on productive capacity and the rights of children with disabilities to receive continual benefits, a survey was conducted at the National Social Security Institute. For such, a retrospective study was conducted of records beginning in 2006, which was when the Benefit Administrative System was automated. Only 38 cases of G71 and similar codes of the International Classification of Diseases compatible with myopathy were detected. The individual analysis of each file among this group of beneficiaries led to the exclusion of more than half the cases.

The pathology and genetics services of the Brasília University Hospital and the FDBH offered assistance in the survey, but no cases were found at these services. Due to the low number of cases encountered, at least half of the participants abandoned the project. Among the 30 original participants, only the authors of this paper remain involved.

Discussion

The epidemiological profile of a disease can be provided by routine information and statistics. When information is not found in the desired form or is deemed either imprecise or incomplete, investigations are performed to obtain the necessary data in a prospective, retrospective or cross-sectional

fashion, which are expressed in terms of either incidence or prevalence. Thus, epidemiological studies are costly and time consuming. The decision to conduct a study of this nature should involve an analysis of the costs and potential benefits stemming from the obtainment of such information.[15]

The importance of conducting an epidemiological study on genetically determined myopathies resides in early diagnosis, which allows improved care (treatment, when possible, palliative care and rehabilitation based on needs), as well as the possibility of pre-symptom detection and genetic counseling through the screening of affected family members. These aspects imply a reduction in material and psychological burdens, an improvement in the quality of life of patients and, to some extent, the limitation of the occurrence of new cases due to mating between individuals with reproductive cell mutations and/or *de novo* mutations. [16,17,18,19,20]

The present paper describes all the difficulties encountered when attempting to conduct an epidemiological study on uncommon diseases, including the design of strategies, limitations in the recruitment and evaluation method based on signs and symptoms, the low degree of reliability regarding the data collected from hospital records, disbelief on the part of the researchers regarding the inexpressive indices obtained and resistance encountered at the hospitals of the FD to the implantation of the project. Besides, one of the possible reasons for low engagement on the part of healthcare providers in referring patients for the study is the fact that the research were not prepared to offer advanced diagnostic tools, such as muscle biopsy and genetic testing. Other possible reason for the low adherence could be the fact that genetic myopathies are mostly untreatable and very slowly progressive disorders.

The lack of a computerized information system in the FD healthcare system, which is in the implantation phase in most hospitals, hinders the identification and survey of precise data. This is illustrated by the attempt to survey electromyography exams with results compatible with myopathies, as it was not possible to retrieve records in most cases. Moreover, existing records were filled out by hand and in a precarious fashion.

The main setbacks encountered were slowness in the service offered, inadequate structure and low accessibility to the investigation methods, even at large hospitals, such as FDBH and Brasília University Hospital. When a suspected case is found, the patient is sent to the only public reference hospital (Sarah Network) capable of molecular biological analysis.[14]

The entire three-year process of the research group illustrates the obstacles encountered during an epidemiological survey, the principal aim of which is to organize neuromuscular disease centers at hospitals in the FD of Brazil and allow integral treatment for this population of patient, including detection, treatment, rehabilitation and the palliative care in the terminal phase of the disease. Despite the difficulties, 62 cases of myopathy were identified. However, it should be stressed that the detailing of epidemiological aspects of the patients was not to object of this study, as innumerous flaws were found in the screening, identification, recruitment and evaluation of these patients, which will be performed in a subsequent phase. The focus herein is merely to describe the difficulties encountered when attempting to carry out an epidemiological study of diseases considered uncommon.

Approximately 3,05 million individuals currently reside in the FD (Brazilian Institute of Geography and Statistics)[21]. Previous studies[22,23] report that the combined prevalence of different types of myopathy ranges from 34.5 to 37.0/100000. Considering these data and possible data losses (late diagnosis, impossibility of completing the diagnosis, precarious care and limited survival), one may infer that the case series identified in the FD falls far short of the expected number. After three years of surveys, only 62 cases were found. Such individuals were mainly concentrated in the most populated region of the FD, which is the municipality of Ceilândia.

In the classic study conducted by Norwood *et al.*[3] 60% of patients were distributed among the following categories (in order of frequency): myotonic dystrophy type 1; Duchenne muscular dystrophy (DMD)/Becker's muscular dystrophy (BMD); facioscapulohumeral muscular dystrophy; and limb-girdle muscular dystrophy. In the present study, the main diagnoses were DMD, limb-girdle muscular dystrophy and myopathy of unknown origin.

Prevalence rates in studies on genetically transmitted muscle diseases are underestimated, since such

diseases lead to an early death, as occurs in DMD, the frequency of which only reflects the incidence and duration of the disease. The incidence of DMD is about one in every 4000 live births of male children, whereas BMD corresponds to 7 to 10% of these cases.[24] In the present study, DMD was the most frequent diagnosis, accounting for 26% of the total number of cases (16 out of 62) and mean age was 10 years. In the last 20 years, individuals with this disease have reached more than 25 years of age, which is a reflection of improvements in palliative care and the use of corticosteroids.[25]

Despite the fatal course of DMD and the possibility of the prevention of recurrence, this issue seems to be completely overlooked by the media, unless the child of a celebrity is affected, 26 as evidenced by the lack of response when the authors of this paper contacted broadcast and print media for the divulgation of the project. The figures seem to be inexpressive from the epidemiological standpoint, but the impact on the families of individuals with a progressive, fatal disease, such as DMD, is highly significant.

Limb-girdle muscular dystrophies accounted for 13 of the 62 cases (21%). This group exhibits considerable genetic, phenotypic, pathogenic and regional variability. The present findings are divergent from data reported in the literature, which describe a prevalence rate fluctuating around 2.3/100000.3

The presumptive diagnosis of myopathy based only on clinical and electrophysiological findings was performed in nearly 20% of the present sample, which underscores the difficult access to genetic investigation methods. A large portion of current studies are able to delineate the molecular profile of these patients.[3,12,20,25]

The prevalence rate of myotonic dystrophies ranges from 5 to 20/100000.25 Due to the fact that this group of diseases affects middle-aged individuals and older adults, nonspecific complaints often go overlooked and patients may never receive the true diagnosis. In the present study, only six cases (less than 10% of the total) of myotonic dystrophy were recorded, which differs from data reported in previous studies[3,27] and suggests considerable failure in the identification of such patients.

The divergent data in the present investigation in terms of the frequency of the diagnoses may be partially explained by the low degree of reliability in the information found on medical charts and the filling out of statistical data at information services. The entire recruitment process is hoped to be improved in a subsequent phase of the project, allowing a detailed evaluation of each of these cases as well as new patients.

Silva *et al*[28] present a Brazilian cohort of ANO5-related myopathy patients that is the largest detailed series of anoctaminopathy outside Europe. The authors emphasized that the study was conducted based on a national collaboration from different neuromuscular centers in Brazil, and a wide range of clinical and molecular characteristics was evaluated in detail, which shows the feasibility and importance of collaborative studies in a developing country.

Our experience of the present paper demonstrates that the conduction of epidemiological studies in Brazil and, more precisely, only in the FD, which does not yet enjoy the recognized academic role of states such as Rio de Janeiro and São Paulo, suggests an arduous journey along an arid terrain despite the technological advances of the 21st Century.

The words of José Pereira Rego (*apud* 15) , who studied yellow fever in the state of Rio de Janeiro in the 19th century, with slight adaptations, are perfectly applicable to the paltry results achieved by our research group in this project: "Arduous was the undertaking, audacious were those ventured it. However, one who knows the difficulties with which one struggles to achieve something, one who is aware of the limitations of society and one who knows the restrictions imposed when undertaking a task of this nature even in more advanced countries and which issues should be studied with every care and criterion will doubtlessly not fail to evaluate how many flaws are found in this study and with how many difficulties we struggled and how much time we spent to achieve work with so many imperfections."

Conclusion:

Whereas genetic myopathies are rare conditions difficult to diagnose, given the scenario of few technological resources, slowly progressive disorder and mostly untreatable, the low number of identified patients in this study is justified. The findings reveal the enormous difficulty clinics have in performing an epidemiological study on neuromuscular diseases in the capital of Brazil.

Conflict of interest: No disclosure
Acknowledgements: This project was partially funded by the Sanofi-Genzyme Laboratory of Brazil Ltd., which was responsible only for divulgation through the production of posters, promotion of lectures directed at the scientific community and general public.

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