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ORIGINAL ARTICLE

Increased prevalence of inherited neuromuscular disorders due to endogamy in Northeast Brazil: the need of community genetics services

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Abstract The aim of this study was to investigate the prevalence of inherited neuromuscular disorders (NMDs) in eight communities in Northeast (NE) Brazil in which there was an elevated rate of inbreeding. A cross-sectional epidemiological study, using the key informant (KI) approach, was performed to estimate the prevalence of NMD among the 48,499 individuals living in these eight communities, located in the backlands of the Paraíba State. Twenty-seven individuals fulfilled the diagnostic criteria for inherited NMD, which means that 1 out of 1,796 inhabitants of this highly consanguineous population was affected by NMD. This is twofold higher than that observed in previous studies in general population and was probably due to a combination of genetic drift and inbreeding. Public policies should be implemented to offer genetics services in high-risk communities.

Introduction

Inherited neuromuscular diseases (NMDs) comprise a heterogeneous group of diseases that primarily affect lower motor neuron, peripheral nerve, neuromuscular junction, or muscles (Amato and Russell 2008). It was previously estimated that the overall prevalence of inherited NMD is 1 in 3,500 individuals (Emery 1991); however, this prevalence may vary significantly due to inbreeding and genetic drift.

Consanguineous marriages are even nowadays a tradition in Northeast (NE) Brazil, which leads to an increased frequency of disabled individuals (Freire-Maia 1957, 1989; Neri 2003; Weller et al. 2012). In several communities of the Paraíba State, the frequency of consanguineous marriages ranged from 6.0 to 41.1 %, with an average of 20.2±9.1 %

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(F =0.00602±0.00253). The average rate of disabled offspring varied from 3.0±0.7 %, in unrelated unions, to 10.4±16.9 %, in first cousins or uncle–niece marriages (Weller et al. 2012).

Recent studies conducted just across the border of Paraíba, on the neighboring state of Rio Grande do Norte, identified 68 individuals with spastic paraplegia, optic atrophy, and neuropathy (SPOAN) syndrome, an autosomal recessive neurodegenerative disorder originally recognized by our group (Macedo-Souza et al. 2005, 2009). In the small community of Serrinha dos Pintos, in which 32 % of unions were consanguineous, 1 in every 250 inhabitants was affected by SPOAN syndrome (Santos et al. 2010).

We hypothesized that, due to the elevated rate of consanguineous unions in these communities, the prevalence of inherited NMD might be also increased. The aim of the present study was to investigate the prevalence of inherited NMD from eight communities located in the backlands of Paraíba State, NE Brazil. Prevalence studies on neurological disorders are important for establishing adequate health services, including of community genetics, and to give guidelines about prevention (El Tallawy et al. 2010; World Health Organization 2010).

Material and methods

A cross-sectional epidemiological study using the key informant (KI) approach, which was previously used to detect disabilities in poor communities (Kapur and Isaac 1978; Wig et al. 1980; Swaddiwudhipong et al. 1994; Mung'ala-Odera and Newton 2007), was conducted in eight communities in Paraíba State, with an overall population of 48,499 inhabitants (IBGE 2010). Sampled communities had a mixed European, African, and Amerindian background, and there were no obvious ethnic or religious differences within or between them. Their economy is mainly based on subsistence farming and on provision of administrative, health, and educational services (Weller et al. 2012).

The selected communities had already participated in a study to determine the percentage of consanguineous marriages and to estimate the inbreeding coefficient in these populations (Weller et al. 2012). Workshops were organized in health centers of each community for professionals of the Family Health Program. These workshops were designed to explain the research objectives and to schedule appointments for visiting families with disabled individuals. The KIs were community health agents (CHAs), which are door-to-door health workers well known and respected in their communities and with high school educational level. They were trained for detecting and referring disabled individuals for further evaluation. This approach has proven to be useful in previous studies (Santos et al. 2010, 2013).

The CHA reported 338 individuals with disabilities, either physical or mental. First data analysis revealed that among the 338 individuals, 256 had some form of motor impairment, and 161 (62.9 %) of them accepted to participate in the study.

The clinical and genetic evaluation of those 161 patients were conducted by three neurologists with background in genetics (FK, JLAM, and AP), two population geneticists (SS and MW), one physical therapist (AASP), and one occupational therapist (CRCG). According to the diagnosis hypothesis, additional tests were performed, including 1 muscle biopsy and 23 molecular analyses. Diagnosis of SPOAN syndrome was based on clinical findings and supported by haplotype analysis (Macedo-Souza et al. 2005). Diagnosis of limb-girdle muscle dystrophy type 2B (LGMD2B) was established by muscle biopsy with immunohistochemistry in one of the affected family members. Spinal muscular atrophy (SMA) type 3 diagnosis was established by multiplex ligation-dependent probe amplification (MLPA) analysis of *SMN1* and *SMN2* genes. All these tests were performed at the Human Genome Research Center at University of São Paulo (www.genoma.ib.usp.br).

Additionally, among the 161 individuals with motor disability, we detected 23 related individuals with spinocerebellar ataxia type 3 (SCA3) (or Machado–Joseph disease). Molecular analysis in 19 of them was performed with support of the neurogenetic network of Hospital das Clínicas de Porto Alegre (http://www6.ufrgs.br/redeneurogenetica/).

Data were tabulated and organized using Microsoft Office Excel 2007, in duplicate entries, and verified by three different investigators. Regression analysis and Spearman's coefficient were used to verify the existence of correlations between F and the prevalence of NMD. A significance level of 0.05 (or, equivalently, 5 %) was adopted.

This study was approved by the National Ethics Research Committee, and all participants or their legal representatives consented to participate (CONEP; http://conselho.saude.gov.br/web_comissoes/conep/index.html).

Results

CHA recognized 338 mental or physically disabled individuals, which represents 1 out of 143 inhabitants, with a prevalence of 697 per 100,000 inhabitants. Motor impairment was present in 161 (47.6 %) of the 338 disabled individuals. Acquired NMD was detected in 12 and inherited NMD in 27 of these 161 individuals (Table 2).

The number of evaluated individuals in each community and the estimated prevalence of NMDs were summarized in Table 1. The prevalence of both inherited and acquired NMDs was 80 per 100,000, with a wide variation among different communities; it was as low as 7 per 100,000 in Uiraúna and as high as 198 per 100,000 in Vieirópolis.

Table 1 Estimated prevalence of disabled individuals affected by acquired and inherited neuromuscular diseases (NMD) in sampled communities from the state of Paraiba, Brazil

Communities	Inhabitants	F[a]	Estimated NMD		Prevalence NMD
			n	Frequency	×100.000
Bernardino Batista	3,067	0.00939	2	0.000652	65
Jericó	7,535	0.00567	9	0.001194	119
Lagoa	4,681	0.01182	6	0.001282	128
Poço Dantas	3,752	0.00663	4	0.001066	107
Santa Cruz	6,471	0.00947	5	0.000773	77
São Francisco	3,364	0.00806	2	0.000595	59
Vieirópolis	5,045	0.0079	10	0.001982	198
Uiraúna	14,584	0.00724	1	0.000069	7
Total	48,499		39	0.000804	80

[a] Inbreeding coefficient of populations

A comparison between genetic and acquired factors that cause motor disability in the sampled communities is shown in Table 2. The result revealed that 77 (47.8 %) of the 161 individuals with motor disability were affected by a genetic disorder, of whom 27 had NMD. The most prevalent acquired disorder among NMD was paralytic poliomyelitis, seen in nine individuals (5.5 %).

The LGMD2B and SMA family clusters were responsible for 63 % of all inherited NMDs. In the community of Lagoa, three new cases of SPOAN syndrome were identified, indicating that this disorder is found in an even larger area than previously recognized. A table with diagnosed conditions in the investigated communities is shown in Fig. 1.

Although statistical analysis did not show a significant correlation between the prevalence of NMDs and the communities inbreeding coefficient (F) (Spearman's rho=0.74), all individuals with an autosomal recessive DNM had consanguineous parents.

Discussion

The KI approach is one of the most efficient strategies for detecting disabled individuals in impoverished communities, but its limitation lies in the inability to identify all cases.

Table 2 Motor disability among 161 individuals from eight municipalities in Paraíba State (both inherited and acquired conditions)

Diagnosis	No.	Percent	Diagnosis	No.	Percent
Inherited neuromuscular disease			Acquired neuromuscular disease		
Limb-girdle muscular dystrophy 2B	10	6.2	Peripheral neuropathy	1	0.6
Spinal muscular atrophy type 3	7	4.4	Diabetic polyneuropathy	2	1.2
Steinert muscular dystrophy	3	1.9	Paralytic poliomyelitis	9	5.6
Becker muscular dystrophy	3	1.9			
Andermann syndrome	1	0.6			
SPOAN syndrome	3	1.9			
	27	16.8		12	7.5
Other inherited diseases			Other acquired diseases		
Spinocerebellar ataxia type 3	23	14.3	Cerebral palsy	40	24.8
Ataxia-telangiectasia	2	1.2	Sydenham's chorea	1	0.6
Tibial aplasia ectrodactyly	1	0.6	Leprosy	1	0.6
Cockayne syndrome	1	0.6	Encephalitis sequelae	2	1.2
Joubert syndrome	1	0.6	Syringohydromyelia	1	0.6
Prader–Willi syndrome	1	0.6	Kyphoscoliosis	5	3.1
Rett syndrome	1	0.6	Multiple arthrogryposis	3	1.9
Sotos syndrome	1	0.6	Myelomeningocele	2	1.2
Sturge–Weber syndrome	1	0.6	Other	18	11.2
McCune–Albright syndrome	1	0.6			
Wilson disease	1	0.6			
Niemann–Pick type C disease	1	0.6			
Osteogenesis imperfecta	3	1.9			
Other	12	7.5			
	50	31.0		72	44.7
Total	77	47.8	Total	84	52.2

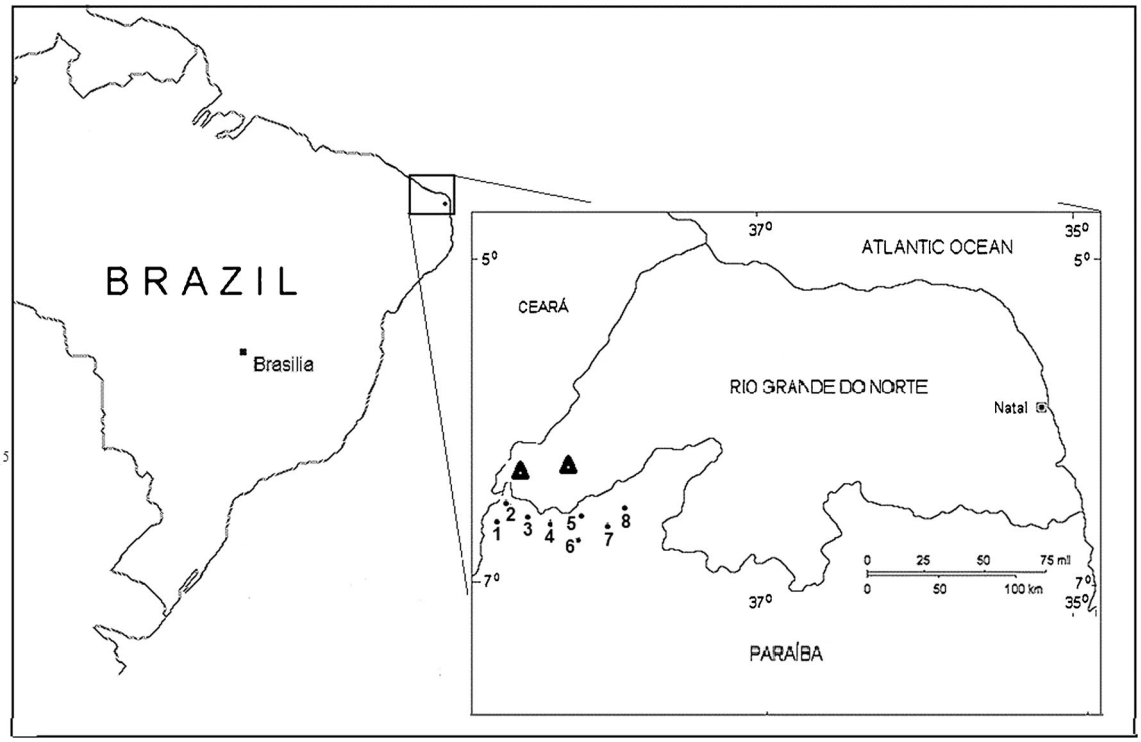

Fig. 1 Distribution of studied communities in the states of Paraíba and Rio Grande do Norte, Northeast Brazil. *1* Bernadino Batista, *2* Poço Dantas, *3* Uirauna, *4* Vieirópolis, *5* Santa Cruz, *6* São Francisco, *7* Lagoa, *8* Jericó. *Triangle* represents the occurrence area of the SPOAN syndrome in the state of Rio Grande do Norte

However, population adherence requires motivation and financial resources, which may explain the number of nonparticipating individuals. This bias may contribute for the underestimation of the true prevalence of NMD in the sampled population.

Despite this limitation, almost half of the disabled individuals evaluated in this study were affected by a genetic disorder and 16.6 % of the total by an inherited NMD. Based on the review of over 150 surveys, Emery (1991) estimated that the total prevalence of inherited neuromuscular disorders in different populations was generally around 1 out of 3,500 individuals. Compared to this previous study, the prevalence of hereditary NMDs was close to twofold increased in the Brazilian communities—27 affected individuals in 48,499 inhabitants or 1 out of 1,796 individuals.

Three clusters of autosomal recessive NMDs, whose manifestation was associated with an increased frequency of consanguineous marriages, were found in the sampled populations: SPOAN syndrome, LGMD2B, and SMA, which were responsible for almost 75 % of cases of inherited NMD. Since all parents of affected individuals were consanguineous, it may indicate that endogamy in the investigated communities indeed contributes for an increased number of cases of inherited NMD.

Among individuals with motor disability, parental inbreeding was present in 39.1 %, which is higher than the observed 25.6 % average frequency of consanguinity in their communities. In a recent study in the same area, it was shown that the number of disabled offspring was 12 % higher among consanguineous than among unrelated parents (Weller et al. 2012).

Different factors may explain the increased prevalence of inherited NMDs in these communities. Distance to large urban centers, travelling costs, and low population density may contribute to geographic isolation, reducing gene flow between populations and increasing genetic drift. These factors are well known to contribute to increased frequencies of genetic diseases in human populations (Bittles 1990, 1994; Bittles et al. 1991; Bittles and Hamamy 2009). Additionally, consanguineous marriages are a cultural tradition of these populations, as pointed out by Weller and colleagues (2012); nevertheless, geographic isolation alone does not explain the high inbreeding and disability rates, since neighboring communities with similar population densities and socioeconomic conditions often had different F values and frequencies of consanguineous marriages.

Unknown cultural factors may play a fundamental role in consanguineous marriages, and efforts should be done to investigate the relation between culture and endogamy in NE Brazil. Therefore, these NMD clusters may be caused by a combination of consanguinity and genetic drift. Furthermore, inherited NMDs could, as seen in SPOAN syndrome, be associated with founder effect, which lead to the introduction of recessive mutations that spread out locally.

Results of this study on inherited NMD are important for the management and planning of health services.

Epidemiological population-based studies provide accurate data required to establish health policies. This study showed that almost half of the physical disabilities found in communities of NE Brazil were caused by genetic factors. In addition to recessive disorders, it was detected that a large family with 23 individuals was affected by SCA3, an autosomal dominant disorder common in continental Portugal and Azores, probably due to a founder effect (Castilhos et al. 2013).

All these patients did not have access to community genetics services. They would have had to travel long distances for diagnosis, counselling, and treatment, because medical genetic specialists are not present nearby (Beiguelman 2000; Marques-de-Faria et al. 2004; Novoa and Burnham 2011). These results provide an evidence of the need of genetics services in high-risk communities in NE Brazil, as recommended by the World Health Organization (2010).

Conclusion

The present findings showed that 1 out of 1,796 inhabitants of the highly consanguineous population was affected by inherited NMD. The twofold increased prevalence was probably due to a combination of genetic drift and inbreeding. Public policies should be implemented to offer genetics services in high-risk communities.

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Conflict of interest The authors declare that there is no conflict of interest.

Compliance with ethics guidelines The data sampling protocol and the consent procedure were reviewed and approved by the National Research Ethics Committee, Brazil (CONEP) (http://conselho.saude.gov.br/web_comissoes/conep/index.html). All persons gave their informed consent prior to inclusion in the study.

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