Research Journal of Biological Sciences 3 (12): 1403-1407, 2008
ISSN: 1815-8846

Neuromuscular Disease in Childhood, a Clinicopathological Study in Iran

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Abstract: A prospective study of the neuromuscular diseases in Iranian children was conducted from 2000-2007 in Markaze Tebbi Koodakan, Tehran University of Medical Sciences, Tehran, Iran. Similar data are scanty outside Europe and North America. This study attempts to determine the type and relative frequency of neuromuscular diseases in Iran. One hundred and sixty five children (<or = 16 years) were assigned to an entity of neuromuscular disease following review of the clinical, biochemical and neurophysiological data and after review of most of available patients records. The common muscle diseases in Iran were muscular dystrophy (47.3%), peripheral neuropathy (17%) and inflammatory myopathy (7.9%). Motor neuron disease was seen in 1.8% of cases. Of the muscular dystrophies, Duchene type (6.1%) was more prevalent. History of consanguinity was present in 56%. Positive family history was seen in 15% of cases. However, 30 (18.2%) cases showed no significant pathology. For this group of neuromuscular diseases further studies are needed. The study has revealed a great variety of pathology affecting children presenting with neuromuscular symptoms. The most prevalent of these were muscular dystrophies which is concordant with most other studies. The high frequency of consanguineous marriage in our cases needs further attention for social programming.

Key words: Muscle, nerve biopsy, neuromuscular disorders, pediatric age group, muscular dystrophy, peripheral neuropathy, inflammatory myopathy

INTRODUCTION

Neuromuscular diseases constitute a complex group of heterogeneous, often inherited disorders. They can be broadly subdivided into disorders mainly affecting the anterior horn cell, peripheral nerve, neuromuscular junction and the muscle fiber. Some multisystem disorders such as myotonic dystrophy and mitochondrial myopathies are traditionally also included (Bailliere, 1995a). An epidemiological study is important not only for monitoring preventive measures, such as genetic counseling, but also for planning hospital resources, rehabilitation services and social welfare programs for the handicapped in a particular population (Packer, 1982). Population surveys that include all types of neuromuscular diseases are rare in Iran and the majority of previous surveys have determined the prevalence of a single disease in a community and no reliable data exists for the rare conditions. Since most neuromuscular diseases are hereditary, their proportions relative to each other vary according to the gene frequency, which may differ between one region and another (Emergy, 1991). The prevalence of the most common types of hereditary neuromuscular diseases was estimated to be 1/3500 population (Bailliere, 1995b). The aim of the present study was to figure the relative frequency of the biopsy proven neuromuscular diseases in Iran (Scola, 2003; Bleggi-Torres, 1994). This report is the result of an analysis of 165 consecutive neural and muscle biopsies obtained over the 7 year period from 2000-2007 in a referral children hospital related to Tehran University of Medical Sciences.

MATERIALS AND METHODS

One hundred and sixty five consecutive muscle and neural biopsies done in the period from 2000-2007 in the department of pathology, Markaze Tebbi Koodakan related to Tehran University of Medical Sciences, Iran, were reviewed. Most of available patients records were reviewed and correlated with the clinical information and other studies including electromyography, nerve

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conduction studies and routine biochemistry studies. All specimens were taken by open biopsy and often obtained from the vastus lateralis muscle and seural nerve. Paraffin embedded or frozen sections were stained with Hematoxylin-Eosin stain, Gomori trichrome and NADH (Nicotinamide adenine dinucleotide). Routine biochemistry studies included Creatine Kinase, LDH (Lactate dehydrogenase), AST (aspartate aminotransferase), ALT (alanine aminotransferase) and ALK. p (alkaline phosphatase) (Richard, 2007). Motor and sensory nerve conduction studies and electromyography (EMG, NCV) (Packer, 1982; David and Jones, 1994), were performed on all but some cases in whom there were no opportunity to do these investigations before the neural and muscle biopsy. Most biopsies were studied by light microscopy and some with the electron microscope.

RESULTS

Reviewing the general pattern of all categories of neuromuscular disease in this series, it is apparent that Iranians do suffer from most of the primary or secondary muscle diseases described in the literature. Since, this study was limited to the patients who underwent muscle and neural biopsy, it might not represent the exact pattern of neuromuscular disease in Iran. There could be many other rare muscle diseases which were not described in this series, because of either biopsy was not done or showed nonspecific findings.

One hundred thirty five cases showed features with exact pathological diagnosis, which were classified into 6 groups (Table1).

- Muscular Dystrophy was the most frequent neuromuscular disease in this study, constituting 47.3% of the cases seen and consanguinity was present in 44 cases. There were 10 Duchene, 9 congenital, 3 limb-girdles and 2 Becker among them.

Most patients in this study, were investigated before institution of dystrophin staining for study of muscular dystrophies. Immunohistochemical analysis for dystrophin was not available in our laboratory before 2005. Such analyses probably would have influenced the figures quoted for the Duchene and Becker and other types of muscular dystrophies.

Seventy eight cases of muscular dystrophy showed mean age of 8.4 years. The youngest one was 4 days and the oldest 14 years old. There were 20 females and 58 males. Positive family history was seen in 15 cases.

Concordances with clinical diagnosis were seen in all cases. Elevated muscle enzymes were seen in 65 patients,

Table 1: Childhood neuromuscular disorders seen by biopsy

Valid	Frequency	(%)	Valid (%)	Cumulative (%)
Muscular dystrophy	78	47.3	47.3	47.3
Motor neuron disease	3	1.8	1.8	49.1
Inflammatory myopathy	13	7.9	7.9	57.0
Peripheral neuropathy	28	17.0	17.0	73.9
Minimal change	6	3.6	3.6	77.6
GSD	7	4.2	4.2	81.8
Not diagnostic	30	18.2	18.2	100.0
Total	165	100.0	100.0	

Table 2: Cross tabulation of biopsy and biochemical enzymes

	Enzyme			
Count	Normal	Annormal	Not available	Total
Biopsy				
Muscular dystrophy	4	65	9	78
Motor neuron disease	2	1		3
Inflammatory myopathy	5	7	1	13
Peripheral neuropathy	8	7	13	28
Minimal change	2	4		6
GSD		4	3	7
Not diagnostic	9	15	6	30
Total	30	103	32	165

Table 3: Cross tabulation of biopsy and electro diagnostic findings

	Electrodiagnostic finding				
Count	Myopathic	Neurogenic	Normal	Not available	Total
Biopsy					
Muscular dystrophy	61	3	4	10	78
Motor neuron disease	1	1	1		3
Inflammatory myopathy	10	1		2	13
Peripheral neuropathy	3	21		4	28
Minimal change	3		2	1	6
GSD	1		3	3	7
Not diagnostic	9	2	7	12	30
Total	88	28	17	32	165

in 4 cases muscle enzymes were normal and in 9 cases, they were not available (Table 2). Electrophysiological studies were available in 68 patients and revealed myopathic pattern in 61 patients, neurogenic pattern in 3 cases and were normal in 4 patients (Table 3).

- Peripheral neuropathy was next in frequency to muscular dystrophy, constituting 17% of the cases seen and consanguinity was present in 15 cases. The majority of peripheral neuropathies were classified as hereditary motor sensory neuropathy type 2 (HMSN2). The age ranged from 2.5-13 years with mean age of 3.4 years. In 11 cases were female and 17 cases were male.

Positive family history was seen in 6 cases. Concordances with clinical diagnosis were seen in 11 cases. Elevated muscle enzyme was seen in 7 patients, in 8 cases muscle enzymes were normal and in 13 cases, they were not available. Abnormal electrophysiological findings revealed 3 myopathic and 21 neurogenic patterns and in 4 cases they were not available (Table 4).

Table 4: Cross tabulation of biopsy and family marriage

	Family marriage		
Count	Positive	Negative	Total
Biopsy			
Muscular dystrophy	44	34	78
Motor neuron disease	2	1	3
Inflammatory myopathy	4	9	13
Peripheral neuropathy	15	13	28
Minimal change	3	3	6
GSD	7		7
Not diagnostic	17	13	30
Total	92	73	165

- Thirteen cases were classified as inflammatory myopathy and consanguinity was present in 4 cases. They included 5 cases of dermatomyositis and 1 case of polymyositis. In 8 cases were female and 5 cases were male. The age range was 2.5-12.8 years with the average age being 7.6 years.

Positive family history was seen in 3 cases. Concordances with clinical diagnosis were seen in 11 cases. Muscle enzymes were elevated in 7 patients, in 5 cases muscle enzymes were normal and in 1 case, they were not available. Abnormal electrophysiological findings were shown in 11 patients and in 2 cases they were not available.

- Seven cases of Glycogen Storage Disease (GSD) were seen and consanguinity was present in all of them. The age ranged from 5 months to 13 years with mean age being 6 months. There were 5 females and 2 males.

Positive family history and concordance with clinical diagnosis were not seen in these cases. Elevated muscle enzyme was seen in 4 patients, in 2 cases muscle enzymes were normal and in 1 case, they were not available. Abnormal electrophysiological findings were shown in 1 patient reported as myopathic process and in 3 cases they were normal, in 3 cases were not available.

- Six cases of minimal change were seen and consanguinity was present in 3 cases. The age ranged from 25 days to 13 years with mean age being 2.8 years. There were 3 females and 3 males.

Positive family history was seen in 5 cases. Muscle enzymes were elevated in 4 patients; in 2 cases muscle enzymes were normal. Abnormal electrophysiological findings were shown in 3 patients reported as myopathic pattern and in 2 cases they were normal, in 1 case they were not available.

- The last reviewed disease in this study was motor neuron disease, which was seen in 3 cases. The patients were 2, 2.5 and 10 years old who presented with muscle weakness and gate problems. Consanguinity was present in 2 patients. There were 2 females and 1 male.

Positive family history and concordance with clinical diagnosis were not seen. Slightly elevated muscle enzyme was seen in one patient; in 2 cases muscle enzymes were normal. Abnormal electrophysiological findings were shown in 2 patients, one reported as myopathic and one as neurogenic pattern and in one case they were normal.

DISCUSSION

Child neuromuscular diseases, as defined by Bailliere (1995b) consist of a rare group of heterogeneous conditions. It is often a severe, crippling and progressive disease of genetic origin and may thus become a heavy strain on both patient and family. Knowledge of neuromuscular epidemiology in children it is important for the assessment of its medical implications (Bailliere, 1995b).

There is a scarcity of data on the distribution of neuromuscular diseases in populations other than those in North America, Europe, Japan and Australia (Radhakrishnan, 1987; Chung, 2003; Jongpiputranich, 2004; Tangsrud, 1988; Hughes, 1996). Since most neuromuscular diseases are hereditary and their proportions relative to each other vary according to the gene frequency, which may differ between one region and another. Examples of this are reflected in studies from Sudan (Darin, 2000; Ahlstrom, 1993) and North Africa, which demonstrated a relatively high proportion of hereditary muscular dystrophy, influenced by high rates of consanguineous marriage.

This hospital based study does not allow calculation of incidence or prevalence rates for the various neuromuscular disorders in Iran but does provide an opportunity to compare their prevalences relative to one another.

The common muscle diseases in Iran were muscular dystrophy (47.3%), peripheral neuropathy (17%) and inflammatory myopathy (7.9%). Of the muscular dystrophies, Duchene type (6.1%) was more prevalent, concordant with observation from North African countries known to have a high incidence of consanguineous marriages (David and Jones, 1994; Darin, 2000).

The proportion of all types of muscular dystrophy in Iran is consistent with the pattern found world-wide

(Emergy, 1991). There were more boys than girls in the series. The predominance of boys is partly due to the X-linked Duchene and Becker types of dystrophy (Bailliere, 1995b), which account for 58 boys of the total 78 patients with muscular dystrophy.

Peripheral neuropathy was next in frequency to muscular dystrophy, constituting 17% of the cases seen. HMSN type 2 was the only recorded entity of peripheral neuropathy and no case of tropical nutritional neuropathy, known to be endemic in Africa, was observed (Osuntokun *et al*., 1987; Osuntokun, 1971, 1973). Males predominated among peripheral neuropathy cases because it is known to affect more males (Chi, 1989).

Dermatomyositis was the most inflammatory myopathy seen (Scola, 2000). No pyomyositis was encountered, in contrast with experience in Africa where it was reported to be the commonest primary muscle disease in hospitalized Nigerians and was equal in prevalence to the group of muscular dystrophy in a community based study (Osuntokun *et al*., 1987; Osuntokun, 1973). The high prevalence in females is compatible with other studies (Scola, 2000).

The common occurrence of spinal muscular atrophies in this country was not fully appreciated. Clinically many of these cases were diagnosed (Chung, 2004) and do not refer for biopsy evaluation, some are diagnosed by genetic studies only. Of the 3 cases of spinal muscular atrophy none of them were clinically diagnosed as spinal muscular atrophy.

The relatively high proportion of muscle biopsies with nonspecific changes (18.2%), which is comparable with Yoke-Sun study (17%) (Singapore, 1986; Lee, 1986; Premasiri, 2003) could be attributable to several factors; one important factor was that sampling, both spatially and temporally. The involvement of the muscles in many muscle disorders is patchy. Some conditions affect muscles without producing diagnosable lesions (Lee, 1986).

In electro diagnostic studies revealed myopathic pattern in 79 cases, neuropathic pattern in 26 cases and was normal in 10 cases. In 20 cases no electro diagnostic data was available. Muscle enzymes were elevated in 88 and 21 cases have normal muscle enzymes and in 26 patients biochemical data was not available (Table 3).

We suggest that discrepancies in electro diagnostic findings are because of difficulty in distinction between myopathic and neuropathic patterns in children (Table 2).

In this study, close parental consanguinity was documented in 56% of children diagnosed by biopsy. This is slightly higher than a rate of 54.6% reported in a community survey from the Eastern Province of Saudi Arabia and less than 63% in study performed later in Saudi Arabia (Salih, 1996, 1980). The data from the present study contrasts remarkably with observations in Europe, North America, Sudan and North Africa (Salih *et al*., 1983; Salih, 1985).

In summary, muscular dystrophy and peripheral neuropathy constitute the bulk of neuromuscular disorders in Iran. Familial cases are remarkable in number and offer opportunities for multicentre genetic surveillance and therapeutic trial programmes.

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