Editorial

Bird's eye view of myopathies in India

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With just over a thousand neurologists catering to the large population of India,[1] neurology consultants find their hands full with the rigors of day-to-day clinical neurology. It is difficult to assimilate the voluminous information on the subject of interest, myology often taking a backseat. This issue of Neurology India is therefore being presented with the idea of providing comprehensive current information to the reader. As the authoritative reviews outline 'state-of-the-art' information on various topics in myology, let us take stock of the Indian situation.

From the available literature in India, it is clear that wide varieties of myopathies exist and are beginning to be recognized more clearly. In India, presently there are only a few centers having the laboratory support to study various aspects of myopathies and it is very likely that only a portion of the existent myopathies have been analyzed to date.

Muscular Dystrophies

The common muscular dystrophies are Duchenne muscular dystrophy (DMD) in childhood and limb girdle muscular dystrophy (LGMD) in adulthood. Early studies on muscular dystrophies have been done by Abraham *et al.* and Desai *et al.* in the 1960s, elucidating clinical features of myopathies.[2-4] Mondkar and Bhabha, in 1984, studied clinical features of 126 cases of muscular dystrophies at the KEM Hospital, Mumbai.[5] In this paper, they discussed a variety of dystrophies besides DMD. In a more recent large study by Das,[6] 27.4% of all myopathies were muscular dystrophies, 30% having DMD and 29.2% LGMD subtypes. In a tertiary neuromuscular center in Mumbai, DMD formed the main myopathy of childhood while limb girdle dystrophy was the most common diagnosis of adolescent and adulthood myopathies.[7]

Duchenne muscular dystrophy

DMD occurs in all communities in India. Though no ethnic variations have been observed, one hospital-based study suggested a higher prevalence among certain Hindu communities of Uttar Pradesh.[8] The phenotype of DMD has been studied in detail by a number of investigators. The differential muscle wasting and hypertrophy giving the 'Valley sign' as described by Pradhan[9] can aid in the diagnosis of DMD/ Becker muscular dystrophy (BMD) patients in cases without calf hypertrophy or late presentation. Due to the prevalent religious concepts and illiteracy, more than one case of dystrophinopathy in a family is not too uncommon in India. I have personally come across parents willing to take chances, in pursuit of a normal male offspring, and as a result having to look after as many as six afflicted children. In general, familial cases with DMD seem to follow similar clinical courses but on occasions, striking intra-familial phenotypic variability has been seen.[10] For example, one family has been described in which three brothers were suffering from a dystrophinopathy; one with a DMD phenotype, the second with a BMD phenotype and the third cousin had only cramp-myalgia syndrome. Two of the three affected children had different deletions in the dystrophin gene.[10] Intra-familial variation with the same in-frame mutation, index case having DMD phenotype and maternal uncle having BMD phenotype is reported in this issue.[11] Manifesting females have been documented[12] and the cardiac involvement has also been studied.[13] Multiplex polymerase chain reaction (PCR) has been used to study the dystrophin gene in many centers in India and information is available from large centers in the north, west and south of the country.[14-16] Analysis of point mutations and prenatal diagnosis has also been available, though at limited centers; Maheshwari *et al.* have reported their experience with prenatal diagnosis.[17,18] An interesting phenomenon of double deletions has also been noted. These patients have two non-contiguous hotspot deletions in the dystrophin gene. The significance is not clear as there are only few reports in the world literature.[10] A most unusual

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instance of possible paternal transmission in a dystrophin-deficient dystrophic pedigree has been documented recently.[19] BMD has been genetically analyzed and the frame shift hypothesis seems to hold true in the majority of patients. In this issue, the review by Nadkarni and colleagues discusses the available genetic information and rehabilitative aspects related to DMD in India.

In India, due to lack of awareness of muscle diseases, parents of affected children often do not know where to seek help. Illiteracy is also an issue which makes counseling difficult. The social structure in India is also not kind to the physically challenged with no availability of ramps for public modes of transport. Home rehabilitation programs,[20] designed for those patients who cannot come for regular visits, has proved to be more successful than clinic-based programs.

Limb girdle muscular dystrophy

LGMD is the most common muscle disease seen in the adult population. The issue is complex and the broad term of LGMD now encompasses many subgroups characterized genetically and by protein abnormalities. Presently, it is indeed difficult but important to identify the subgroups of LGMD. The information on LGMDs in India is at an early stage, only few subgroups having been studied clinically and immunocytochemically. Sarcoglycanopathies and dysferlinopathies have been thus characterized up to a point.[21-27] Three series each are available on these two subjects, highlighting the clinical and laboratory features of cohorts form different parts of India. The review by Khadilkar and Singh describes the available information on the subject from India. Besides large series, unusual family studies of patients with muscular dystrophy and dopa responsive dystonia or mental subnormality and chorea have been reported.[28,21] As can be perceived, much further work in this field awaits attention. At the present point in time, it is not possible to comment on the relative frequency of the LGMD subtypes in India, but there is a growing feeling that dysferlinopathies are common. It needs to be emphasized that the available Indian LGMD information awaits genetic confirmation. Besides LGMDs other muscular dystrophies are also encountered in India.

Other muscular dystrophies

Facioscapulohumeral dystrophy (FSHD) is seen infrequently and published data is scarce. In a series of 211 cases of muscular dystrophy, Srinivas[29] the FSHD constituted only 2.3% of patients and Das[6] had 1.3% FSHD phenotype. In FSHD patients, the differential wasting and hypertrophy of the muscles around the shoulder girdle is known to form the 'poly hill sign' of Pradhan.[30] Another appearance called the 'shank sign' has also been reported.[31] Myotonic muscular dystrophy [MyMD] is less common in India. Worldwide, the prevalence of myotonic dystrophy is variable. In Caucasian populations, it forms the most common dystrophy of adulthood whereas it is very rare in Negros. In India, MyMD is encountered but the frequency is far less than that of LGMDs in the population. Gourie Devi[32] found myotonic dystrophies to form only 8% of all muscular dystrophies. This relatively low prevalence possibly relates to the population genetics. Basu *et al*. has studied the CTG repeats in these patients with myotonic dystrophy and found similarity in the molecular anatomy of 90% of the Indian patients with Caucasians. In the remaining 10%, the expansion of the CTG repeat was of a new haplotype suggesting a unique founder effect probably indigenous to the Indian population.[33]

Inflammatory myopathies

All types of inflammatory myopathies are encountered,[34-37] in India. The clinical significance of this group of myopathies lies in their potential of reversibility and hence the neurology clinician is 'looking to diagnose' inflammatory myopathies. However, the bulk of the literature is now suggesting that these conditions are not very common and differential diagnosis can be difficult. The particular difficulty is with sporadic limb girdle syndromes of other origins, like dystrophies or metabolic myopathies. As immunological factors in muscular dystrophies are being elucidated further, the borderland between dystrophies and inflammatory myopathies is being clarified. Sundaram and colleagues, in this issue, highlight the importance of using the immune markers on the muscle tissue in the Indian situation. One interesting point is the rarity of inclusion body myositis (IBM) in the Indian literature. While the mainstream literature is diagnosing IBM with more frequency, only case reports of IMB are available form India. Gayathri[38] reported five patients (four sporadic and one hereditary), and all had progressive muscle weakness with spared cranial nerve innervated muscles. Large series of inflammatory myopathies have also carried this point. It is difficult to know whether the cases are missed out or there is a true paucity of these patients in this part of the world and we need more studies looking at this problem. In Karnataka, South India, in the year 1986, an epidemic affected a large number of patients with inflammatory myopathies and the information on these patients has been documented. The characteristic features were a short febrile illness followed a few days later by myalgia, edema of extremities, severe motor weakness and involvement of multiple other systems. The disease was monophasic and response to immunomodulation was favorable.[39]

Neuromuscular junction disorders

The clinician can not afford to miss a neuromuscular junction disorder. They are so treatable! The most common of them, myasthenia gravis, usually does not result in diagnostic difficulty, but uncommon presentations can be foxing, as are the Lambert Eaton syndrome and acquired neuromyotonia. The subgroups of myasthenia with anti-Musk antibody behave differently and may be challenging to diagnose and treat. In India, the anti-MUSK antibodies have been available in the recent times and information on the MUSK-positive cases is gathering. In this issue, Singhal *et al*. have discussed their long experience with myasthenia over 43 years in Mumbai, analyzing over 800 patients. The male preponderance is striking and seeking an explanation. However, such male preponderance is also encountered amongst Indians in Singapore, as they point out.

Congenital myopathies

Patients with congenital myopathies are seen by pediatric and adult neurologists alike. They represent the completely different group of diseases wherein the muscles do not develop well, unlike the dystrophies where they develop to disintegrate. The information on congenital myopathies in India is limited. In a study from Bangalore, 100 cases of congenital myopathies (CM) were diagnosed over a period of 20 years and the spectrum of CM consisted of centronuclear myopathy,[39] congenital fiber type disproportion,[35] central core disease,[9] multicore disease,[7] myotubular myopathy,[5] nemaline myopathy[4] and one case of CM with tubular aggregates.[40] In a north Indian study, four nemaline myopathy cases out of 15 were identified.[41] Merosine-negative muscular dystrophy, congenital dystrophy resembling Fukuyama disease and congenital fiber type disproportion have been documented in case reports.[42-44]

Metabolic myopathies like the osteomalacic myopathies have been documented in older Indian literature. Though it is less common at present in India, Irani reported 15 female patients of whom eight had constantly worn the burkha when outdoors. Notably these patients were multiparous with prolonged periods of lactation. The striking features were bone pains and pelvic limb girdle weakness.[45,46]

Distal myopathies

When a patient presents with distal weakness, neurogenic conditions like hereditary neuropathies and spinal muscular atrophies need consideration, but a small proportion of distal weakness is a result of myogenic diseases. These distal myopathies, though rare, are important and a lot of information on the classification, pathophysiology and genetic aspects has emerged in the recent years. The main distal myopathy in the Indian context would seem to be dysferlinopathy, wherein the proximo-distal phenotype is the most common. Vacuolar myopathies with distal presentation have not been reported in the Indian literature. Case reports of unspecified distal myopathies are available.[47,48]

Mitochondrial myopathy

Case series of mitochondrial myopathies have been published from India. In a large study from Hyderabad,[49] the most common clinical syndrome associated with ragged red fibers (RRFs) on muscle biopsy was progressive external ophthalmoplegia with or without other signs. Kearns-Sayre syndrome and myoclonic epilepsy with RRFs was seen less often. From New Delhi, Mehndiratta and colleagues[50] have reported a series of 14 patients with mitochondrial cytopathies. In this series, 12 patients could be categorized into well-defined syndromes, while two belonged to an undefined group. In the defined syndrome categories, three patients had MELAS (mitochondrial encephalopathy, lactic acidosis and stroke-like episodes), three had MERRF (myoclonic epilepsy and ragged red fiber myopathy), three cases had KSS (Kearns-Sayre Syndrome) and three were diagnosed to be suffering from mitochondrial myopathy. Case reports of mitochondrial diseases are also available, depicting MNGIE syndrome, cardiomyopathy and ataxia.[51,52] Recently, mitochondrial genetics has been made available in India in the private sector and the genetic information on these diseases is expected to increase with time.

Thus, the available information on myopathies in India confirms the existence a variety of disorders. The relative prevalence of LGMDs, myotonias and IBMs seems to be different in the Indian population and further work will provide information in these areas as the laboratory facilities become available on larger scale.

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I do hope that readers enjoy this issue.

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