A study of the Clinical Profile and Outcome measures in patients with Duchenne Muscular Dystrophy.

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Introduction:

Duchenne Muscular dystrophy (DMD) is one of the commonest forms of muscular dystrophy and is a devastating neuromuscular disorder with relentless progression. It starts in childhood with delayed milestones, abnormal gait, frequent falls, and difficulties in climbing stairs and rising from squatting position, contractures and calf muscles enlargement. About a third of them have IQ below 70. Over a period of time, there is progressive decline in muscle strength with loss of ambulation at a mean age of 9.5 years. Other features include respiratory insufficiency, scoliosis and cardiomyopathy. Eventually, death occurs from respiratory insufficiency or cardiac causes at a mean age of 19 years. The diagnosis is based on clinical features, raised serum Creatine phosphokinase (CPK), absence of dystrophin in muscle biopsy and finding of mutation in dystrophin gene. Treatment goals are to maintain ambulation as long as possible, prevent contractures, and provide psychological support. These can be achieved with physiotherapy, bracing, surgical correction of scoliosis and corticosteroids. Other treatments aiming at the correction of the gene defect itself are not yet available for clinical use.

Problems with diagnosis and management

DMD is a common inherited disorder but still can have diagnostic problems, especially in terms of timing of the diagnosis as early features of developmental delay and clumsiness while walking may be not be recognised as a manifestation of disease process. An early diagnosis and initiation of treatment are important, considering the

beneficial effects of steroids and inflammatory changes seen in early part of the disease. Gene based test are helpful but may be negative in some patients with smaller mutations and at uncommon sites, they may also not distinguish between those with various levels of protein deficiency. Muscle biopsy with immunohistochemistry for loss of dystrophin remains the gold standard for diagnosis, characterisation and prognostication. Treatment options are limited with corticosteroids and physiotherapy showing benefit in prolonging the duration of ambulation with additional beneficial effects on cardiac functioning. Other drugs are tried with variable results but none with proven effect on survival or cure potential. Gene therapy has been tried but with limited success due to the large size of dystrophin gene, problems with finding suitable vectors for transportation of the products, and other related problems. At present, corticosteroids with physiotherapy remains the cornerstone of treatment, and in addition, management of scoliosis, contractures, cardiac and respiratory illness, until newer modalities of treatment like stem cell therapy using myogenic precursors with capability of reaching the target muscles by systemic delivery are found feasible and translated into DMD patients.

There are few studies aimed at describing the clinical profile, natural history, progression of the disease over a period of time and the effect of multidisciplinary therapy, which includes both drug and non pharmacological

methods, including Physiotherapy and Occupational therapy on children with this devastating disorder.

The purpose of this study was to look at the natural history of a cohort of patients attending a comprehensive multidisciplinary clinic dedicated to the management of neuromuscular disorders. The patients with DMD are seen

in the clinic and a comprehensive assessment by made by the Neurologist, Physiatrist, Occupational and Physiotherapist and a Clinical Geneticist, where the initial work up including muscle biopsy is planned. After ascertaining the diagnosis, treatment options including pharmacological measures and non pharmacological measures like endurance enhancing and stretching exercises and advice on need based ADL's. Genetic counselling is done by the Clinical geneticist. These patients get followed up once every 6 months.

This study looks at the entire aspect of clinical profile including the developmental aspects, early symptomatology and a chronological record of various stages of the disease and this is correlated with the genetic aspects,

Histopathological data, treatment options, both pharmacological and non pharmacological, using a structured proforma. The natural history is obtained from both the treated group and historical controls seen in the clinic.

Aims of the study:

To study the natural history, the rate of progression of disease in patients with Duchenne Muscular dystrophy and the impact of treatment on outcome measures.

Objectives of the study:

1. To study the disease related milestones including time to stop ambulation and confinement to wheel chair during the course of illness in Duchenne muscular dystrophy.

2. To assess the muscle power and functional measures, anthropometric and goniometric changes and correlate these measures with the various activities of daily living using validated assessment scores.

3. To compare the outcome measure of time to stop ambulation in patients who received the comprehensive treatment for at least 2 years with the historical controls.

4.

Review of literature:

Dystrophinopathies include a spectrum of X linked recessive muscle diseases caused by mutations in DMD gene. The milder forms are asymptomatic increase in serum creatine kinase and muscle cramps with myoglobinuria and isolated quadriceps myopathy. The severe forms are Duchenne/Becker's muscular dystrophy (DMD/BMD) and DMD - associated dilated cardiomyopathy when the heart is primarily affected.

Historical aspects of Dystrophinopathies

Edward Meryon (1852) and John Little (1853) described families with delayed motor milestones, calf enlargement, progressive inability to walk, contractures and death at an early age. G.B.A Duchenne (1868) gave the diagnostic criteria which include weakness and hypertrophy of muscles with onset in the legs, hyperlordosis with wide-based gait, progressive course over time and absence of bladder or bowel dysfunction or sensory disturbance.

William Gowers deduced the genetic basis for the disease. Lindenbaum R H (1979) and Davies K E (1983) revealed mutation in the specific Xp21 position in patients with DMD and BMD. The defective gene was identified by Monaco A P. Peter E Becker proposed that the less symptomatic patients reflected milder mutations in the same gene. Kunkel L M (1986) identified the DMD gene located at band Xp21 and provided molecular genetic confirmation of X-linked inheritance pattern.[1, 2, 3]

Incidence and prevalence:

DMD is the most common childhood onset muscular dystrophy. It affects 1 in 3500 boys, with an overall incidence of 25:100,000 live male births per year and prevalence of 63 cases per million. Approximately 50 % of muscle diseases in India are Duchenne Muscular dystrophies. [3, 4, 5]

Sex distribution:

DMD almost exclusively affect males because of X-linked inheritance. Rarely, skewed random inactivation of healthy copies of X chromosome causes Becker phenotype in females. Females with Turner syndrome (XO) or uniparental disomy or those with translocations between the X and autosomal chromosomes may similarly manifest the Duchenne phenotype.

Age group:

DMD clinically manifests in 3 - 7 years age group. Mean age at diagnosis without family history is 4 years, 10 months (range - 16 months to 8 years).[6]

Genetics:

DMD is caused by mutations in the DMD gene localized to short arm of X chromosome which encodes for dystrophin protein.[4]

DMD gene:

It is one of the largest known genes (0.1% of the human genome and 2.3 mega bases). It contains 79 exons (0.6% of the gene) and large introns (99.4% of the gene). Its large size makes it susceptible to mutations, with one third of all mutations arising de novo.[7, 8, 9,]

DMD gene mutations and disease/ co-relation:

One third of cases are due to spontaneous mutations, rest have X linked inheritance. Gonadal mosaicism accounts for approximately 20% cases.

Majority of mutations are intra-genic deletions (65-72%) in the hotspot spanning exons 45-53, with most being deletions of exon 45, and 45-47. Duplications are found in 7% of patients, mostly in a minor hotspot spanning exons 2-20. 20% cases have point mutations, small deletions or insertions. Most of the mutations are nonsense, frame shift or splice site mutations. Mutations lead to loss of the reading frame, resulting in a severe reduction or complete absence of dystrophin protein. Size and position of the deletion often does not correlate with the phenotype. Mutations that disrupt the open reading frame, resulting in an abnormal/ truncated dystrophin cause DMD, while mutations maintaining the open reading frame, resulting in a shorter and partly functional protein cause BMD (reading frame rule). 90% of the cases of DMD and BMD

conform to this rule. [10, 11, 12, 13, 14]

Dystrophin protein:

It is a 3685 amino acid, 427kDa cytoskeleton protein and member of β spectrin/ α actinin family. It is expressed in Skeletal, Cardiac & Smooth Muscles. Brain has B isoform which is functionally homologous to muscle isoform. It localizes to cytoplasmic face of sarcolemma, as a component of dystrophin associated glycoprotein complex (DGC). It consists of an N-terminal actin binding domain, 24 spectrin like repeat units, interspersed by four hinge regions, followed by a cysteine rich and a C terminal domain. The cysteine rich domain binds to laminin 2 via alpha and beta dystroglycan, acting as mechanical link between actin in the cytoskeleton, and the extracellular matrix (Figures 1 and 2).[13, 15, 16]

Functions of dystrophin protein:

- Role in stabilization of muscle membrane during contraction
- Part of link between intracellular cytoskeleton & extra cellular matrix, essential for force transduction.

Proposed mechanisms of disease pathogenesis:

Absence of dystrophin at the plasma membrane leads to

- Delocalization of dystrophin associated proteins from the membrane, disruption of cytoskeleton with resultant membrane instability and increased susceptibility to mechanical stress (possible role of dystrophin in resealing mechanisms).

- Altered membrane permeability and abnormal calcium homeostasis leading to activation of proteases such as calpain.
- Oxidative damage and apoptosis.
- Inflammatory response mediated by mast cells and dendritic cells.
- Absence of NO synthase at the subsarcolemmal membrane causes functional ischemia in areas of muscle during exercise. [13,17,18]

These lead to muscle fiber degeneration, initially there is regeneration of muscle fibers which with disease progression in overwhelmed with replacement of lost muscle fibers with fibro fatty tissue. Absence of dystrophin secondarily affects the synthesis of the Dystrophin associated proteins, which are reduced by 90%. Therefore, in DMD, functional deficits are the result of the absence of dystrophin and deficiency of Dystrophin associated proteins.[14]

Animal models of DMD with mutation in DMD gene:

Commonly studied, preferred and used is the mdx mouse. Several strains of mdx mouse have been characterized. Other models include hypertrophic feline muscular dystrophy and canine X linked muscular dystrophy models (golden retriever muscular dystrophy dog and German short haired pointer). Canine models are better phenocopies of human disease than other animal models, but limited by short lifespan, problems with breeding and cost.[19]

Clinical features:

DMD presents with progressive weakness in limbs since childhood.

Affected children are normal at birth, later they are noted to have delayed motor milestones. Mean age of by which, walking is attained is around 18 months (range 12-24 months). When the boys begin walking, the clumsiness seen in all toddlers persists. Within 2 to 3 years children are noted to have abnormal wide based gait with waddling/toe walking, inability to run compared to their peers and climb stairs, difficulty to squat and getup with use of Gower's maneuver to do so. A frequent complaint from parents of affected, 4 to 5 year old boys is that their son is unable to keep up with his peers in athletic endeavors. Standing posture is abnormal with increased lumbar lardosis and wide stance to increase stability. Often, at this stage the calf muscles are enlarged and rubbery on palpation (pseudo hypertrophy) due to fatty and fibrotic infiltration of necrotic muscles. Another explanation is compensatory hypertrophy of the secondary to weak tibialis anterior muscles, which tend to be more affected. Hypertrophy may become generalized and usually increases with age. Some relatively spared muscles may have true hypertrophy. By 5 or 6 years they have laboured stair climbing and moving upward requires support of the bannister. At around 6 or 7 years, they start having spontaneous falls due to abrupt knee buckling. At about 8 to12 years, there is severe deterioration in functional capabilities, as they cannot climb stairs or stand up from the floor. They stop walking by 9 -13 years and begin using a wheelchair by a mean age of 9.5 years. The respiratory muscle strength begins to decline at around a mean age of 8 years.

Generally, proximal muscles of the lower limbs are the first to be involved followed by proximal upper limb muscles. Neck flexors, wrist extensors, quadriceps, tibialis anterior, biceps, and triceps muscles are affected more than the neck extensors, wrist flexors, deltoids, hamstrings, gastrocnemii, and solei. Ankle plantar flexors and invertors are remarkably spared throughout the course

of illness. Cranial musculature is usually spared. Infraspinatus and deltoid muscles are enlarged and between them, muscles forming the posterior axillary fold are wasted (Valley sign). Deep tendon reflexes tend to parallel muscle fiber loss, slowly diminish and ultimately disappear. [3, 4, 6, 13, 14, 20]

Contractures at the iliotibial bands, hip joints, and ankle joints are seen in most patients by 6 years of age. Limitation of knee, elbow and wrist extension occur around 8 years of age, while shoulders are spared until late into disease. By 10 years, 70% of children are disabled by contractures, hips and knees lock at 90° and the feet are in an exaggerated equinovarus position. Asymmetric weakening of paraspinal muscles causes kyphoscoliosis, usually appearing after loss of ambulation.

Progressive respiratory impairment with weak cough causes atelectasis with recurrent episodes of pneumonia. Most have progressive dilated cardiomyopathy. Patients develop terminal respiratory or cardiac failure, usually by the late teens or early 20 years of age. Life expectancy is prolonged by 6 to 25 years with respiratory support. [3, 4, 6, 13, 14, 20]

The Outlier's comprise around 15% of the Dystrophinopathies, otherwise fulfilling the criteria for DMD, but have milder progression. They have relatively preserved neck flexors. They are able to climb stairs without support at 8 years and at 12 years of age still can climb stairs with support from railing. Forced vital capacity is usually 90% of predicted. [20]

BMD has a later onset of skeletal muscle weakness with patients' being

ambulatory even in their 20's. Pattern of weakness and wasting closely resembles DMD. Muscles of the pelvic girdle and thighs are prominently involved with relatively less involvement of anterior tibial and peroneal muscles. Neck flexor weakness appears late into illness. Forearm muscles, hand muscles and ankle plantar flexors are relatively preserved until late into illness. Significant facial weakness is generally not a feature of BMD. Calf hypertrophy is early and almost an universal feature. Contractures and scoliosis are not as prominent as in DMD and ambulation is never lost before 16 years of age. Despite the milder skeletal muscle involvement, heart failure from DCM is a common cause of morbidity and death. Cognitive impairment is not common/ severe as in DMD and the mean age of death is around the fifth decade.

Mild end of the spectrum includes men with onset of symptoms after age 30 years, who remain ambulatory even into the sixth decade. Other forms are BMD with subclinical skeletal muscle involvement, elevated serum CPK, calf hypertrophy, cramps, myalgia, and exertional myoglobinuria. [20]

DMD and Cardiac disease: Cardiomyopathy and Arrhythmias

Incidence of cardiomyopathy increases steadily in teenage years, with 1/3 being affected by 14 years, ½ by 16 years and all patients' after18 years of age. It is commonly dilated cardiomyopathy (DCM), can also be hypertrophic form. Preclinical cardiac involvement is seen in 25% of patients < 6 years of age, commonly with a persistent tachycardia. Despite the high frequency of cardiomyopathy, most patients are relatively asymptomatic due to physical

inactivity. Dystrophin deficient cardiomyocytes have reduced threshold sarcolemmal injury under mechanical stress. Cellular repair mechanisms and regeneration are insufficient, leading to progressive loss of cardiomyocytes. Characteristic cardiac lesion is focal necrosis with mononuclear infiltrate. Focal involvement may appear as wall motion defects with a predilection for posterobasal and posterolateral segments of the left ventricular wall due to fibrosis in these areas. These areas are referred to as micro infarcts and may have associated chest pain and release of troponin. There is relative sparing of the interventricular septum, and comparatively minimal involvement of the right ventricle and atrial myocardium. Degenerative changes also involve the conducting system. Finally four chamber dilation and failure occurs.

Electrocardiogram changes often appear in the late first decade, including sinus tachycardia, tall R wave in lead V1, and inferolateral Q waves. Echocardiogram shows valve motion, wall thickness and motion abnormalities. Tissue Doppler can identify myopathic changes earlier, reflecting ongoing damage to myocardium. Magnetic resonance imaging is sensitive in detecting subclinical disease.

Conduction/rhythm disturbances include Sinus node dysfunction, AV node dysfunction, atrial fibrillation and ventricular tachycardia/fibrillation. They increase in frequency as ventricular dysfunction progresses.

Selective Cardiomyopathy

Some males can have minimal or mild weakness with DCM. Onset is in late

teens with rapidly progressive congestive heart failure over 1 to 2 years. Manifesting female carriers with DCM have onset in 5th decade with congestive heart failure and atypical chest pain. They have slowly progressive disease over more than 10 years. [13, 20, 21, 22, 23]

Orthopedic complications

Scoliosis develops in almost all, and impairs the vital capacity. It progresses significantly after boys lose ambulation, and maintenance of ambulation slows the rate of progression. Long bone fractures usually due to falls are common, affecting 21-44% of boys. Half of them occur in independently ambulant boys, with 20-40% losing ambulation as a result. Osteoporosis is present in most patients. Loss of bone mineral density begins even when boys are still ambulant, and continues to diminish with age.[13, 24]

Malignant hyperthermia

DMD patients are thought to have risk of malignant hyperthermia like reactions if exposed to anesthetics such as halothane or succinylcholine.[25]

Respiratory complications

Respiratory insufficiency due to restrictive lung disease is common. The vital capacity decreases at a rate of 8 -12% per year, after 10 years of age. When it reaches less than one Litre, the risk of death within the next 1 - 2 years is

relatively high. Obstructive sleep apnea causes sleep disordered breathing in the first decade in up to one third of patients, with hypoventilation occurring in the second decade. [13, 26, 27]

Brain and dystrophinopathy:

A nonprogressive intellectual disability and hyperactivity are seen in around 30% of patients with DMD. These features are due to deficiency of the brain isoform of dystrophin. Brain may show cortical atrophy with neuronal loss, heterotopias, gliosis, neurofibrillary tangles, dendritic abnormalities and disordered architecture._

A. Specific cognitive profile associated with DMD.

IQ is shifted 1 SD lower than normal (average 85). 30% of boys have IQ of < 70 with about 19% of them in the mentally retarded range. They do well on written memory, long term memory tests and visuospatial skills. They perform poorly on tests of verbal expression, digit span, spelling, serial position memory, mathematics, verbal comprehension, and story memory. Each of these measures assesses verbal working memory.

B. Neuropsychiatric Disorders in dystrophinopathy

Incidence of Attention-Deficit Hyperactivity Disorder (ADHD), Autism and Obsessive Compulsive Disorder is higher in DMD patients. [28, 29, 30, 31]

Female carriers:

Majority of the female carriers are asymptomatic. About 2 - 20% of carriers

have clinically evident muscle weakness. Weakness is usually progressive, mild to moderate, proximal and asymmetric with onset from 16 to 48 years. The arms are more affected then legs, with more involvement of shoulder abduction, elbow flexion and knee extension. Some have myalgia or cramps without weakness. CPK levels are raised in 50 - 60% of carriers. Cardiac involvement is usually subclinical, although severe heart failure has been reported. In one cross sectional study dilated cardiomyopathy was seen in 8% and left ventricular dilatation in 19% of carriers. Carriers do not have reduced life expectancy or increased risk of cardiac death. There is no association between the degree of muscle weakness and cardiomyopathy. Around 20% of carriers have abnormal dystrophin immunostaining on muscle biopsy, with a mosaic pattern of dystrophin positive and dystrophin negative fibers. [13, 20, 32, 33]

Serum enzymes:

1. Serum Creatine phosphokinase (CPK) concentration:

Characteristic finding is raised serum CPK levels, at least 10 to 20 times (often 50 to 200 times). Levels greater than 10,000 mU/mL are common. Serum CPK concentrations are high even in newborns, high CPK levels at birth can form basis of neonatal screening for DMD. Levels peak at 2 - 3 of age and then decline with increasing age at about 20% per year, due to progressive loss of dystrophic muscle fibers. Normal concentrations have been reported in DMD associated DCM. There is wide variability in serum CK concentration among DMD/BMD and carriers.[4, 13, 20, 34]

2. Serum Alanine transaminase and Aspartate transaminase

Levels are raised in DMD and tend to correlate with CPK levels.

3. Other enzymes raised in DMD include Aldolase and Lactate dehydrogenase. Most of these are not specific for muscle and are generally not useful in the diagnosis of DMD. [13, 34]

Electromyography (EMG):

Needle EMG shows short duration, low amplitude polyphasic motor unit potentials. Fibrillation potentials, positive sharp waves and complex repetitive discharges may be detected due to denervation and some reinnervation in necrotic muscles. Over time, the motor units become very small and some areas become electrically silent. Electromyography is rarely required for diagnosis of DMD. [4, 13, 20]

Molecular genetic testing:

Molecular genetic testing is now the mainstay of diagnosis.

1. **Multiplex polymerase chain reaction (PCR)**

Covers 19 exons at the two deletion hotspots, detects 90-98% of all deletions, although duplications and rarer mutations cannot be identified.

2. **Multiplex ligation dependent probe amplification (MLPA)**

This test is more sensitive technique for detecting deletions. All 79 exons are covered by two sets of probes, with individual exons depicted as a single peak.

This allows gene dosage abnormalities to be detected, allowing detection of duplications and carriers as well as deletions. If MLPA testing is negative, DMD gene can be tested for point mutations.

3. **Direct sequence analysis of the DMD gene**

Here DMD gene can be tested for point mutations. This is available on a research basis only due to labor intensive and costly nature.

4. **Targeted high density oligonucleotide comparative genomic hybridization microarray**

High resolution analysis of the gene can be done, allowing identification of deletions, duplications and unidentified deep intronic mutations. [13, 35]

Muscle magnetic resonance imaging:

MR is not usually performed for diagnosis, but may be useful to evaluate progression of muscle involvement over time. Abnormal signals are seen in gluteus maximus, adductor magnus, quadriceps, biceps femoris, rectus femoris and gastrocnemii muscles.

Muscle biopsy:

It remains the gold standard for diagnosis.

Light microscopy:

Early stages

- Necrotic or degenerating muscle fibers in clusters with invasion/

phagocytosis by macrophages

- Inflammatory cells at perimysial and endomysial sites(predominantly macrophages and CD4+ lymphocytes)
- Clusters of regenerating muscle fibers with basophilic cytoplasm
- Increased variability of muscle fiber size
- Type 1 fiber predominance with some hyper contracted muscle fibers and type II B deficiency.
- Internal nuclei and split fibers are not common as in other dystrophies.

Later stages

- Significant replacement of muscle fibers by fibro fatty tissue.[13, 20, 36]

Detection of dystrophin in muscle biopsy sample:

Dystrophin in muscle biopsy sample can be demonstrated by immunostaining or western blot analysis, using antibodies directed against different epitopes of dystrophin. Generally antibodies are directed towards amino terminus, carboxy terminus and rod domains. Western blot analysis helps quantification of the amount and size of protein. [13, 36]

Management

1. Physiotherapy:

It aims at maintaining muscle function, joints mobility and preventing contractures. It should begin at 3 - 4 years of age or at diagnosis, with

stretching of Achilles tendon, hip flexors and iliotibial bands as a daily regimen. Passive stretching and night time ankle foot orthoses (AFO) are used in ambulant stage to delay development of contractures. Daytime AFO's are not recommended as they may impede walking ability. Knee ankle foot orthoses may be used to prolong ambulation and standing. Their use may be of benefit as children who walk or stand beyond 13 years are less likely to require spinal surgery and contracture development is delayed. Manual wheelchairs should be provided early as they help in conservation of energy. Special seating and a head rest should be used to prevent abnormal postural adaptations. In non-ambulant children passive or active assisted exercise should be continued for comfort and contracture prevention. Breathing exercises are also an important component of physiotherapy. [13, 14, 20, 36]

2. Corticosteroid Therapy

Prednisolone, prednisone and deflazacort are shown to be effective in DMD.

Proposed mechanisms by which steroids improve strength in DMD:

- Alteration of regulation of genes in muscle fibers
- Slowing of the rate of skeletal muscle breakdown
- Reducing cytotoxic T cells/ anti-inflammatory effect
- Lowering cytosolic calcium concentrations
- Increasing myogenic repair. [37, 38]

Efficacy of treatment:

Steroids improve muscle strength within 10 days, maximal at 3 months and maintained up to 18 months, with improvements in functional testing (e.g. time to arise from supine to standing, time to walk nine meters) and muscle mass, as measured by urinary creatinine excretion. Non-randomized studies of long-term daily corticosteroids suggest that ambulation may be prolonged by up to three to five years, and that life expectancy is improved. Steroids also appear to have a positive effect on preservation of respiratory muscle strength, cardiac function and lowering the frequency of dilated cardiomyopathy, reducing the prevalence/

severity of scoliosis.[39, 40, 41, 42, 43, 44]

Optimal age to begin and duration of treatment:

There are no good studies on the optimal age to begin treatment or the optimal duration of treatment. Common regimen is to start at the time of decline of muscle strength and frequent falls and to stop when ambulation is lost. Some continue steroids beyond the loss of ambulation, for the possible protective effect on respiratory and cardiac function.[44, 45] Studies are lacking on the use of steroids in very young children and nonambulant patients. As muscle biopsies show inflammatory changes in the early disease, there is a case to use steroids in early disease and also in pre-symptomatic siblings, who have the disease.

Inter compound efficacy:

There are no large randomized controlled trials comparing deflazacort with Prednisolone/ prednisone. All the three compounds are likely to be equally effective, but have slightly different side-effect profiles.[13]

Regimes and optimum dose:

The most common daily dosage regimes are 0.75 mg/kg/day prednisone or Prednisolone and 0.9 mg/kg/day deflazacort. Lower doses of 0.3 mg/kg/day still result in improvements in strength and function, but to a lesser degree, but may be used if side-effects require a decrease in dose. Higher doses of 1.5 mg/kg/day do not result in additional benefits, and alternate daily doses of 1.25 mg/kg and 2.5 mg/kg did not achieve the sustained benefits of daily dosing. Other types of intermittent dosing such as Prednisolone 10 days on and 10/20 days off, and twice weekly schedule (5 mg/kg/dose) have also been shown to be beneficial. None of these regimes have been tested against the daily dosing schedules so that their relative efficacy in the long term is not known.[44, 45, 46, 47, 48]

Monitoring for efficacy:

Includes muscle strength, functional performance and FVC.

Side effects:

Common side effects are weight gain (40%), hypertension, behavioral changes,

growth retardation, cushingoid appearance (50%) and cataracts. Trials suggest a lower incidence/ severity of weight gain with deflazacort compared to prednisone, but higher incidence of cataracts.

Vertebral fractures have been detected in 32-40% of boys on long-term corticosteroids. Long bone fractures are also twice as likely compared to steroid naïve patients. Of the fractures occurring during the steroid therapy, 84.9% were in the lower limbs whereas the percentage of fractures between upper and lower limbs was evenly distributed during the no steroid period (52.5% and 47.2%). Increased fracture rate in steroid treated boys could be due to prolonged independent ambulation and increased body weight. Other side effects include acne, excessive hair growth, and gastrointestinal symptoms.

Monitoring has to be done for weight gain and bone density along with dietary advice and behavioral changes. If excessive weight gain occurs dose should be decreased.[13, 40, 44, 49, 50]

Studies regarding the efficacy of prednisone in treating individuals with BMD are limited.

3. General management and surveillance

This includes symptomatic management and surveillance of orthopedic, cardiac and respiratory complications.

Cardiac disease

Cardiomyopathy without screening progresses asymptomatically until features of heart failure emerge, probably explained by the low physical activity due to weakness. Heart failure is primary cause of death in 10% of patients; this is expected to rise as life expectancy has increased for DMD patients.

Surveillance/ cardiac evaluation:

DMD/BMD patients - beginning at approximately 10 years, or at the onset of cardiac signs and symptoms, annual complete cardiac evaluation

Female carriers - initial evaluation to be done in late adolescence or early adulthood, or earlier if symptomatic.

Evaluation includes an electrocardiogram and echocardiogram, with magnetic resonance imaging if required. Holter monitoring should be considered in patients with cardiac rhythm abnormalities.

Management:

There are indications of benefit with ACE inhibitors and beta blockers, alone or combined, in those with left ventricular dysfunction. Pre-treatment with ACE inhibitor preserved systolic function with mortality benefit (decreased mortality). Whether the addition of β blockade and/or prolonged glucocorticoids therapy will yield further benefit is unknown in presymptomatic group. With ventilatory support, DMD patients survive longer. In these older patients arrhythmias play a prominent role in survival (cause of mortality). Internal cardioverter defibrillators can be effective in them. The prophylactic use of antiarrhythmic agents has not been adequately studied. [23, 51]

Respiratory disease

Baseline pulmonary function tests and respiratory evaluations should begin at age 8 to 9 years and before ambulation is lost and then annually.

Polysomnography for sleep disordered breathing and nocturnal hypoventilation should be performed at the time of loss of ambulation.

Acute respiratory crisis due to infections require antibiotics, chest physiotherapy and respiratory support if needed. Nocturnal noninvasive intermittent positive pressure ventilation (NIPPV) is helpful for nocturnal hypercapnia. Benefits include increased quality of life, reduction and delay of onset of daytime hypercapnia and improved life expectancy to 25 - 30 years. Further progression of respiratory failure requires fulltime ventilation.[13, 52, 53]

Orthopedic issues

Maintenance of ambulation, postural support after loss of ambulation and also steroid therapy are important to prevent/ reduce contractures and scoliosis.

Monitoring should begin before loss of ambulation. Surveillance

X rays for scoliosis should be done yearly from 9 years of age. Once scoliosis is seen, assessment for surgical correction has to be done. The average age of scoliosis surgery is 14-15 years. To qualify for surgery, the scoliosis should be greater than 25 degrees with vital capacity > 30% of predicted. Scoliosis surgery is effective in correcting scoliosis, preventing further deformity and improved respiratory function, but has no effect on life expectancy. [13, 50, 54]

4. Bone health

Maintenance of bone density is important to prevent fractures, particularly with steroid therapy. Supplementation of 1000 mg/day of calcium and 400 units of vitamin D should be considered in all patients. Long bone fractures should be treated with early mobilization to avoid fracture precipitating loss of ambulation. Vertebral fractures can be treated with intravenous bisphosphonates. There is insufficient evidence for the use of prophylactic oral bisphosphonates.[55]

5. Nutrition and gastrointestinal issues

Nutritional support should include advice on weight control, sodium restriction and calcium/ vitamin D intake. In later stages with difficulty in swallowing discussion of feeding tube is indicated.

6. Other forms of therapies (under trial)

Amino glycosides

Up to 15% of DMD patients have gene mutation known as a premature stop codon. Amino glycosides have been shown to over read stop codon mutations. In the mdx mouse, in vivo gentamicin therapy resulted in dystrophin expression at 10%-20% of that in normal muscle. So it may have a role in patients with

premature stop codons.[4, 13, 56]

Oxandrolone

It is an anabolic steroid with anabolic effect on skeletal muscle myosin synthesis. It is has effects similar to prednisone, with fewer side effects. A randomized, prospective, controlled trial showed significant mean change in quantitative muscle strength. It may be useful before initiating therapy with steroids as it accelerates linear growth and may be beneficial in slowing the progression of weakness. Long-term effects need to be studied.[57]

Creatine monohydrate

In a randomized, controlled, cross - over trial there was improved hand grip strength and increased fat free mass compared to placebo but no functional improvement was noted.[58, 59]

Cyclosporine and Azathioprine

Cyclosporine was reported to improve clinical function in DMD. Due to reports of cyclosporine induced myopathy in patients receiving it for other reasons, its use in DMD remains controversial. Azathioprine has not been found to have any role.[60]

Histone deacetylase inhibitors

Showen to produce improvement in mdx mouse by inducing the expression of the myostatin inhibitor follistatin.

Genetic approaches

a. Gene therapy

Gene therapy aims to deliver DNA encoding dystrophin to the muscle. Problems with gene therapy include large size of gene, immune response to protein and vector agents. Approach of gene therapy has evolved form use of plasmids to viruses (adeno viruses) to deliver dystrophin sequences. Advances in viral delivery, including functional dystrophin mini- and micro genes and gutted vectors with large insert capacity and lowered immunogenicity. These have showen good results in mdx mice.

b. Antisense oligonucleotide exon skipping: They can be used to redirect splicing and induce exon skipping to restore the reading frame, and are ideal for out of frame deletions or duplications. Dystrophin production in an mdx mouse model was seen after its use. Successful exon skipping was recently demonstrated after intramuscular injection of Antisense oligonucleotide into tibialis muscle in four patients.

c. PTC124: It promotes ribosomal read through of stop codons, allowing continuation of translation and production of a functioning protein. It restored dystrophin levels in mdx mice, with an associated improvement in muscle function and decrease in CPK levels. Phase 1 studies in healthy adult volunteers showed that it is well tolerated. A Phase 2 study of 26 boys showed increased full length protein expression and decreased CK levels, but without significant functional changes or muscle strength.[4, 13, 61, 62, 63]

Myoblast transplantation and Stem cell therapy

Initially immortal myogenic cell line derived from adult satellite cells/

myoblasts were transplanted, this showed promise, but subsequent studies showed that they were rejected by the host cell mediated immune response. In addition the cells that survived this immune destruction did not migrate more than few millimeters away from the injection site.

Self-renewing, immune-privileged stem cells have been shown to proliferate longer than myoblast cells, to migrate from the circulatory system after intra-arterial injection and to be more effective than myoblast cells in muscle regeneration and dystrophin expression after implantation.

Autologous myogenic stem cells with ex vivo gene correction strategies were transplanted, but again limited by the difficulty in producing an appropriate integrating vector to accommodate the large dystrophin/utrophin gene and the limited life span of the myogenic cells obtained from Duchenne muscular dystrophy patients.

Bone marrow derived stem cells have shown to remodel muscle, may be useful to remodel dystrophic muscle.

Recently, vessel associated fetal stem cells known as mesoangioblasts/ pericytes have been shown to provide widespread rescue of dystrophy after intra-arterial injection.[4, 13, 63, 64]

Utrophin

It is a protein homologue of dystrophin in the sarcolemma, may compensate for dystrophin deficiency if it is upregulated. Various factors that increase utrophin expression are being explored, such as heregulin and L-arginine, but most are

still in the very early stages.[65] _____

Genetic counseling:

Genetic counseling is provided by trained healthcare professionals.

Assessment of risk to Family Members

a. Parents of a proband: Father of an affected male will not have the disease nor will he be a carrier of the mutation. Woman with an affected son will be an obligate heterozygote. Woman with more than one affected son and no other family history of DMD, have either germline mutation or mosaicism for a DMD gene mutation. If proband is the only affected family member, he may be having a de novo DMD disease causing gene mutation or his mother may have a de novo DMD disease causing gene mutation or she has inherited a mutation from her mother (who is a carrier or has mosaicism). Molecular genetic testing combined with linkage analysis can determine the point of origin of a de novo mutation which is important for determining which members of the family are at risk.

b. Siblings of a proband: The risk to other siblings depends on the carrier status of the mother. If the mother has a disease causing mutation, the chance of transmitting it in each pregnancy is 50%. Male siblings who inherit the mutation will be affected and female siblings who inherit the mutation will be carriers.

c. Offspring of a proband: Males with DMD usually die before reproductive age or are too debilitated to reproduce. Males with BMD and DMD related DCM may reproduce. All the daughters are carriers. None of the sons will

inherit their father's DMD mutation.

d. Other family members of the proband: Proband's maternal aunts and their offspring may be at risk of being carriers or being affected (depending on gender, family relationship and carrier status of the proband's mother).

Testing and Counselling of family member's:

All women related to an affected person by maternal linkage should be screened for carrier state. Females who are identified as carriers should be informed about risk for dilated cardiomyopathy and should be advised to be under regular monitoring. Before pregnancy they should be told about the risk of having an affected sibling and the availability of prenatal testing.

Materials and methods:

Patients attending the neuromuscular clinic of our hospital were screened for inclusion into the study.

Inclusion criteria:

Patients with Dystrophinopathy (n=69; 68 boys and 1 girl), (confirmed by absence or reduced levels of dystrophin on immunostaining of muscle biopsy), who were seen in the Neuromuscular clinic of Christian Medical College, Vellore during the period January 2007 - December 2008 were included in the study.

Patients with the spectrum of Dystrophinopathies were broadly subdivided in **group I** (DMD) and **group II** (Outlier's / BMD) as follows -

1. Patients who lost ambulation before 12 years of age, irrespective of age of onset of disease were considered to have DMD, if they had not been treated.

2. Patients who were ambulant even after 12 years, irrespective of age of onset of disease were considered to have either Outlier or Becker's phenotype, if they had not been treated.

3. On the other hand if patient was administered treatment before age of 12 years, he was considered to be having DMD, if age of onset was within 5 years and Outlier or BMD if age of onset was > 5 years, to remove any confounding effect of treatment.

These patients were studied both prospectively and in a retrospective manner over 24 months during 2007 – 2008 when they were seen in the Neuromuscular

clinic of our hospital.

In the clinic, patients were seen by a multidisciplinary team consisting of a Neurologist (specialized in neuromuscular diseases), Physicians form the Medical Genetics and Physical & Medical Rehabilitation department, physiotherapist and occupational therapist (specialized in neuromuscular diseases). Patients were assessed by the entire team and based on the inputs; plan of management was decided for each patient on an individualized basis.

Role of Neurologist: Neurologist was involved in clinical assessment of muscle power and functional status, ascertainment of diagnosis, initiation of treatment, monitoring of treatment related improvement or side effects.

Role of Physician from Physical and Medical department: The Physiatrist was involved in assessment of functional status, monitoring of motor power, goniometric changes and assessed the functional disability at periodic intervals and give valuable advice on stretching and endurance exercises required, including respiratory exercises with incentive spirometer. The requirements, at different stages were planned in discussion with the Physiotherapists and Occupational therapists and were individualized based on the requirement of the patient - including modification of household environment and providing wheel chairs.

Role of Physician from Medical Genetics department: The Clinical Geneticist was involved in genetic testing of appropriate cases, counseling of family members regarding the disease and helping parents of the patient on

issues of planning family (future pregnancies), determing of risk in other siblings and screening of them with Serum Creatine phosphokinase to diagnose presymptomatic patients.

Role of Physiotherapist and Occupational therapist: They were involved in assessment of muscle power and functional status, physiotherapy and occupational therapy with special reference to activities of daily living, education about modification/ arrangements to be made at home for helping in performance of daily activities without much assistance.

Each patient's charts were analyzed for clinical data and data was also collected on direct examination of the patient during follow up. All patients were scheduled to have follow-up examinations at six month intervals. Life time events were analyzed from birth with respect to motor milestones, age of onset of symptoms, and first symptom noted, age at presentation to hospital and diagnosis, diagnostic delay, family history, nature of the illness in terms of wasting, weakness, gait, contractures, functional performance on specified tasks, progression of the illness and various milestones achieved during the course of illness like Gower's sign, loss of ambulation, respiratory distress, toe walking, other gait abnormalities, spinal deformities, progression of falls, age at wheel chair or bed bound stage, cardiac status and age at death. Also noted was the progression of changes in the weight, height, CPK, complications if any related to steroid therapy. Data was collected for all the patients as per the proforma attached.

Muscle force was measured according to Medical Research Council scale of 2 upper and 2 lower limb muscles. We measured muscle power in following muscles: right deltoid, right biceps, right quadriceps and right iliopsoas. We also calculated total/ cumulative MRC score by adding individual MRC scores of 4 muscles (Right deltoid, right biceps, right quadriceps and right iliopsoas). Functional grading was done for squatting and getting up, walking, getting up from chair and climbing stairs using GSCS system (Table 1). [66]

Contractures were measured by goniometry. Goniometric measurements are in degrees around a set axis. To measure the angles around a joint, the goniometer is placed over the fulcrum of the joint. The stationary arm of the goniometer is placed along the stationary line of the body, and the movable arm on the moving part of the body. The patient is asked to move the joint in the desired direction, following the movement with the movable arm of the goniometer. The starting and ending value are recorded as noted on the goniometer. Thus the range of motion of the joint is calculated and noted if there is any lack of motion in the joint.

Table 1. GSCS system for functional grading

Graded gait - A score assigned for 10 m of walking.
Grade 1 – normal.
Grade 2 – mild waddling, lardosis and/or toe walking.
Grade 3 - moderate waddling, lardosis and/or toe walking.

Grade 4 – severe waddling, lardosis and/or toe walking.
Grade 5 – walks only with assistance (i.e. canes, braces, crutches)
Grade 6 – stands, unable to walk
Grade 7 – confines to wheel chair
Graded stairs - A score assigned for walking up four stairs.
Grade 1 – climbs without assistance
Grade 2 – supports one hand on thigh
Grade 3 – supports both hands on thigh.
Grade 4 – climbs in upright position but with aid of railing.
Grade 5 – climbs while clinging to the railing with both hands
Grade 6 – manages to climb only a few steps
Grade 7 – unable to climb stairs.
Graded chair - A score assigned for rising from a chair to standing.
Grade 1 – normal
Grade 2 – with wide base and/or difficulty, but without support
Grade 3 – with support on one thigh
Grade 4 – with support on both thighs.
Grade 5 – with support on arms of chair or table
Grade 6 – not possible.
Graded Gower – A score assigned for getting up from a sitting
Grade 1 – normal
Grade 2 – butt first manoeuvre, one hand on floor
Grade 3 - butt first manoeuvre, two hands on floor.
Grade 4 – unilateral hand support on thigh
Grade 5 – bilateral hand support on thighs
Grade 6 – arises only with aid of object (table, chair, etc)
Grade 7 – unable to arise

Analysis of Data

These patients were studied both prospectively and in a retrospective manner.

For the purpose of analysis, patients were subdivided into four groups.

Group I a – DMD patients who were seen for the first time in the

neuromuscular clinic and diagnosed during the study period (2007 - 2008)

Group I b – DMD patients who were on treatment before inclusion into the study and have follow up data for more than 2 years

Group I c – DMD patients who were on treatment with follow up or treatment duration less than 2 years.

Group II – BMD/ Outlier phenotypes

Stastical tests were used to determine significance of the values obtained and for comparison among groups.

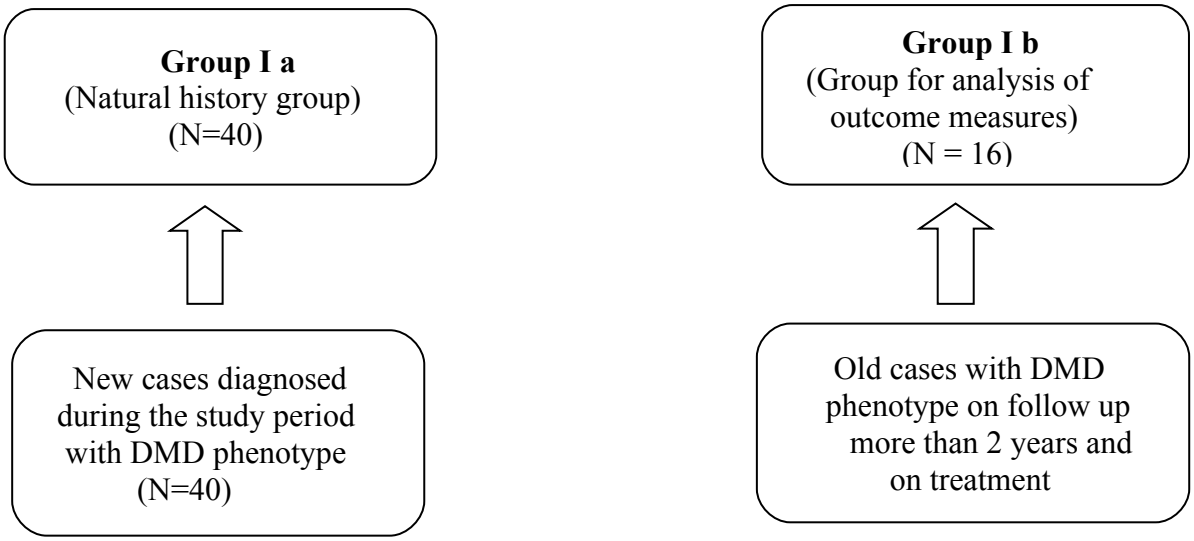
Analysis of Group I a patients for natural history of illness.

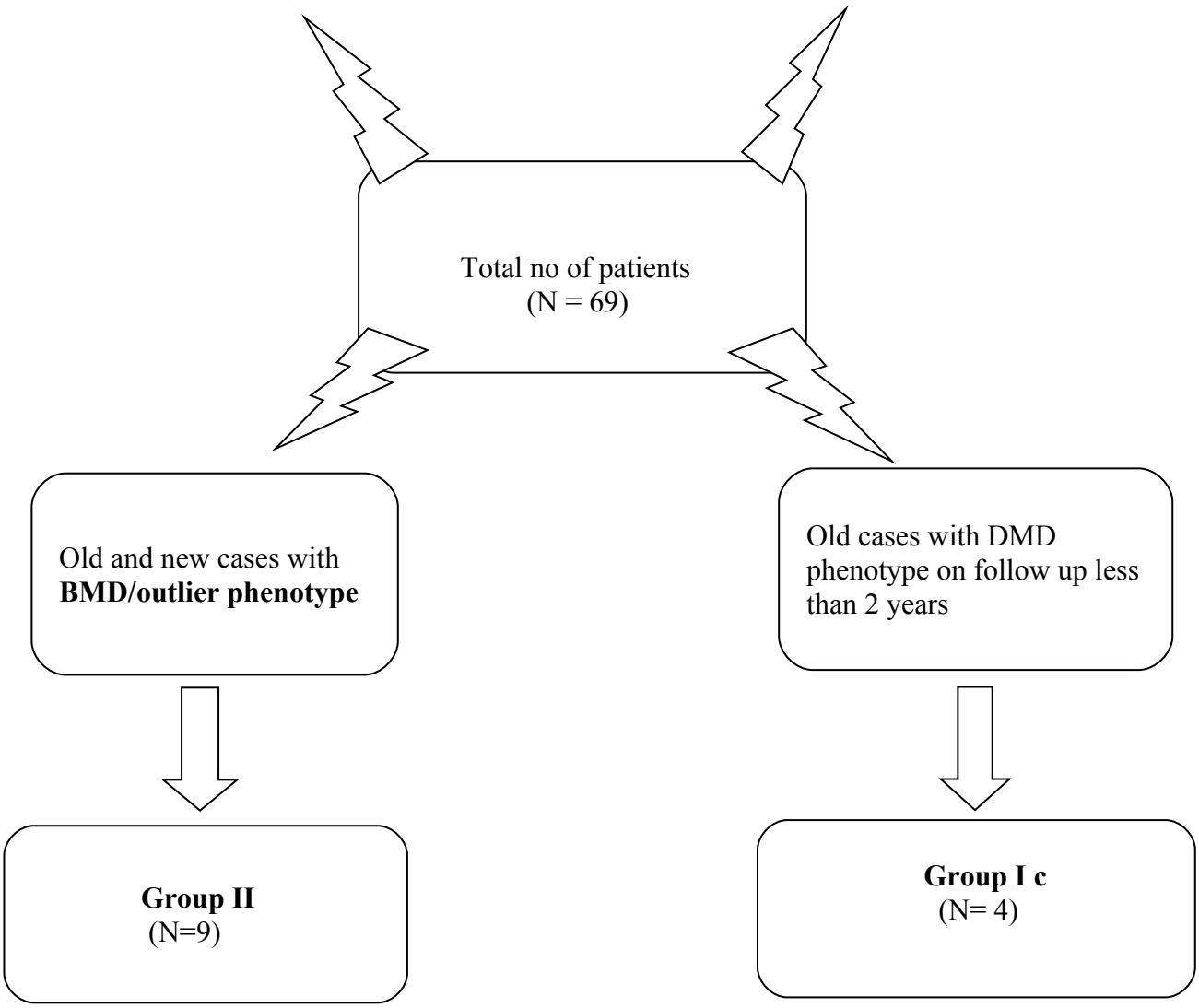
Group I a consisted of new patients whose course of illness was not modified by any therapeutic measures till presentation to our neuromuscular clinic. As they did not receive any treatment, they were considered as natural history group.

Analysis of group I b patients for treatment outcomes.

Group I b was on treatment for more than 2 years before evaluation in current study. As group I b was under treatment, this group was compared with group I a (which had not received treatment) for various parameters.

FLOW CHART SHOWING THE VARIOUS GROUPS




Total no of patients
(N = 69)
Old and new cases with
BMD/outlier phenotype
Old cases with DMD
phenotype on follow up less
than 2 years
Group II
(N=9)
Group I c
(N= 4)

Results:

Patient population and study groups:

A total of 69 patients were studied. 68 were boys and 1 was girl. 60 (86.96%) patients were in group I, of them, 40 (57.97%) patients were in group I a, 16 (23.18%) patients were in group I b, and 4 (5.89%) were in group I c. 9 (13.04%) patients were in group II.

Table 2. Number of patients in each group during the study period

Frequency (%)	At first visit	At entry into study	At 6 months	At 12 months	At 18 months
Group I a	40	40(100)	13(32.5)	6(15)	3(7.5)
Group I b	16	16(100)	13(81.25)	9(56.25)	7(43.75)
Group I c	4	4(100)	2(50)	2(50)	1(25)
Group II	9	9(100)	3(33.33)	2(22.22)	0
Total	69	69(100)	31(44.93)	19(25.54)	11(15.94)

Of those patients seen at entry into study, 11 (15.94%) patients had completed more than 18 months of follow up, 19 (25.54%) patients had completed more than12 months of follow up, 31 (44.93%) had completed more than 6 months of follow up (Table 2).

Clinical features:

The mean age at onset of first symptom was 3.93 years in group I (among the subgroups, it was 3.6 years in group I a, 4.31 years in group I b, and 4.5 years in group I c) and 8.44 years in group II. At presentation to our hospital, mean age was 7.7 years, 6.56 years, 7.5 years and 11.78 years respectively in groups I a, I b, I c and II. At entry into the study, the mean age was 7.88 years in group I a, 9.5 years in group I b, and 12.44 years in group II.

Table 3. Age at onset of illness, presentation and entry into study

Mean age in years (Standard Deviation,SD)	At first Symptom	At presentation	At entry into study
Group I	3.93(1.54)	7.38(1.98)	8.4(2.22)
Group I a	3.6(1.26)	7.7(2.15)	7.88(2.1)
Group I b	4.31(1.45)	6.56(1.46)	9.5(1.6)
Group I c	4.5(2.65)	7.5(1.3)	9(1.83)
Group II	8.44(1.51)	11.78(1.48)	12.44(1.51)

At entry into current study, patients in the group I b were older than those in group I a (mean age 9.5 v/s 7.88 years). There was delay between symptom onset and diagnosis in all groups (Table 3). 9 patients were told to have muscle disease elsewhere before they came to us.

Developmental milestones:

In group I, 35 (58.3 %) patients had delayed motor and of them 6 (10 %) had delayed language milestones also. In group II, 3/9(33.33%) had delayed motor milestones and 2/9(22.22%) had delayed language milestones. The mean age (SD) at walking without support was 1.75(.93) years in group I and 1.33(0.5) years in group II.

Symptoms at presentation:

In group I, first symptom noted by parents was difficulty in getting up from squatting position without support in 32 (53.3%) patients, inability to run as fast as compared to their peers in 10 (16.7%) patients, waddling gait in 5 (8.3%) patients, toe walking in 2 (3.3%) patients and repeated falls in 9 (15%) patients.

One (1.6%) patient was diagnosed after he was found to have raised hepatic enzymes while being evaluated for a febrile illness elsewhere. One (1.6%) patient had not attained independent ambulation till 7 years of age when he presented to us. In group II, 8(88.9%) patients presented with difficulty to get up from squatting position and 1 (11.1%) patient presented with repeated falls.

Symptoms during the course of illness at various time intervals:

Table 4. Age of onset of disease related symptoms

	Group I		Group II	
	Frequency (%)	Age in years (SD)	Frequency (%)	Age in years (SD)
Uses Gower's	59(98.3)	4.25(1.54)	9 (100)	8.33(1.73)
Waddling gait	44(73.3)	6.41(1.58)	9 (100)	9.78(1.64)
Repeated falls	51(85)	6.16(1.45)	9 (100)	9.89(1.45)
Toe walking	7(11.7)	4.71(1.60)	2 (22.22)	10(2.83)
Cannot run	59(98.3)	4.10(1.64)	9 (100)	8.56(1.74)
Calf enlargement	4(7.33)	6	1(11.11)	9
Dyspnoea on exertion	1(1.7)	7	2 (22.22)	10.50(2.12)
Dyspnoea at rest	-	-	1 (11.11)	13

The mean age at onset of difficulty to get up form squatting position without support was 4.25 years in group I and 8.33 years in group II. The mean age at onset of inability to run as fast as other peers was seen at 4.10 years in group I and 8.56 years in group II. The mean age at onset of waddling gait was 6.41 years in group I and 9.78 years in group II. The mean age at onset of toe walking was 4.71 years in group I and 10 years in group II. Calf enlargement

was seen in at mean age of 6 years in 4 patients of group I and at 9 years in one patient in group II. Among the symptoms during the course of illness, difficulty in getting up from squatting position and inability to run as other peers were common in all groups (Table 4).

Table 5. Frequency/ age of appearance of mile stones among the subgroups.

Frequency (%) / Age in yrs (SD)	Group I a (N = 40)	Group I b (N = 16)	Group I c (N = 4)	Group II (N = 9)
Cannot walk without support	9 (22.5)	5 (31.26)	1 (25)	1 (11.11)
	7.67(1.3)	9.60(1.67)	11	13
Cannot stand without support	9 (22.5)	3 (18.78)	1 (25)	1 (11.11)
	8.33(1.58)	9.67(2.31)	11	14
Wheel chair bound	8 (20)	2 12.52)	1 (25)	1 (11.11)
	8.63(1.30)	11.50(.71)	12	14

The mean age to reach wheel chair bound state was 8.63 years in group I a (8 patients), 11.50 years in group I b (2 patients) and 14 years in group II (1 patient) and 12 years in group I c (one patient). Overall there was trend towards prolonged ambulation in group I b compared to group I a (Table 5).

School performance and general intelligence

Poor school performance was reported by parents in 7 (11.7%) patients and good in 22 (36.7%) patients of group I. 3 (5%) patients in group I had attention deficient hyperactivity disorder. School performance was poor in 2 (22.22%) and good in 5 (55.56%) patients of group II.

Family history:

Positive family history was seen in 14 (23.33%) patients of Duchenne muscular dystrophy. 6 patients (8.7%) had affected siblings, 2 patients (2.9 %) had

affected cousins, and 6 patients (8.7%) had affected maternal uncle. One family had many members affected, including cousins and maternal uncles. One female patient who was symptomatic had no affected relatives.

MRC scores on initial observation:

Table 6. MRC scores in individual muscles at first visit/ presentation

Mean score (SD)	Deltoid	Biceps	Iliopsoas	Quadriceps	Cumulative score
Group I a	3.52(.75)	3.62(.65)	2.98(.89)	2.98(.95)	13.17(2.94)
Group I b	4.12(.42)	4.06(.30)	3.56(.47)	3.65(.47)	15.40(1.14)
Group I c	3.87(.62)	3.75(.5)	3.25(.5)	3.25(.5)	13.8(1.65)
Group II	3.72(.66)	3.77(.50)	3.27(.61)	3.16(.55)	14(2.12)

The mean MRC score in deltoid was 3.52, in biceps was 3.62, in iliopsoas was 2.98, in quadriceps was 2.98 and in tibialis anterior was 3.72 in group I a patients. In group I b patients the mean MRC scores were, 4.12, 4.06, 3.56, 3.65, and 3.84 respectively in deltoid, biceps, iliopsoas, quadriceps and tibialis anterior muscles. In group II patients MRC scores were, 3.72, 3.77, 3.27, 3.16 and 3.94 respectively (Table 6).

Table 7. MRC scores at entry into study in all patients

Mean score (SD)	Deltoid	Biceps	Iliopsoas	Quadriceps	Cumulative score
Group I a	3.46(.75)	3.57(.69)	2.93(.92)	2.87(1.02)	12.93(3.06)
Group I b	3.62(.42)	3.65(.5)	2.9(.68)	3.03(.8)	13.2(2.19)
Group I c	3.5(.40)	3.75(.5)	3(.81)	3.25(.5)	13(1.77)
Group II	3.83(.79)	3.66(.43)	3.05(.46)	3.11(.54)	13.33(1.52)

The cumulative MRC score (Sum of MRC scores of deltoid, biceps, iliopsoas and tibialis anterior) at first visit was 13.17 in group I a, 15.40 in group I b, 14

in group II and 13.8 in group I c (Table 6). The cumulative score at entry into the study was 12.93 in group I a, 13.2 in group I b, 13.3 in group II and 13 in group I c (Table 7). Across all groups, weakness was prominent in the pelvi-femoral muscles and both iliopsoas and quadriceps were equally involved in 26/69 (37.68%) from the onset of illness. Power in quadriceps was less then iliopsoas in 13(18.84%) patients.

Table 8. Facial weakness and axial weakness

Frequency (%)	Group I a	Group I b	Group I c	Group II
Facial weakness				
Mild	14 (35)	7 (43.75)	3 (75)	2 (22.22)
Moderate	12 (30)	4 (25)	1 (25)	1 (11.11)
Neck flexor weakness				
Mild	29 (72.5)	10 (62.5)	4 (100)	8 (88.89)
Moderate	8 (20)	5 (31.25)		1 (11.11)
Severe	2 (5)	1 (6.25)		
Axial weakness (Truncal)				
Mild	13 (32.5)	2 (12.5)		5 (55.56)
Moderate	16 (40)	12 (75)	3 (75)	3 (33.33)
Severe	11 (27.5)	2 (12.5)	1 (25)	1 (11.11)

Facial weakness was present in 44 (63.78%) patients, mild in 26 (37.68%) patients and moderate in 18 (26.08%) patients. Neck flexors weakness was seen in all patients, mild in 51(73.91%), moderate in 15(21.74%) and severe in 3(4.3%) patients. Axial (Truncal) muscle weakness was seen in all patients, mild in 20(28.99%), moderate in 34(49.27%) and severe in 15(21.74%) patients). Axial weakness was profound in group I patients, (moderate to severe in 67.5% patients of group I a, 87.5 % of group I b and in all patients of group I c) (Table 8).

Functional grades:

Table 9. Functional (GSCS) grades at entry into study

Mean (SD)	Squatting	Walk	Chair	Stairs	cumulative score
Group I a	4.58 (1.93)	3.55(1.99)	3.40(1.66)	4.18(1.89)	15.72(7.15)
Group I b	4.03(1.52)	3.31(1.62)	3.13(1.26)	4.13(1.54)	14.69(5.63)
Group I c	4(1.41)	3 (.82)	2.75(.96)	4	13.75(3.09)
Group II	4.67(1.33)	3.22(1.72)	3.22(1.30)	3.78(1.48)	14.89(5.64)

The mean score in group I a for getting up from squatting position was 4.58, for walking it was 3.55, for getting up form chair it was 3.40 and for climbing stairs it was 4.18. For those in group I b scores were 4.03, 3.31, 3.13 and 4.13 respectively. The cumulative scores were 15.72 in group I a, 14.69 in group I b, 14.89 in group II and 13.75 in group I c (Table 9).

Distribution of GSCS and MRC score in patients of a given age.

The mean values of GSCS scores and MRC scores of patients presenting at a particular age was taken and plotted against the age of the patients of group I a and group I b. Over time there was gradual decline in MRC scores and GSCS scores during the course of illness. These occurred at a slower rate in group I b (Figures 3, 4, 5 and 6).

Over all MRC and GSCS scores were better in treated group (group I b) across all age groups compared to the natural history group (group I a). Patients in group I b were younger than the other groups at presentation to the hospital and were older than the other groups when they were first seen during the study period.

Comparison of grade of walking and power in iliopsoas/ quadriceps in group I a patients.

With disease progression, there was decline in the muscle power and worsening of the functional status, evident by increasing GSCS score. As the power in the lower limb muscles decreased there was worsening of gait, even with power less than 3, patients with ambulant with moderate to severe waddling; only when power was less than 2, they lost ambulation. So functional ability and decline in MRC score progress over time, but functional ability appears to be relatively preserved even with severe muscle weakness (Figure 7). This correlation was statistically significant with 2 sided Pearson chi square value, $p < 0.01$. In addition loss of ambulation correlated more with power in quadriceps, as power became less than 2, most patients lost independent ambulation.

Deep tendon reflexes were absent in 13(18.84%) patients, only ankle jerk elicitable in 41(59.42%) patients, reflexes were sluggish in 5 (7.24%) patients, and normal in 10 (14.28) patients. Patients with absent deep tendon reflexes were those with advanced disease.

Spinal deformity was present in 66 (95.65%) patients, increased lumbar lardosis in 53(76.68%), scoliosis in 6(8.79%) and both in 7(10.14) patients. 23(33.33%) patients had wide based stance.

Contractures were commonly seen at ankle in 56(81.16%), at knee joint in

12(17.39%) patients, at hip joints in 8(11.39%) and at elbow joint in 1(1.4%) patient. There was progressive increase in the degree of contractures over the course of illness (Table 10). The degree of ankle contracture in the group 1b, was steadily increasing at the various timelines, when compared to group 1a, and these patients (1b) with better MRC scores, continued to be ambulant. The natural history group (1a) had lower MRC scores across time lines and 9/40 had lost ambulation under the age of 10.

Table 10. Ankle contracture (in degrees)

Mean (SD)	At start of study	6 months	12 months	18 months
Group I a	12.50(5.88)	11.54(3.75)	13.33(5.16)	13.33(7.63)
Group I b	13.13(7.04)	14.17(6.68)	16.67(7.07)	18.57(6.9)
Group I c	15(5.77)	20	20	20
Group II	14.44(5.27)	16.67(5.77)	20	

Serum Creatine phosphokinase levels:

Mean Serum CPK at presentation was 11354.58(7327.2) in group I a patients, 12032 (5783.09) in group I b patients, 10634 (3880.42) in group II patients and 13487(5119.29) in group I c patients. When the mean Serum CPK values analyzed according to age, values were more than 50 times normal during first decade (range – 1395 to 33000) after which there was decline in the values as the disease progressed (range – 1512 to 7456) (Figure 8). We had 3 bed bound patients, first patient was 8 years old boy with Serum CPK value of 1395, and second boy was 12 years old with under follow up since 18 months with Serum CPK values of 1512, 2321 and 3863. Third boy was of 15 years, bed bound

since 12 years of age with Serum CPK of 763.

Analysis of serial Sr CPK values in 5 of our patients with follow up more than 3 years also showed that there was gradual decline in the levels with increasing age and disease duration in most of them (Figure 9).

Electromyogram (EMG):

EMG was available for analysis in 49 (71.01%) patients, On Nerve conduction studies, CMAP's were of normal amplitude in 25(51.02%) patients, reduced in amplitude in both upper and lower limbs in 11(22.45%) patients, reduced in lower limbs in 9(18.37%) patients and reduced in upper limbs in 4(8.16%) patients. Needle EMG showed spontaneous activity in the form of positive sharp waves in 4 (8.16%) patients and positive sharp waves with fibrillations in one (2.04%) patient. Interference pattern was myopathic in all the 49 patients.

Electrocardiogram (ECG) changes:

ECG's of was analyzed in 35 patients (30 of Duchenne's phenotype and 5 of Becker's phenotype). In 30 patients with Duchenne's phenotypes (groups I), ECG showed sinus tachycardia in 15 (50%) of the patients, prominent R in V1 (> 4 mm) in 29 (96.66%) patients, R > S in V1 in 19 (63.33%) patients, R > S in V2 in 21 (70%) patients. All these features were more common in the nonambulant group than the ambulant group in these patients. In Becker's phenotypes (group II, 5 patients), one (20%) showed sinus tachycardia, all 5(100%) had R wave in V1 > 4mm, 3(60%) patients had R > S in V1 and 4(80%) patients had R > S in V2 (Table 11).

Table 11. Electrocardiogram changes in 35 patients

Group (Frequency)	heart rate > 100	R in V1 > 4mm	R/S in V1 > 1	R/S in V2 > 1
Duchenne's phenotypes (group I)				
Nonambulant (7)	5(71.42%)	7(100%)	5(71.42%)	6(85.71%)
Ambulant (23)	10(43.47%)	22(95.65%)	14(60.87%)	15(65.2%)
Total	15(50%)	29(96.66%)	19(63.33%)	21(70%)
Becker phenotypes/ Outlier's (group II)				
Nonambulant (1)		1		1
Ambulant (4)	1(25%)	4(100%)	3(75%)	3(75%)
Total	1(20%)	5(100%)	3(60%)	4(80%)

Echocardiography (Echo) findings:

Echocardiography reports of 30 patients were analyzed.

Table 12. Echo findings (mean values and standard deviation)

Group	Ejection fraction (%)	LVESV	LVEDV	LVEDD
Duchenne's phenotypes (group I)				
Nonambulant (11)	61.91(3.36)	18.73(6.8)	44.73(12.61)	34.36(3.04)
Ambulant (15)	60.00(2.33)	21.67(14.19)	44.27(10.14)	32.07(3.95)
Becker phenotypes/ Outlier's (group II)				
Nonambulant (1)	57	36	82	44
Ambulant (5)	61(2.64)	24.00(6)	60.33(19.03)	38.33(3.21)

The mean Ejection Fraction (EF) was more than 60% in group I a, I b and I c patients. One patient in group II had EF of 57%, who had lost ambulation. Left ventricular end systolic volume (LVESV) and end diastolic volume (LVEDV), Left ventricular end diastolic diameter (LVEDD) were normal in group I patients. They were increased in one patient of group II. Wall motion abnormalities were not documented in any of these patients. There was no difference in the values between ambulant and non ambulant groups in

Duchenne's phenotypes. Echo parameters were different in the Becker's phenotype patients who were ambulant and nonambulant (increased LVEDV and LVEDD) (Table 12).

Histopathological findings on muscle biopsy:

All showed myopathic features. Overall architecture was preserved in 31 patients (44.9%), mildly disrupted in 25 (36.2%) and effaced in 13 (18.8%) patients. Commonly seen changes were fiber size variation, atrophic and hypertrophic fibers, ring fibers, regenerating fibers, myophagocytosis, and necrotic fibers. In addition fibrosis was seen in endomysial region in 27(39.1%) patients, perimysial regions in 4 (5.7%) patients or in both places in 38(55.1%) patients. It was focal in 2(2.9%) patients, mild in 35(50.7%) patients, moderate in 14(20.3%) patients and extensive in 18(26%) patients. Fatty infiltrates was seen in interfasciular in 5(7.2%) patients, in intrafascicular region 1(1.45%) patient or in both regions in 38(55.1%) patients. Inflammatory infiltrates were seen in 21 patients, in perivascular region in 16(23.2%) patients and endomysial region in 5(7.16%) patients. The time of disease onset to biopsy was less in patients showing inflammatory infiltrates. Type 1 fiber predominance was seen in 8(11.6%) patients and type 2 fiber predominance was seen in 2(2.9%) patients.

Immunostaining for dystrophin:

44(63.78%) patients had absence of dystrophin **2** and **3**. 16(17.78%) patients

had absence of **1**, **2** and **3**. 1(1.4%) patient had absence of dystrophin **1** and **2**. 4(5.8%) patients had absence of dystrophin **2**. 4(5.8%) patients had absence of dystrophin **3**. Revertant fibers were seen in 14(20.28%) patients, few in 4(5.8%) and occasional in 10(14.5%) patients.

Treatment aspects:

Patients were initiated on physiotherapy / and medications. In the present study group all were on regular physiotherapy and stretching exercises. They were also initiated on breathing exercises with incentive spirometer.

Table 13. Medications, dosage and duration.

Parameter	Group I a	Group I b	Group I c	Group II	Total (%)
Prednisolone	1	4	1	2	8(11.59)
Deflazacort	26	12	3	5	46(66.66)
No treatment	13			2	15(21.74)
Mean age of starting treatment in years (SD)	7.23 (1.90)	6.69 (1.74)	7.25 (.96)	10.57 (1.27)	
Follow up in months (SD)	5.6 (6.16)	43.13 (25.1)	15.5 (3)	9.89 (15.50)	

8 (11.59%) patients were on medications with Prednisolone (mean dose - 1 mg per kg body weight) and 46 (66.66%) patients were on deflazacort (mean dose of 0.96 per kg body weight), given on alternate days. 15(21.74%) patients were not initiated on medication as they were in advanced stage at the time of presentation. The mean duration of follow up was 5.60 months, 43.13 months, 9.89 months and 15.50 months in groups I a, I b, II and I c respectively. 6(8.69%) patients had follow up of more than 6 years, 12(17.39%) patients had

24 - 48 months follow up, 8(11.59%) patients had 13 -23 months follow up, 16(23.19%) had 7 -12 months and 27(39.13%) patients had less than 6 months follow up (Table 13). In addition to steroids all patients were on Calcium and Potassium supplementation.

Treatment related complications

On evaluation during the study period, patients treated with steroids in group I b (16 patients) had weight gain. On comparison with healthy controls, at presentation to hospital before starting steroids, one (6.25%) patient had BMI above 95 th percentile for age, 3(18.75%) patients were more than 85 th percentile, 3(18.75%) had BMI above the 50 th percentile for age, and 9(56.25%) had BMI below the 50 th percentile for the age. When seen during the study period (when they were on steroids for more than 2 years), one (6.25%) patient had BMI more than 95 th percentile for age, 3(18.75%) had above 85 th percentile for age, 6(37.5%) had BMI above the 50 th percentile for age and 6(37.5%) were below the 50 th percentile for the corresponding age (Figure 10). There was no significant difference in Prednisolone group and deflazacort group in terms of weight gain in our study.

On comparison of height of group I b patients with the normative for the same age (ICMR values), at presentation to the hospital (before starting steroids), 8(50%) patients were above the 50 th percentile of height for the age and 8(50%) patients were below the 50 th percentile. None of the patients had values below the 10 th percentile (Figure 11).

On assessment during the study (when they were on steroids for than 2 years), 16(100%) patients were below the 50 th percentile and out of these 8(50%) were below the 10 th percentile for the corresponding age matched values (Figure 12). This was probably related to the steroid therapy. Two (12.5%) patients had osteoporosis documented on DEXA scan and one (6.25%) patient had fracture of femur shaft during physiotherapy (stretching exercises). One patient was found to have features of depression and was initiated on Sertaline in consultation with Psychiatrist.

Outcome measures:

For outcome measures, patients of group I b were compared with group I a. Comparison was done to analyze the differences in them with respect to changes in functional grade (GSCS) and MRC scores over time, and age at loss of ambulation.

The mean functional grade (GSCS) for all parameters at a given age was calculated by taking mean values of all patients presenting at that age. For example GSCS for squatting at 7 years was derived from the mean grade of squatting of all patients who had entered the study at 7 years of age.

From analysis of this data it was evident that there was gradual decline in the functional status (seen as increase in the GSCS score) over the course of illness up to 7 or 8 years after which there was steep decline in the scores in group I patients. In the group I b patients there was decline in the grades but at slower rate than group I a (Figure 13).

The mean MRC score and cumulative score was derived in the same way as the GSCS grade was done. On analysis the data there was gradual decline in the muscle power over the first 8 years and then rapid progression (Figure 14). There was gradual progression of GSCS and MRC grades over time in the treatment group. On comparison with the group I a curves, it was seen that that decline was slower and each disease related milestones appeared at a later age in group Ib.

Mean GSCS was lower (14.69 v/s 15.72) and mean MRC score was higher (13.2 v/s 12.93) in group I b, and the age at entry into the study was higher in group I b (9.56 v/s 7.88) (Table 14). Overall there was shift in the curve to the right side, that is all disease related milestones occurred at a comparatively later age in treated groups.

Table 14. Statistical analysis:

Mean (Std deviation)	Mean age at entry into study	Mean GSCS at entry into study	Mean MRC at entry into study
Group I a	7.88(2.1)	15.72(7.15)	12.93(3.06)
Group I b	9.56(2.2)	14.69(5.63)	13.2(2.19)
Mann Whitney test (sig -2 tailed)	0.011	0.935	0.898

The difference in the MRC scores and GSCS scores was not significant between the two groups but there was significant difference in the mean age between the two groups. That is group I b patients have preserved power and functional ability for/ at a given age than natural history group (group I a) (table 14).

7(17.5%) patients in group I a were confined to wheel chair before 10 years of

age; in group I b all patients below 10 years were ambulant till follow up, two (12.5%) patients were ambulant with support (Table 15).

Table 15. Comparison of ambulation in group I a and I b.

Parameter/age in years	6	7	8	9	10	11	12
Group I a (40 patients)							
Cannot walk without support	2	2	3	1	1		
Cannot stand without support	2		2	4		1	
Wheel chair bound		2	1	4		1	
Group I b (16 patients)							
Cannot walk without support		1		1	1	2	
Cannot stand without support		1				2	
Wheel chair bound						1	1

Two (12.5%) patients in group I b lost independent ambulation and became wheel chair bound after 11 and 12 years of age respectively. In our study group, loss of ambulation before 10 years in patients on treatment was less common, but patients not on treatment usually lost ambulation before 10 years of age. Group I a patients lost ability to walk without support at ealier age (mean age -7.67 years) compared to group I b (mean age – 9.60 years), which was significant ($p = 0.034$). Group I a worsened further to reach wheel chair stage again at an earlier age (mean age – 8.62 years v/s 11.50 years), which was significant statistically ($p = 0.019$) (Table 16).

Table 16. Statistical analysis – t test for equality of means

Parameter		Frequency	Mean(SD)	Sig. (2-tailed)
Cannot walk without support	Group I a Group I b	9 5	7.67(1.32) 9.60(1.67)	.034
Wheel chair/bed bound	Group I a Group I b	8 2	8.62(1.30) 11.50(.71)	.019

Analysis of a subgroup of 7 patients in group I b

In group I b, 7(43.75%) patients were seen in the clinic more than 3 times during the study period. Their age at presentation was 6.43 years (1.99), age at entry into study was 9 years (2.58), age at onset of first symptom was 4 years (1.63), age at onset of difficulty to squat and get up was 4 years (1.63), inability to run was 4.57 years (1.9), inability to walk without support was at 8 years (1.41) in 2(28.57%) patients. Facial weakness was seen in 5(71.42%) patients at entry into study, mild in 3(42.86%) and moderate in 2(28.57%) patients, during the study period one patients developed mild facial weakness and another patient with mild weakness, worsened to moderate weakness. Axial was mild in 1(14.29%) patient, moderate in 5(71.42%) patients and severe in 1(14.29%) patient. Over the study period there was gradual progression of GSCS grade, about 3 units per year. There was decline in the MRC scores, in the range of 0.18 to 1 units per year. At entry into the study 6(85.71%) patients had GSCS score of 9-15, and one (14.29%) patient had score in the range 16-21(Table 17).

Table 17. Parameters during study period in 7 patients of group I b

	At first	At entry	At 6	At 12	At 18

	visit		months	months	months
Mean GSCS		13.29 (3.09)	14.71 (3.86)	16.29 (4.86)	17.86 (5.58)
Mean MRC score	15.14(.9)	13.79 (1.65)	13.29 (1.87)	13.07 (2.05)	12.79 (2.1)
Change in GSCS			2.86(3.24)	3(2.58)	3.04(2.4)
Change in MRC		.93(.61)	1(1.53)	.57(.84)	.18(1.12)
GSCS grade change					
> 21					1
16-21		1	4	4	3
9-15		6	3	3	3
<9					
Sr CPK	9690.86 (4691.46)	8318.20 (4753.15)	13581.67 (3732)	11928 (7148.72)	16951 (11385.8)

Over the follow up period, 3 (42.86%) patients worsened with GSCS in 16-21 range and at 18 months one (14.29%) patient worsened further to enter GSCS > 21 range. There was weight gain with BMI at first visit being 15.3, 16 at entry into study and 16.74 at end of the study period. There was decrease in the number of falls over the study period.

Table 18. Frequency of falls during the study period.

Frequency	At start of study	At 6 months	At 12 months	At 18 months
Rarely falls (< 1 per wk)	1(14.3%)	-	3(42.9%)	4(57.1%)
Occasional falls (2 – 4 / wk)	3(42.9%)	5(71.4%)	3(42.9%)	3(42.9%)
Daily falls	2(28.6%)	2(28.6%)	1(14.3%)	-
Repeated falls (> 4 per day)	1(14.3%)	-	-	-

1(14.29%) patient used to have repeated falls, 2(28.58%) patients used to have daily falls, 4(57.16%) patients used to have occasional or rare falls when they had evaluated at entry into study. At the end of study all 7(100%) patients were

having occasional or rare falls with none of them having repeated falls (Table 18). Ankle contractures were seen to increase over time, at entry into study, 2(28.58%) patients had 10 degrees and 4(57.16%) patients had 20 degrees of contractures. At the end of study, 2(28.58%) patients had 10 degrees, 4(57.16%) patients had 20 degrees and 1(14.29%) patients had 30 degrees of contracture.

Comparison of GSCS grades with other parameters in group I

Patients with GSCS > 21, compared to patients with GSCS < 15 had greater delay in onset to diagnosis (4.9 v/s 3 years), greater degree of ankle contracture (18 v/s10.42), lower Sr CPK (4590.83 v/s 13283), severe grades of facial and axial weakness and more frequency of scoliosis in addition to lumbar lardosis.

Table 19. GSCS at presentation and associated clinical variables

GSCS/ parameters	< 15 (N=39)	16 – 21 (N = 9)	> 21 (N =12)
Onset (yrs)	3.77 (1.42)	4.22 (1.92)	4.25(1.66)
Presentation (yrs)	6.64(1.41)	9(1.32)	8.58(2.71)
onset – presentation	2.85(1.34) yrs	4.78(1.85) yrs	4.08(2.61) yrs
Ankle contractures	11.03 (5.98)	13.33 (5)	18.33 (3.89)
Sr CPK	12588.33	11464.89	8876.92
MRC score	15.10 (1.43)	13(1.64)	10.25 (3.01)
Facial weakness Mild Moderate	 18(46.2%) 4(10.3%)	 5(55.6%) 2(22.2%)	 1(8.3%) 11(91.7%)
Axial weakness Mild Moderate Severe	 2(5.1%) 35(89.7%) 2(5.1%)	 1(11.1%) 7(77.8%) 1(11.1%)	 1(8.3%) 3(25%) 8(66.7%)

Spinal deformity			
Scoliosis	2(5.1%)	2(22.2%)	5(31.7%)
Lardosis	35(89.7%)	6(66.67%)	4(33.3%)
Both	2(5.1%)	1(11.1%)	3(25%)

On Statistical analysis there was significant correlation between axial/ facial weakness and grades of GSCS ($p < 0.01$). With other parameter there was no significant correlation (Table19). In patients with GSCS > 21, on histopathology, architecture was effaced in 50 % compared to 10.3% in GSCS < 15 group. There was no stastical correlation between other variables and grades of GSCS ($p > 0.05$) (Table 20).

Table 20. GSCS at presentation and associated Histopathological variables

GSCS/ parameters	< 15 (N=39)	16 – 21 (N = 9)	> 21 (N =12)
Architecture Normal	21(53.8%)	2(22.22%)	3(25%)
Mild loss	14(35.9%)	5(55.6%)	3(25%)
Effaced	4(10.3%)	2(22.22%)	6(50%)
Inflammation Focal	6(15.4%)	1(11.1%)	1 (8.3%)
Mild	5(12.8%)		1(8.3%)
Moderate	1(2.6%)	1(11.1%)	
Severe			
Fibrosis grade Mild	18(46.2%)	5(55.6%)	6(50%)
Moderate	9(23.1%)	1(11.1%)	3(25%)
extensive	11(28.2%)	3(33.3%)	2(16.7%)
Dystrophin absent 2,3	22(56.4%)	7(77.8%)	7(58.3%)
1,2,3	13(33.3%)	2(22.2%)	1(8.3%)
2	1(2.6%)		1(8.3%)
3	1(2.6%)		

1,2	1(2.6%)		
Revertant fibers Few	2(5.1%)	1(11.1%)	1(8.3%)
occasional	7(17.9%)		1(8.3%)

Ankle contractures and disease pattern in group I a and I b.

31 patients had 10 degrees and 19 patients had 20 degrees of ankle contracture. 5 did not have contracture at entry into the study (Table 21).

Table 21. Ankle contracture and disease pattern

Groups	Contracture in degrees	Ambulant		Total
		No	Yes	
Group I a	absent	0	3	3
	10	2	22	24
	20	7	5	12
total		9	30	39
Group I b	absent	0	2	2
	10	0	7	7
	20	5	2	7
total		5	11	16

There was increase in the degree of contracture at the ankle joints with increasing age of the patient. With worsening of the MRC score and GSCS grades, there was progression in ankle contractures. Most of the patients with greater degree of contracture were of older age, having low MRC score, higher GSCS score. Most of the patients who were ambulant, both in group I a and I b were having 10 degrees of contracture and most of the nonambulant patients were having greater degrees of contractures. During the course of illness there was a period during which these patients were ambulant and had milder grade

of contracture, probably as a compensatory measure for better locomotion,[14] but over time as the weakness in the muscles increased there was worsening of the contractures and the loss of balance between compensatory measures is lost, progressing to loss of ambulation (Table 22).

Discussion:

Dystrophinopathies were commonest among the various muscle diseases seen in our neuromuscular clinic. They constituted 45.01% (131 of the 291 diagnosed cases of primary muscle diseases) of all the primary muscle diseases seen in the clinic over the last 5 years.

The present study was carried out on 69 patients (68- boys; 1- girl). The mean age of the patients at entry into the study was 7.88(2.1) years in group I a, 9.5(1.6) years in group I b, 9(1.83) years in group I c and 12.44(1.51) years in group II. Group I b patients were relatively older than those in group I a at entry into the study.

In our study, 55.1% of patients had delayed motor milestones. The mean age at walking without support was 1.75(.93) years in group I and 1.33(0.5) years in group II. These were comparable to the average of 18 months reported in literature. One boy aged 7 years in our series never walked without support. In addition 11.6% had delayed language milestones. Both delayed motor and language milestones have been reported in other studies.[5, 67, 68]

The mean age (SD) at first symptom onset was 3.93(1.54) years in group I. In other studies of Duchenne Muscular dystrophy, the mean age at onset were 4.8 years (Gulati et al, 2005), 5.4 years (Ahuja et al, 2000), 3 years, 8 months (Thong et al, 2005) and 2.4 years (Anthonie et al, Dutch survey) [69, 70, 71, 72] Age of

first symptom onset in our study was similar to that in study by Thong et al and Gulati et al. Onset was at earlier age in Dutch study compared to other studies. The mean age at first symptom in group II was 8.44 (1.51) years.

In group I, first symptom noted by parents was difficulty in getting up from squatting position without support in 32 (53.3%) patients, inability to run as fast as compared to their peers in 10 (16.7%) patients, waddling gait in 5 (8.3%) patients, toe walking in 2 (3.3%) patients and repeated falls in 9 (15%) patients. One (1.7%) patient was diagnosed after he was found to have raised hepatic enzymes while being evaluated for a febrile illness elsewhere. One (1.7%) patient had not attained independent ambulation till 7 years of age when he presented to us. In a similar study of Duchenne's Muscular dystrophy (Thong et al, 2005), the most common presentation was developmental delay, followed by frequent falls, lower limb weakness, calf enlargement, unusual gait and frequent cramps.[71] In another study (Anthonie et al, Dutch survey) 47.6% patients had locomotor problems initially and 3 cases were diagnosed co-incidentally in presymptomatic stage by elevated creatine kinase.[72]

In group II, 8(88.9%) patients presented with difficulty to get up from squatting position and one (11.1%) patient presented with repeated falls.

The mean age (SD) at presentation to hospital was 7.38 (1.98) years in group I and 11.78 (1.48) years in group II. There was significant lag period between the

first symptom noticed by the parents to the time of evaluation and diagnosis in all the groups. This delay in diagnosis has been reported even in other studies. [71, 72] Reported mean diagnostic delay usually varies between 2 and 3 yrs (range 0 to 6 yrs). In a retrospective study of patients with DMD referred initially for orthopedic consultation because of clumsiness, the first referral took place at age 3 years but the correct diagnosis of DMD was not made on average until 2 years later.[14] In a study by Gulati et al (2005), this difference was 2.6 yrs (mean age at onset - 4.8 years and at presentation - 7.4 years) [69] and 3 years, 6 months in another study by Thong et al (2005).[71] Although developmental delay and other early symptoms are often noted before 5 yrs of age, they are often taken lightly both by the parents as well as the attending physician, except in some cases with family history of myopathy. This leads to delay in initiation of appropriate treatment and genetic counselling.

We studied various disease related milestones at various time intervals during course of the illness and compared it with other studies. In our study difficulty to get up from squatting position and inability to run were present in most of the patients (98.3%). In group I, the mean age (SD) of appearance of difficulty in squatting and getting up was at 4.25 (1.54) years, inability to run and keep pace with peers as other peers at 4.1(1.64) years, abnormal gait or stance and features of waddling at 6.41(1.58) years, toe walking at 4.71(1.60) years, calf enlargement at 6 years and repeated falls form 6.16(1.45) years. In a similar

study, use of Gower's manoeuvre to get up was seen at 5 years, waddling at 6 years.[68] In another study by Gulati et al (2005) the commonest symptoms were difficult to run (56.6%), followed by difficulty in getting up from floor (16.6%).[69]

In group I a (natural history group), Inability to walk without support was seen at mean age of 7.67(1.3) years in 9(22.5%) patients. Of them 8 (20%) patients were confined to wheelchair at a mean age of 8.63(1.30) years. In similar studies of Duchenne's muscular dystrophy, the age at confinement to wheel chair in nontreated patients was, 9.21(1.48) years (King et al 2007), [50] 9.5 years (range 6 -12 years, Anthonie et al, Dutch survey).[72] 9.9(0.3) years (De Silva et al, 1987)[75] and 11(0.67) years (Pradhan et al, 2006).[76] On comparison, loss of ambulation in our study (in natural history group) was similar to that in the studies by King et al and Anthonie et al. Loss of ambulation was at a later age in the study by Pradhan et al (11 years), which could be due to the addition of some cases of Outlier's in the study group as the upper limit for the age of onset was 7 years for inclusion in the study, whereas it was 5 years for classifying as DMD in our study.

5(31.25%) patients in group I b, 1 each in group II and I c could not walk without support at entry or during the study period. Of them 2 in group I b, one each in group I c and II became confined to wheel chair during the study period.

2 (22.22%) patients in group II (BMD/outlier's) were noted to have dyspnoea on exertion at mean age of 10.50 years and 1 (1.7%) patient in group I a had dyspnoea on exertion from 7 years of age. This is in accordance with literature that BMD patients who are relatively more active tend to have cardiac manifestations whereas DMD patients do not do so due to restricted physical activity by the end of first decade. In a study by Gulati et al (2005, 30 patients, mean age 10.1 years), symptoms or signs suggestive of cardiac dysfunction were seen in only 3(10%) patients.[69]

School performance was poor in 7 (11.7%) patients and good in 22 (36.7%) patients of group I of our study. In a similar study (Thong et al, 2005, 21 patients of DMD), 7(33.33%) had learning difficulties, 9(42.85%) had satisfactory school performance and 4(19.04%) had dropped out of school due to unknown reasons.[71]This difference could be due to different ethnic background and environment factors among the two groups. 3(5%) patients of DMD had features of attention deficit hyperactivity disorder requiring psychiatric assessment and therapy. In a study of DMD patients, ADHD was seen in 11.7% patients compared to 7 % in general population.[31] In our study it appeared in the range for general population.

Family history was present in 23.33 % of the DMD patients in our study. In

other studies family history was positive in one third of patients (Gulati et al, 2005)[69], 18.5% patients (Ahuja et al, 2000)[70] and 23.8% (Thong et al 2005).[71] We had one family with many members affected (patient - cousins - maternal uncles), but the patients were evaluated only when they were symptomatic. This stresses that despite years of experience and availability of good screening tools, the screening tools are still underutilized stressing on need for educating primary care physician about the disease.

Weakness was seen in cranial, axial and limb muscles, more in the proximal muscles. Facial weakness was common in Duchenne's phenotypes (group I) (68.33%) compared to group II (44.44%). With disease progression facial weakness worsened. This has not been commonly reported in literature. In the limbs, pelvi-femoral group was more affected than the other groups; in 39(56.25%) patients quadriceps was equally weak and of them 13(18.84%) had power less than that in iliopsoas. As the disease progressed, tibialis anterior, proximal upper limbs and later distal muscles were involved. Axial muscle weakness was common/ severe in the DMD group compared to BMD/ Outliers. Axial weakness was seen in early stages, worsening with decline in limb power and functional grades. Presence of higher grades of facial and axial weakness co-related with higher GSCS grades, which was stastically significant.

There was gradual decline in the MRC scores over years, with rapid decline in

the later part of the first decade and just before the time of loss of ambulation. This is evident from the distribution of the MRC scores over years and the corresponding figures.

GSCS grades also correlated with the decline in MRC scores over years, but the functional ability appeared to better preserved at even lower MRC scores. On comparing the functional grades of walking with power in iliopsoas and quadriceps, patients lost ambulation only when power was less than 2 in these muscles. In similar study by Parreira et al (2007), there was co-relation between the decline in MRC scores and in the Hammersmith motor disability score test, which was proportional.[73] In our study, there was decline in the muscle power but functional status appeared to be relatively preserved. This relative preservation of functional status could be because of the compensatory measures acquired over time by these patients.

Skeletal deformities were seen in 66 patients, increased lumbar lardosis in 53(76.8%), scoliosis in 6 (8.7%) and both in 7 (10.1%) patients. 23(33.33%) patients had wide based stance. Scoliosis was present in patients with advanced disease. Of the 6 patients with scoliosis, 4(66.67%) patients had GSCS > 21 at presentation.

Contractures were commonly seen at ankle in 56(81.16%), at knee joint in 12(17.39%) patients, at hip joints in 8(11.39%) and at elbow joint in 1(1.4%)

patient. There was progressive increase in the degree of ankle contracture with disease duration. Ankle contracture appeared first of all the joint contractures followed by knee, hip and later upper limb joint involvement. There appeared to be a period during which patients have milder degrees (≤ 10 - 15) of ankle contracture and are ambulant. As the disease advances, the weakness worsens beyond the levels of compensation, and patients' progressively lose ambulation and have rapid increase in contractures as they become bed bound. On comparison of the ankle contractures in patients in group I a and I b, degree of contracture and progression was more in group I b. There appeared to be a favorable degree of ankle contracture in patients who are ambulant with good MRC scores during the course of illness which helps in ambulation as a compensatory measure for a longer period of time.

Creatine phosphokinase levels were raised more than 50 times normal in most patients, especially in the early stages. With progression of disease, the CPK levels decline. There can be low Sr CPK values < 1000 - 2000 as seen in three of our patients in advanced disease stage. So, low Sr CPK does not rule out Duchenne's muscular dystrophy, especially in patients who present at an advanced stage of illness.

EMG was available for analysis in 49 (71.01%) patients, CMAP's were of normal amplitude in 25(51.02%) patients, reduced in both upper and lower

limbs in 11(22.45%) patients, reduced in lower limbs in 9(18.37%) patients and reduced in upper limbs in 4(8.16%) patients. Positive sharp waves were seen in 4 (8.16%) patients and positive sharp waves with fibrillations in one (2.04%) patient. Interference pattern was myopathic in all the 49 patients.

ECG changes were common in our study. In the 30 patients with Duchenne's phenotypes (group I), prominent R wave was seen in V1 (> 4 mm) in 29 (96.66%) patients, R > S in V1 in 19 (63.33%) patients and R > S in V2 in 21 (71%) patients. Sinus tachycardia was seen in 15(50%) patients. Among the ambulant and nonambulant groups, R>S in V1 was common in nonambulant patients (71.42% v/s 60.86%). In a study by Ahuja et al (2000, 27 patients, mean age 9.7 years) sinus tachycardia was seen in 62.9% patients, R>S in V1 in 44.4% patients. In a study by Gulati et al (2005, 30 patients, mean age 10.1 years) R>S in V1 was seen in 76.6% and 30% had Q waves in lateral leads. [69, 70] Prominent Q waves in lateral leads were not seen in our patients.

In Becker's phenotypes (group II, 5 patients), one (20%) showed sinus tachycardia, all 5(100%) had R wave in V1 > 4mm, 3(60%) patients had R > S in V1 and 4(80%) patients had R > S in V2. These changes suggest involvement of the posterior basal myocardium in these patients.

In our study, Echocardiogram parameters of Duchenne phenotypes (group I) including ejection fraction, left ventricular end systolic and end diastolic

volumes and end diastolic diameter were normal, with no differences between ambulant and nonambulant groups. In Becker's phenotypes, one patient had increase in left ventricular volumes and diameter, with other patients having normal values. In a similar study by Ahuja et al (2000, study group having 14.8% nonambulant patients and mean age of 9.72 years) there was no evidence of any cardiac dysfunction on echocardiogram in any of the patients. In an another study by Gulati et al (study group having 63.3% nonambulant patients and mean age of 10.1 years) mean ejection fraction was < 50% in 17.8 % patients and mean was 52.5% (SD - 6.3).[69, 70] Our study group was similar to that of Ahuja et al, as 57.7% of the our patients were ambulant and mean age of our patients when echocardiogram was done was less than 7.7 years. Absence of echo abnormalities in our patients may be due to younger age of our DMD patients. Over all cardiac symptoms are less common in younger DMD, but ECG abnormalities are more frequent than echocardiogram abnormalities.

Muscle biopsies showed myopathic features, fibrosis, adipose tissue infiltration, inflammatory infiltrates and absent dystrophin staining. Absence of dystrophin **2, 3** was the commonest pattern noted.

Diagnostic testing can also be done with gene based tests or western blot tests. 4(5.8%) of our patients with biopsy suggestive of Dystrophinopathy had negative test when analyzed for deletions in dystrophin gene before biopsy was

done.

Of the 69 patients, 54(78.26%) were on treatment, 46(66.67%) on deflazacort, and 8(11.59%) on Prednisolone. All patients were on physiotherapy including stretching exercises.

The mean age at starting steroids was 6.69 years in group I a, 7.23 years in group I b and 7.23 years in group I c. The mean dose was 0.96 mg per kg for deflazacort and 1 mg per kg for Prednisolone given on alternate days.

When treatment was started, 2(2.9%) of our patients were 3 years of age, 1(1.4%) was 4 years and 4(6.9%) were 5 years of age. Others were more than 5 years of age at the time of starting steroids. In our patients in group I b, the mean age at starting steroids was 6.69 years. In a study by Merlini et al (2003) on early treatment with Prednisolone in younger DMD patients (range 2.4 to 4 years), there was beneficial effect (delaying the time to loss of ability for rising from the floor).[74] Most of our non treated patients, who lost ambulation, did so before 10 years of age. Of the 7 patients more than 10 years in group I b (treated group), 6 patients continued to walk even after 10 years of age. There are no guidelines for optimal age of starting steroids in DMD patients. [44, 45]The study by Merlini et al and our study show that early use of steroids can be beneficial in DMD.

At entry into study the mean age was 7.88 v/s 9.56, mean cumulative MRC score was 12.93 v/s 13.2 and mean cumulative GSCS was 15.72 v/s 14.69 in group I a (untreated) and group I b (treated) respectively. Stastically there was no significant differences in the mean MRC and GSCS scores but the age to achieve same MRC and GCSC scores was significantly less in treated group than in untreated group ($p = 0.011$) i.e. treated patients tended to have higher grade of GSCS and lower MRC scores for the corresponding age.

There was significant decrease in the frequency of falls after starting treatment.

There was a significant difference in the age to reach stage of inability to walk without support (7.67 v/s 9.60) and wheel chair bound stage (8.63 v/s 11.50) in the two groups, with treated one remaining ambulant for longer time.

6(37.5%) of the 16 patients in group I b were ambulant after 10 years age compared to 2(5%) of the 40 patients in group I a. 7(17.5%) patients in group I a were confined to wheel chair before 10 years of age, where as in group I b all patients below 10 years were ambulant till follow up, with two (12.5%) patients being ambulant with support. In a similar study (De Silva et al, 1987) of Prednisolone in Duchenne muscular dystrophy, mean age at confinement to wheel chair was 9.9(0.3) years in the control group and 12.2(0.5) years in the treated group, 13.1(0.5) years in the group treated for more than 2 years. Of the 20 patients in treated group 4(20%) were confined to wheel chair before 10

years of age compared to 12 of the 22(54.54%) patients in the control group who were confined to wheel chair.[75] In another study (Pradhan et al, 2006), 44 patients were started on 0.75 mg/ kg / day of Prednisolone. 15 patients had follow up for > 2 years. Prednisolone treated patients became wheel chair bound at the mean age of years 14.08(.75) years compared to 11(.67) years in controls (22 patients), with a gain of about 3 years in terms of independent walking. [76] In another study (King et al, 2007, 143 patients, 75 in treatment group), the mean age at loss of ambulation was 9.21(1.48) years in non treated group and 12.52(3.02) years in treated group, with a gain of 3.3years of independent ambulation.[50] Our study results were similar to that in study by De Silva et al and King et al with gain of 3 years of ambulation or differences in the age at confinement to wheel chair. Patients in the other study by Pradhan et al lost ambulation at later date, which could be explained by the upper limit of age at symptom onset of 7 years in this study, compared to 5 years in our study. Some patients with Outlier/BMD phenotypes may have been include in this study.

Over all there was role of steroids in decreasing the progression and prolonging ambulation in DMD patients, as more number of a given age group patients on treatment were ambulant compared to those who had not received therapy. There was difference between performance on functional tests ability and muscle power. An increase in muscle force due to steroids has been reported in earlier studies, which was not seen in our study, but the decline was significantly slower in the treated group. Thus medical therapy and physical

therapy in the form of structured approach individualized for each patient can help prolong ambulation and improve quality of life.

Body weight had increased in our patients on steroids but none qualified as obese. One of the patient required reduction of Prednisolone dosage due to weight gain, but none of the patients required withdrawal of therapy due to weight gain. Weight gain is reported in up to 75-80% of the patients on steroid therapy.[13] In a similar study by Pradhan et al (2005), of the 44 patients initiated on steroid therapy, 14 required withdrawal of therapy due obesity and cushingoid features.[76]

There was decrease in the rate of increase in height after starting steroids. 8(50%) patients were below the 50 the percentile for age matched values at the time of starting steroids. When they were evaluated during study period (when they were on steroids for more than 2 years), 16(100%) patients were below the 50th percentile and out of these 8(50%) were below the 10th percentile for the corresponding age matched values.

One (1.4%) patient had osteoporosis related fracture. Long bone fractures as a result of falls are common, affecting 20.9% of patients (Mc Donald et al, 2002), half of them losing ambulation as a result. [77] Fractures rates were lower in our study and were also not described in the study by Pradhan et al, where as they occurred at higher rates in other studies. These differences may be due to ethnic

differences, differences in the climate and associated exposure to sunlight and calcium/ vitamin D supplementation which was given in both our study and the study by Pradhan et al, along with steroids. Cataracts were not observed in our study groups.

All our patients were told about the possibility of weight gain and decrease in height related to steroid therapy and dietary measures. Calcium supplementation were given to all the patients from the time of initiation of steroids, this may the reason for lower incidence of fractures in our patients. Various studies have reported on the steroid related complications, so appropriate dietary advice, vitamin D and calcium supplementation, prevention of falls, regular assessment for cataracts are important to prevent steroid related complications.

Our patients did not have regular bone densitometry and spinal curvature assessment based on spine x rays. These two were the limitations of our study.

Conclusions

- In our Neuromuscular Clinic, Dystrophinopathies form the commonest of muscle disorders; they constituted about 45% of the primary muscles diseases.

- There is progressive decline in the muscle power and also functional ability. Without therapy patients become wheel chair bound by age of 8 to 9 years. Steroid therapy helps to maintain/ slow the decline and prolong duration of ambulation by another 2 to 3 years.

- Most of our patients had facial weakness and significant axial weakness even in the initial stages, which worsened with disease progression. This progression of axial and facial weakness may indicate late stage of disease with impeding loss of ambulation. Facial weakness and axial weakness has not been hitherto been reported in Dystrophinopathies.

- Quadriceps was involved early in many patients, being as weak as iliopsoas in 56.25% patients and weaker than iliopsoas in 18% patients.

- Changes in muscle force and functional ability progresses at different rates. Functional changes are more helpful to assess disease progression and to evaluate the effects of therapy in ambulant DMD patients.

- Contractures occur as a compensatory measure, initially they help in ambulation, but as weakness progresses, and any further increase in

contractures will hamper ambulation. Ankle contractures below 20 degrees are common in ambulant patients and greater degrees of contractures are seen in nonambulant patients.

- While on therapy there can be steroid related weight gain, stunted growth and osteoporosis which is important as increase in weight can impair ambulation and falls may lead to fractures in weak bones, so weight gain and bone density has to be monitored.

- In our study, there was lower incidence of fractures, may be due racial differences and early supplementation with vitamin D/ calcium with education about fractures/ falls.

- Multidisciplinary approach, through a specialized clinic with members from all concerned specialities, involving early diagnosis, medical and physical therapy, genetic counselling, with supportive care in the late stages improve quality of life in Duchenne Muscular dystrophy patients. Such an approach can address all the aspects of the disease process and provide an individualized care for each patient, according to their requirements.

Structured approach for management of Duchenne muscular dystrophy

DMD is progressive illness with significant morbidity and mortality. There are various phases in the natural history of the illness, which may be different in individuals. Due to the progressive nature and different phases, therapeutic measures need to be structured to benefit each phase of illness and each individual. These measures should address medical, rehabilitative, genetic and psychosocial aspects and terminal care issues related to the illness.

Structured approach involves multidisciplinary management, involving neurologist, physicians from physical and medical rehabilitation and medical genetic department, physiotherapist, occupational therapist and social worker. It should ideally begin from antenatal period or neonatal period and continue as the patient's disease evolves over time.

Early symptomatic stage (usually < 5 years)

During this period, boys have early feature like inability to run and climb stairs, squat and get up, gait abnormalities.

There are few studies on early initiation of steroids in DMD, but considering the biopsy findings of inflammation in early stages, beneficial role of steroids, there appears to be role for steroids in this period, with vigilant

observation for complications related to steroid therapy.

Boys should be initiated on daily strength and flexibility exercises, and stretching exercises. Education about disease course, physical activity, prevention of falls and dietary intake should be given.

Symptomatic phase – intermediate (usually 5 years to 8 years)

During this period, boys show features of muscle weakness, falls and contractures, in addition various compensatory measures like ankle dorsiflexion, increasing lumbar lardosis and widened stance, which help in ambulation and to maintain the base of support under the centre of mass of the body. During this period boys should have steroids, regular physiotherapy, Achilles tendon stretching exercises to prevent severe contraction which may impair balance and ambulation and dietary advice to prevent weight gain. AFO's should not be used for ambulation because fixing the ankle at 90 degrees impairs balance and diminishes the walking ability. When plantar flexion is more than 20 degrees, only then patient may have balance problems, so contractures less than 20 degrees should not be corrected/ treated surgically as it helps maintain knee extension during stance phase. During this period patients should be advised about falls and increased risk of fractures due to steroid therapy related oteopenia. They require calcium supplementation and screening with DEXA annually. If fractures occur, appropriate treatment to be done so that early mobilization is achieved, to prevent loss of ambulation, worsening of weakness and

contractures due to non ambulation. Occupational therapy should be given to help in daily activities with assistance. DMD patients have IQ scores one SD below the normal, with more impairment of verbal memory and expressive language. They may require special education, oriented to cope with these deficits. Behavioral changes related to disease and steroid therapy to be monitored. During this period there is progressive decline in respiratory functions, so patients should be monitored and advised regarding breathing exercises with incentive spirometer.

Symptomatic phase – late (usually 8 years to 12-14 years)

With progression in weakness, compensatory mechanism become less effective, gait becomes more abnormal. With severe quadriceps weakness they cannot walk and once knee flexion contracture develops they cannot stand. Stretching exercises should be continued and orthotics may be used to maintain ability to stand. At this stage, patients should have wheelchair to maintain independent mobility and conserve energy. During this phase scoliosis develops and worsens, so patients should be regularly screened with spine x rays every 6 months from about 10 years of age, wheel chair should have an appropriate pressure distributing seat cushion, and proper head lateral trunk supports. Patients should have cardiac and respiratory evaluation, which should be repeated annually. Steroids and calcium supplements should be continued with dietary advice.

Symptomatic phase – dependant/ terminal (Usually 14 years and above)

During this period spinal deformity (scoliosis) continues to worsen, respiratory and cardiac complications appear. When scoliosis is of sufficient degrees, (usually 20 - 30 degrees) to impair seating and respiration, correction should be done. Early surgery may be helpful as scoliosis in DMD is progressive, with progression paraspinal muscles are replaced by fibro fatty tissue making, surgical dissection difficult, and with increasing age there is decrease in forced vital capacity. (With FVC < 35% patients are at high risk for pulmonary complications). Preoperatively, all patients should have a cardiac and pulmonary function assessment. Release of other contractures to help seating should be considered. Patients should be continued on steroids (as it may help to maintain respiratory functions, respiratory exercises and supportive measures). When they have pulmonary insufficiency assisted ventilation at night with nasal masks with end expiratory pressure (bi-level positive airway pressure) may help. With further worsening they may require continuous ventilator support. Cardiac functions may decompensate and require therapy with ACE inhibitors and Beta blockers. Patients at this stage have difficulties in essentially all activities of daily living skills, including transferring, feeding, and dressing, thus requiring full time assistance.

Psychosocial support is essential at each stage to help cope with the chronic illness.

Assessment of presymptomatic cases

In families with history of DMD, diagnosis can be established early in the antenatal period with fetal muscle biopsy and after birth by screening for serum CPK. In those without family history, diagnosis is usually delayed till patients gross features. DMD boys usually have delayed milestones, abnormal gait and running which if evaluated can help in early diagnosis. This would require education about the early manifestation of the disease among general population and primary care physicians. Genetic counselling to be considered to help parents in planning further pregnancies and screening other siblings and individuals at risk.

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APPENDICES -1

PROFORMA FOR ANALYSIS OF DUCHENNE MUSCULAR DYSTROPHY

Name: Age (yrs): Hospital no:
Age at presentation to hospital: Age at entry into study:
Age at first symptom onset:

First complaint noticed and age:

- Delayed milestones
- Waddling gait
- Toe walking
- Cannot squat and get up without support
- Cannot run
- Cannot climb stairs
- Repeated falls
- Fatigue
- Cramps/pain in legs
- Calf enlargement
- Foot abnormality
- Spinal deformity
- Dyspnoea on exertion
- Sibling of DMD patient
- Learning difficulties
- Others

Milestones: (by years)

- Walking without support
- Running
- Calf enlargement
- Toe walking
- Uses Gower's
- Waddling gait
- Cannot run
- Cannot climb stairs without support
- Repeated falls
- Cannot walk without support
- Cannot stand without support
- Wheel chair/Bed bound
- Dyspnoea at: exertion : rest
- Spinal deformity

Behavioural changes: Hyperactivity / autistic features/others
School performance: Good / average / poor
Family history: Consanguinity/ affected sib's/ affected uncle/ others
Functional scoring: Start 6 months 12 months 18 months

- Squatting/getting up
- Walking
- Getting up from chair

- Climbing stairs
- Falls / day
- ADL's

Contractures: (deg) first visit start 6 months 12 months 18 months

- Ankle
- Knee
- Hip
- Iliotibial band

Hypertrophy: Calf / deltoid / brachioradialis / quadriceps / hamstrings / triceps / glutei

Muscle strength first visit start 6 months 12 months 18 months

- Neck flexors
- Facial muscles
- Bulbar muscles
- Deltoid
- Biceps
- Iliopsoas
- Gluteus maximus
- Knee ext
- Tib anterior

Spinal deformity: Scoliosis / kyphosciolosis

First visit Start 6 months 12 months 18 months

Height (cms)

Weight (kgs)

Sr CPK First visit start 6 months 12 months 18 months

ECG:

- HR R - V1 > 4 mm
- R/S – V1 R/S – V2
- Blocks Arrythmia's
- RVH BVH

ECHO:

- EF LVESV

- LVEDV LVEDD
- Wall motion abnormalities

BIOPSY:

- Myopathic features:
- Fibrosis: endomysial/ perimysial/ both/ absent
- Fibrosis grade: focal/mild/ moderate/ extensive
- Adipose tissue: interfasciular/ intrafascicular/ both/ absent
- Adipose tissue: focal/mild/ moderate/ extensive
- Inflammation: perivascular/ endomysial/ both/ absent/ nodular aggregates/ granulomas
- Inflammation: focal/mild/ moderate/ extensive
- **Dystrophin absent: 1 / 2 / 3 / 1,2 / 1,2,3 / 2,3**
- **Dystrophin weak: 1 / 2 / 3 / 1,2 / 1,2,3 / 2,3**
- Revertant fibres: absent/ occasional/ few/ many
- Sarcoglycan staining: Alpha - present/ absent/ weak Beta - present/ absent/ weak

  Delta - present/ absent/ weak Gamma - present/ absent/ weak
- Merosin staining: present/ absent
- Calpain staining: present/absent/ reduced
- Dysferlin staining: present/ absent/ reduced.

Medications:

- Started at age (yrs)
- Dose
- Complications: Decreased growth / weight gain / fractures / hirusitism.

Overall performance: better/ good / same / worse