REVIEW ARTICLE

Duchenne muscular dystophy: A short review and treatment update

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Haluk TOPALOGLU MD[1]

1.Yeditepe University Department of Pediatrics, İstanbul, Turkey

Corresponding Author
Topaloglu H.MD
Yeditepe University
Department of Pediatrics,
İstanbul, Turkey
Email: htopalog@hacettepe.edu.tr

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Abstract

After advances in clinical care and newer efforts in therapeutic approaches, life span has lengthened in Duchenne muscular dystrophy (DMD). Starting from eary 1980s, each decade lead to a five year gain. DMD is not simply a monogenic X-linked disorder, it is a multisystemic condition. Pulmonary, cardiac, endocrine, gastrointestinal, and bone health aspects need careful monitoring along with pyschology, physiotherapy, social and family as a whole. Molecular treatments are becoming facts, which some are already at hand. Some others are expected to be available within the next two years.

Keywords: Duchenne muscular dystrophy; Clinical care; Newer treatments

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Introduction

Duchenne muscular dystrophy (DMD) is an x–linked recessive genetic disorder that affects 1 in 3600-6000 male live births(9). Girls may be solely carriers or sometimes present with symptoms. DMD is caused by mutations in the dystrophin gene which results in a severe reduction or absence of stability. Lack of functional dystrophin results in degeneration of muscle fibres (1, 2). Becker muscular dystrophy (BMD) is also caused by dystrophin gene mutations. Typically it presents later and progresses more slowly. If a boy with dystrophin deficiency is still able to walk after the 16th birthday, he is considered as a BMD.

Clinical features

The onset is usually after the child has walked, which is later than 18 months in most cases as there is a delay in milestones. Early signs include difficulty with jumping, running, climbing steps and rising from the floor. Typically boys may display toe walking or a waddling gait. On

examination the child may have calf hypertrophy, hypotonia, or may demonstrate Gowers' sign (the boys touches knees while raising from a squatting position and this duration is longer than 2-3 seconds) (3). DMD is also associated with non-motor manifestations. DMD children have a high prevalence of cognitive delay and learning and behavioural problems (4). Rarely austistic features is part of the spectrum. Speech delay and failure to thrive may be present in at least half of boys with DMD. DMD is always associated with high levels of creatine kinase (CK) Increased levels of lactate dehydrogenase (LDH), alanine aminotransferase (ALT) and aspartate aminotransferase (AST). DMD should therefore be considered with unexplained rises in liver function dysfunction, even going as far as performing liver biopsies. In about half of the cases there is a family history denoting X-linked recessive inheritance, and the remaining half are de-novo mutations (3).

Diagnosis

Diagnosis should be made quite early, beacuse delays may lead to several medical and social complications. CK is is simple and inexpensive test which is very sensitive once the symptoms suffice the suspicion of DMD (5). The diagnosis of DMD is confirmed by genetic testing (6). About 70% of DMD is caused single or multi exon deletion or duplication studied by multiplex ligation-dependent probe amplification (MLPA). If MLPA result do not show a visual abnormality, the second step is to sequence the gene in full (6). Female relatives of DMD patients hould be offered genetic testing for carrier status. A small number of female carriers might present with muscle symptoms, such as pain, cramps or weakness, and learning or behavioural problems (7). Female carriers are also at risk of heart problems (8). Cardiovascular monitoring is recommended for all female carriers every 3-5 years (6). Mothers of DMD patients, along with all female carriers of reproductive age, should be offered family planning early with discussion about possible pre-implantation or prenatal genetic testing. In most instances females only carry the abnormal gene with no symptoms due to X-inativation patterns. About 10% of female carriers are prone to develop muscle and cardiac symptoms as they age. Cardiac weakness is usually around age 40 or so. Serum CK is not the ideal test beacuse it may be normal. The gold standard test for carrier detection is the MLPA just like in boys.

Other forms

Dilated cardiomyopathy: These patients usually have minimal or mild muscle weakness, however they develop overt cardiomyopathy by 20-30 years of age. The condition is due to lack of production of dytrophin exclusively in cardiac muscle (9-10).
X-linked myoglubulinuria: This is also a rather mild condition in which patients do not mainfest muscle symptoms but there is myoglobulinuria mainly after exercise. The abnormality is the DMD gene is mostly in the mid-domain regions such as 10-22 (11).

Treatment

Optimal care of DMD is best achieved by a multidisciplinary team. Speech and language therapists also have an important role in the overall clinical care of children with DMD. (3, 12). Cardiac monitoring is essential from diagnosis in view of the risk of dilated cardiomyopathy. Additional specialists, such as respiratory physicians should also be part of the care providing group.
Ambulation has been shown to be prolonged with

early initiation of glucocorticoid therapy (13), a mainstay of DMD treatment. Glucocorticoids (0.75 mg/kg/day of prednisolone or 0.9mg/kg/day of deflazacort on daily or intermittent regimes) improve muscle function over time, delay the development of respiratory complications, and postpone or avoid scoliosis, even cardiomyopathy 3, 6). However, from a pediatrics perspective these recommended dosages are quite high (personal opinion) and can not be maintained on the long run. Glucocorticoid treatment is associated with side effects, including weight gain, cushingoid appearance, behavioural changes, delayed puberty, reduced growth, increased risk of fractures (including vertebral fractures), cataracts and hair growth (13, 14). A lower steroid dose may be required for patients who suffer from unacceptable side effects or do not tolerate the recommended dose. The child will stop to walk eventually and this is not preventable. It is outmost important to maintain muscle function and minimize contractures and deformity once walking is ceased. A team of physiotherapists, orthopaedic surgeons and occupational therapists are integral part of the health providing group.

Primary care in DMD

Primary care is an age dependent approach. Younger children are follwed at routine intervals almost like healthy counterparts, except they deserve yearly cardiac examinations. As the boy grows older such as age beyond 11-12 closer monitoring should become in action. They should be provided appropriate vaccination such as pneumococcal vaccine and yearly influenza vaccines. While on steroids live vaccines should be avoided if possible. A proper nurtition and weight balance is of significant importance. Cardiovascular health and fitness should be encouraged. There is always the risk of adrenal insufficiency if steroids are stopped suddenly and this may create a case of emergency. DMD boys and their families may need psychological support over the follow-up preriods and this is natural (3, 6, 15).

During follow-up

Cardiac: Despite the protective effect of oral steroids, DMD is associated with a primary dilated cardiomyopathy, however this usually faced during later stage of the disease. This can lead to heart failure or arrhythmias. Children may not be symptomatic until very late in disease progression due to immobility. Patients may be investigated by ultrasound echocardiograms, cardiac MRI and 24 hour holter monitoring. Cardiologists may start cardioprotective medications including ACE-inhibitors and beta-blockers (16). The new trend is to initiate these medications early, even before symptoms start in a preventive manner.

Respiratory: DMD patients have an increased risk of respiratory complications. Vaccinations are a pre-requisite. Serial monitoring of lung function and sleep studies can detect deterioration in respiratory function, more likely to occur in the non-ambulant phase. Survival can be prolonged by lung volume recruitment, assisted coughing, nocturnal assisted ventilation, and continuous non-invasive ventilation(17, 18).

Endocrine and metabolic: Long-term steroids increase risk of osteoporosis. DMD patients commonly develop pathological low-trauma vertebral or long bone fractures (19). Bi annual dual energy X-ray absorptiometry (DEXA) scans and spine radiographs or lateral DEXA radiographs is recommended in steroid treated patients to identify asymptomatic vertebral

fractures. Calcium and vitamin D supplementation is a proper means of prophylactic measure. Input from an endocrinologist may also be required to manage glucose intolerance and obesity and the need of intravenous biphosphonate.

Gastrointestinal: Management to prevent obesity with propser diet should be provided. Dysphagia may develop which may be hazardous to speech. Due to chronic corticosteroid treatment, gastroprotective therapy should be given in the presence of symptoms. Gastric motility problems may lead to gastrostomy tube placement for undernutrition, dysphagia and aspiration at a later stage.

Orthopaedic: It is necessary to monitor patients for joint contractures and potential scoliosis. Musculoskeletal problems require a multidisciplinary approach, including physiotherapy, occupational therapy, rehabilitation specialists, orthoses or surgery (20). The number of patients requiring this has diminished since the establishment of steroid therapy.

Innovative therapies

Pharmacological: In this group active studies are to include several growth factors (such as insulin like growth factor-IGF-1) to promote regeneration, myostatin inhibitors to supress myostatin which is a negative muscle regulator, and vamorolone, an innovative steroid are currently being investigated as potential alternatives to corticosteroids aiming to maintain efficacy profile whilst reducing or avoiding the side effects associated with traditional corticosteroids. For this purpose NF-kB inhibitors (e.g edasalonexent) are also in consideration (21). There is another study actively recruting patients with pamrevlumab in order to block the fibrosis in muscle with this monoclonal antibody. For all ongonig clinical trials the reader is advised to visit the site www.clinicaltrials.gov One additional potentially interesting study is the tamoxifen study, currently going on in several countries in Europe. Tamoxifen has anti-fibrotic properties in principal. All these are non-mutation dependent strategies.

Cellular therapy: Several stem cell therapies have been considered since 1980s or even earlier. Myogenic stem cells, mesangioblasts (stem cells within vasculature), and direct myoblast transfer have been tried in DMD boys unfortunately with no success. The main limitation has been efficacy and developing immunological rejection. As it stands stem cell therapy in DMD is considered as 'stem cell tourism'.

Molecular or genetic: We can name these newer generation efforts within the scope of individually based therapies. (22). We now have a working example: Ataluren (also called Translarna), has now been approved by several countries following some regulations as a treatment for DMD with a Management Access Agreement. Ataluren is a mutation specific therapy ("stop codon read through"), affecting approximately 15% of the DMD population. This is an oral molecule taken daily. It is considered as a 'disease modifying molecule', hence should not be considered as a cure (22, 23). Other therapeutic approaches currently tested in clinical trials include: mutation-specific strategies aiming to correct the underlying genetic cause of the disease (e.g. exon skipping) (24-26). Eteplirsen is an antisense-oligonucleotide to skip exon 51 of the DMD gene. It is available on the market, however with reservations related to efficacy. Another potential similarly acting molecule for exon 51 skipping Drisapersen has not been approved at the final stage of the phase III clinical trial (25). Other academically interesting

anti-sense oligonucleotide drugs in the pipeline are Casimersen for exon 45, Golodirsen for exon 53, and Suvodirsen for exon 51 skipping, respectively (22). Among these Viltolarsen has been in the forefront with a backbone publication (ref). In my new institute in İstanbul, currently we have 8 boys recruited on an international basis, a phase III placebo controlled trial (personal experience). Gene therapy can be considered on the horizon. Currently there are four groups engaged in delvering the DMD gene by varying methods. One example is the micro-dystrophin gene delivered in AAV9 virus. Since 2018 four boys aged 4-6 were treated with gene therapy with an admirable improvement rate of 25-30% from the baseline (27). Curently there is a new series of boys with more than 60 subjects and this is ongoing. However, there are multi-fold hurdles with gene therapy to include the timing, dosage, remainings of the viral vector, burden on innate immunity, and availablity on national levels (28).

Scientific community is highly motivated with developments in innovative therapies in DMD just over a few years. Experts in the field possess very optimistic views for these new molecules. At this stage the discussion is not the time of emergence or availability of them. These drugs are wiil be expensive costing up to several million dollars which places governmental bodies and health care providers in a difficult position financially based upon the cumulative cost of several hundred re-imbursements every year causing a true burden on the health economy globally (29, 30)

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Author's Contribution

Dr haluk Topaloglu designed, managed and wrote the manuscript

Conflict of Interest

None

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