DIAGNOSIS AND MANAGEMENT OF DUCHENNE MUSCULAR DYSTROPHY

Part 1: Diagnosis, and neuromuscular, rehabilitation, endocrine, and gastrointestinal and nutritional management

OVERVIEW[1]

Duchenne muscular dystrophy (DMD) is a lethal X-linked recessive neuromuscular disorder caused by mutations in the dystrophin gene, leading to progressive muscular damage and degeneration.

The 'DMD care considerations' were first published in 2010. They have been updated to reflect several important developments, including the improved survival of patients with DMD, evolving diagnostic and therapeutic approaches, an increasing emphasis on quality of life and psychosocial management and experience with existing therapies, and emerging therapies.

Part 1 covers diagnosis, neuromuscular management, rehabilitation management, endocrine management and gastrointestinal management. Endocrine management is a new topic.

The survival of patients with DMD has improved with multidisciplinary care

DIAGNOSIS[1]

Achieving a timely and accurate diagnosis of DMD is a crucial aspect of care. Suggestive signs and symptoms in early childhood include weakness, clumsiness, Gowers' sign, difficulty with stair climbing, and toe walking.

A creatine kinase (CK) test should be carried out in patients with unexplained increases in transaminases, in patients with any abnormal muscle function if there is a family history of DMD, and in all patients not walking by 16–18 months, or displaying Gowers' sign or toe walking.

If serum CK is increased, dystrophin gene deletion and duplication testing is usually the first confirmatory test. If deletion or duplication testing is negative, genetic sequencing should be done to screen for the remaining types of mutations. If genetic testing does not confirm a clinical diagnosis of DMD, muscle biopsy should be performed to test for the presence of dystrophin protein by immunohistochemistry of tissue cryosections or by western blot of a muscle protein extract.

Patients should be referred promptly to a neuromuscular specialist to avoid diagnostic delay.

Genetic counselling should be offered to family members of individuals with DMD, with carrier testing for female relatives.

NEUROMUSCULAR MANAGEMENT

The neuromuscular specialist will serve as the lead clinician, taking overall responsibility for care of the person with DMD. The neuromuscular specialist coordinates each patient's multidisciplinary care, and defines an individualised treatment plan designed to meet the particular needs and goals of each patient and family. The mainstays of DMD treatment are physiotherapy and glucocorticoids.[1]

GLUCOCORTICOID THERAPY

The long-term use of glucocorticoids has been shown to result in:[1]

- Loss of ambulation at later age
- Preserved upper limb and respiratory function
- Avoidance of scoliosis surgery

The 2018 International Care Considerations recommends following an initial consultation with the family, a discussion regarding side effects and a nutritional consultation should occur before any glucocorticoid treatment is initiated.[1]*

EMERGING THERAPIES

Several potential treatments have been tested for DMD over recent years. These include dystrophin restoration therapies that target the specific change in the dystrophin gene that causes DMD. Some of these treatments have received regulatory approval. Other drug classes in clinical trials include drugs targeting myostatin, anti-inflammatory and antioxidant molecules, compounds aiming to reduce fibrosis, compounds aiming to improve mitochondrial function, and compounds aiming to regulate utrophin.[1]

Patients should be counselled on signs, symptoms and management of adrenal crisis, and be educated on administration of intramuscular therapy at home.[1] Glucocorticoids should not be stopped abruptly, but weaned through the PJ Nicholoff Steroid Protocol.[1,2] If side effects are unmanageable or intolerable, the glucocorticoid dose should be reduced.[1]

*Well documented side effects of long-term corticosteroid use can include; weight gain and obesity, acne and warts, cushingoid features, growth retardation and delayed puberty, cataracts, immune/adrenal suppression, glucose intolerance, hypertension, adverse behavioural changes, gastro-oesophageal reflux, peptic ulcer, gastritis, osteoporosis and myoglobinuria.[3]

REHABILITATION MANAGEMENT[1]

Rehabilitation assessment includes measures of passive ranges of motion, muscle extensibility, posture and alignment, strength, function, quality of life, and participation in normal activities for everyday life. Assessment by rehabilitation specialists is recommended every 4–6 months, or more frequently if there are clinical concerns, or the patient's status or needs change.

Direct physical, occupational, and speech and language therapy should be provided in outpatient and school settings and continue throughout adulthood. Daily stretching and orthotic interventions are required for prevention of contracture and deformity. Physical therapists should prescribe, monitor and guide exercise. Pain must be assessed and addressed in individuals at all ages.

The maintenance of passive ranges of movement and muscle extensibility can optimise movement, maintain ambulation and prevent contractures and deformities

ENDOCRINE MANAGEMENT[1]

NEW TOPIC

IMPAIRED GROWTH

Linear growth should be assessed every 6 months until completion of puberty, and height should be plotted on a standardised growth curve. A decline in growth trajectory should prompt referral to an endocrinologist. Routine use of recombinant human growth hormone to treat DMD growth failure is not recommended.

DELAYED PUBERTY

Absence of pubertal development by the age of 14 years should prompt referral to an endocrinologist for hypogonadism investigations. Testosterone replacement therapy is used to treat hypogonadism, where its potential benefits usually outweigh its potential side effects.

ADRENAL INSUFFICIENCY

Prevention of life-threatening suppression of the hypothalamic-pituitary-adrenal (HPA) axis should be prioritised through patient education and appropriate glucocorticoid tapering rather than abrupt discontinuation.

GASTROINTESTINAL AND NUTRITIONAL MANAGEMENT[1]

Individuals with DMD often have gastrointestinal or nutritional complications including weight gain or loss, nutrient imbalance, fluid imbalance, low bone density, dysphagia and mandibular contracture.

At each clinic visit, a registered dietitian nutritionist should assess nutritional status, track weight and height, and create a specific nutritional plan. A physical therapist should be consulted to design appropriate exercise programmes for individuals who are at risk of becoming overweight. A speech-language pathologist should be consulted to assess individuals for suspected dysphagia. A gastroenterologist should be consulted for management of constipation, gastroesophageal reflux and gastrointestinal motility concerns, and when gastrostomy tube placement is needed.

NUTRITIONAL, SWALLOWING AND GASTROINTESTINAL ASSESSMENTS

Every visit

- Assessment by registered dietitian nutritionist
- Monitoring of weight and height; alternative height estimate should be used for non-ambulatory patients

Every 6 months

- Questions about dysphagia, constipation, gastro-oesophageal reflux and gastroparesis

Annually

- Assessment of serum concentrations of 25-hydroxyvitamin D
- Assessment of dietary calcium intake

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References: 1. Birnkrant DJ, *et al. Lancet Neurol.* 2018;17:251–267. 2. Kinnett K, Noritz G. *PLoS Curr.* 2017; 9: DOI: 10.1371/currents.md.d18deef7dac96ed135e0dc8739917b6e. 3. Nascimento Osorio A, *et al. Neurologia.* 2018; DOI: 10.1016/j.nrl.2018.01.001 [Epub ahead of print].