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Myotonic Dystrophy Type 1: A Review of Its Diagnosis and Management

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Abstract

Myotonic Dystrophy Type 1 (MD1) is an autosomal dominant neurological condition. It affects multiple systems and organs leading to physical and at time mental disabilities. Although there is no current definitive cure for MD1, several available therapeutic interventions could be implemented to improve the prognosis and quality of life of patients with MD1. This article will review MD1's etiology, multisystem involvement and its therapeutic modalities.

Keywords: Myotonic Dystrophy Type 1; Muscle Weakness; Multiorgan; Cataract; Genetic Mutation; Treatment

Abbreviations

MD1: Myotonic Dystrophy Type 1; DMPK: Dystrophia Myotonica Protein Kinase; MBNL: Muscle Blind Protein; GI: Gastrointestinal; EMG: Electrodiagnostic Testing; DHEA: Dehydroepiandrosterone; IGF1: Insulin-Like Growth Factor 1.

Introduction

Myotonic dystrophies (DMs) are autosomal dominant myotonic diseases that affect multiple systems. Their clinical presentations include myotonia characterized by the inability of skeletal muscles to relax following voluntary contraction or electrical stimulation and muscular dystrophy manifested by progressive weakness and loss of muscle mass in addition to cardiac, digestive, ocular, and endocrine abnormalities [1,2]. There are two types of myotonic dystrophies; Type 1 (MD1) or the classic type is also known as Steinert disease first described in 1909 and its genetic defects discovered in 1992 [3]. Type 2 (MD2) discovered in 1994, is less common, has a later onset of clinical manifestation, and was formerly known as proximal myotonic myopathy. Despite clinical and genetic similarities, MD1 and MD 2 are distinct disorders requiring different diagnostic evaluation and therapeutic interventions. The congenital form of myotonic dystrophy is only present in MD1 [3]. This article is primarily focused on the diagnosis and therapeutic management of MD1.

Etiology

MD1 is caused by a noncoding CTG repeat expansion within the dystrophia myotonica protein kinase (DMPK) gene RNA-binding proteins such as muscle blind protein (MBNL), which result in dysregulated alternative splicing, mRNA translation impairments, and mRNA instability [4]. When transcribed into CUG/CCUG-containing RNA, mutant transcripts aggregate as nuclear foci that sequester RNA-binding proteins, resulting in spliceopathy of downstream effector genes [5]. Early genetic testing of MD1 is of paramount clinical importance in order to initiate the various supportive measures and therapeutic modalities that could effectively decrease its medical morbidities and its mortality [4]. Although MD1 has no definitive cure its early detection and management

of its multiple systems involvement could improve patients' prognosis and quality of life.

Clinical Presentations

Congenital MD1: Although rare, it is considered the most severe form of MD1, with a prenatal onset, that is distinct from adult onset DM1 [6]. It usually presents with respiratory distress which leads to mortality during the neonatal period [4]. Associated clinical features include weakness due to muscle hypotonia, feet deformities in the form of clubfeet, feeding and gastrointestinal difficulties manifested by constipation, diarrhea and at times fecal incontinence [4,7]. Surviving new born gradually acquire muscle strength, however they continue to experience lifelong mental, behavioral disturbances and learning disabilities [7].

Childhood MD1: Surviving children aged 1 to 10 years, gradually acquire muscle strength, however they continue to experience lifelong mental, behavioral, cognitive disturbances and learning disabilities [7]. Children with MD 1 could exhibit symptoms of autism spectrum disorder, attention deficit hyperactivity disorder, and mood disorders [7,8].

Adult-Onset MD1: Although muscle weakness with hypotonia are among MD1 most prevailing symptoms many patients would develop medical co-morbidities which may include cardiac conduction abnormalities, respiratory muscle weakness, and/or ocular, neuropsychiatric symptoms, gastrointestinal, urogenital, endocrine and dermatological complications[4].

Muscle Weakness

MD1 whole mark presentation is generalized skeletal muscle weakness developing in facial, neck, and distal limb muscles. The skeletal muscle weakness concurrently occurs with muscle wasting and atrophies [9]. All cranial muscles are potentially affected, producing a characteristic appearance of ptosis, wasting of temporalis and masseter, and facial weakness [10]. Ptosis and atrophy of the temporal muscles are one of the MD1 characteristics that are expressed in frontal balding appearance in male patients [11]. With symptoms progression, some patients continue to exhibit a strong distal to proximal gradient, whereas others develop shoulder and hip girdle weakness. Severe weakness of the ankle dorsi- and plantar-flexors often produces a flail ankle with marked instability of stance [11]. A common sign is percussion myotonia in the thenar muscle and, grip myotonia on activation which present with delayed grip release after handshaking or screwing on the cap of a bottle. Repeated use of the muscle can reduce the myotonia and muscle stiffness which is clinically described as 'warm-up' phenomenon [11,12]. The progression of myotonia ultimately leads to immobility, respiratory insufficiency, dysarthria, and dysphagia, which cause severe disability and mortality during the late stages of adult-onset MD1 [13].

Cardiac Manifestations

It is reported that 80% of patients with MD1 would develop cardiac complications including conduction defects, arrhythmias, and could progress to severe bradycardia or asystole due to atrioventricular block, and risk of ventricular tachycardia is also elevated and could lead to severe ventricular systolic dysfunction and tachyarrhythmias [14]. Cardiac arrhythmias are considered a major cause of mortality in MD 1, behooving clinicians to regularly monitoring and promptly treating these cardiac complications [13,15].

Ocular Involvement

Several ocular functions are affected by MD1 [16]. Eyelid ptosis and eye muscle weaknesses can lead to abnormal eye movements such as sluggish and non-conjugated saccades, impaired adduction, divergent strabismus, miosis, and sluggish pupillary reaction [17]. Retinal changes may be asymptomatic and usually have a benign course; however some patients may develop severe visual impairment [18]. Some patients may have low intraocular pressure which may not cause any significant disturbing symptoms [19]. Cataracts have been reported in approximately 90% of MD1 [16]. The cataract has special characteristics and has been called a "Christmas three-catarac" due to its polychromatic, rosette-like cloudiness in the lens appearance [16]. Some patients may develop cataract at an early age without any other symptoms of MD1 [20]. The occurrence of cataracts in patients younger than 50 years is considered a marker to alert clinicians to consider MD1 [10].

Neuropsychiatric Features

MRI brain scans do not usually show any significant atrophy in patients with MD1, but rather a pattern of diffuse white-matter change [21]. Personality changes could also occur in the context of developing avoidance and decreased perception of the severity of the signs and symptoms of the illness resulting into a lack of recognition of daily life difficulties [22]. Cognitive difficulties in the various domain of language, memory, visual attention, processing speed, visuoconstructive abilities and executive functions have been observed with a distinct pattern whereby the executive functions, language, and visual memory showing earlier impairment, while verbal memory, visual attention, and processing speed are manifested later during the course of the disease progression [23]. Sleep difficulties occur throughout the disease course with a tendency toward excessive daytime sleepiness and not necessarily related

to the presence of underlying obstructive sleep apnea [24]. The physical manifestation combined with the emotional stress of coping with the chronicity and disabling effects of MD1 could also contribute to the development of secondary symptoms of depression and anxiety [25].

Respiratory Insufficiency

Significant breathing problems can result from muscle weakness and myotonia of the diaphragm, abdominal and intercostal muscles. Respiratory muscle weakness frequently evolves, leading to respiratory failure [26]. Subsequently lowering oxygen blood saturation and leading an increase blood carbon dioxide levels. Obstructive and central sleep apnea and an impairment of the hypoxic ventilator drive could also occur [27]. Although the causes of the central respiratory drive impairment in MD1 are still unknown it has been hypothesized as the main precipitant of respiratory failure rather than respiratory muscle weakness [28]. Chronic respiratory impairment is the primary cause of mortality and morbidity in DM1.

Gastrointestinal symptoms

Dysfunction along the entire gastrointestinal (GI) tract is common in MD1 [29]. Common problems include dysphagia, abdominal pain and bloating, especially after eating, slow gastric emptying, gastroesophageal reflux, constipation, diarrhea and “irritable bowel” symptoms, gallstones with gallbladder disorders, dilated colon, which could lead to fecal impaction, megacolon and even perforation of the bowel; and anal incontinence [30]. GI symptoms could be the initial and dominant clinical characteristic of MD1and thus should alert clinicians against ignoring or underestimating their potential risk of precipitating aspirations and pneumonia [31].

Genitourinary Complications

MD1can affect the pelvic floor muscles contributing to urinary incontinence [32]. Increased urinary frequency, urgency and stress incontinence occur in many patients with MD1 [33]. The effects on the uterine muscle could lead to obstetric complications and possibly causing premature onset of labor, cesarean section, postpartum hemorrhage, and neonatal deaths [34]. Screening for these disorders is of paramount importance in a clinical setting and the need to explore treatment approaches earlier in the course of the illness to prevent morbidity and mortality.

Endocrine Dysfunctions

MD1may affect the function of many endocrine glands leading to adult primary testicular failure and insulin resistance predisposing to diabetes [35]. Benign and malignant thyroid nodules, hypothyroidism, bone fractures could also be a manifestation of elevated parathyroid hormone and adrenocorticotropic hormone levels [35]. Hypogonadism and infertility could affect males [36], and miscarriages could occur in female patients [37].

Dermatological Features

The most common skin manifestations of MD1 are early frontal balding or alopecia more typical in male than female patients [38]. Pilomatricomas the noncancerous tumors that grow in hair follicles and appear as hard lump on the skin of the head and neck, and epitheliomas which are tumors of the epithelium, the tissues of the skin or mucous membrane that cover the surfaces of organs and other structures of the body could commonly occur in MD1 [39]. There seem to be also an increased likelihood of morphofunctional, proliferative and inflammatory skin lesions [40]. Although MD1 does not appear to be associated with preneoplastic or neoplastic skin lesions there is a possible increased risk of developing malignant epitheliomas as basal cell carcinoma [39] and melanoma [41]. Primary care clinicians need to be aware of the rare and the common cutaneous manifestations of MD1 are frequently missed or misdiagnosed [42].

Diagnosis of Myotonic Dystrophy Type 1

The diagnosis of MD1 can be confirmed from a comprehensive and integrated medical history, family history, physical examination, and genetic studies [4]. To reach an accurate diagnosis clinicians need to pursue the following steps:

- Clinical history: Including symptoms, age of onset, and family history [43].
- Physical examination: To assess muscle weakness, stiffness, and other signs of myotonia [44].
- Supporting laboratory studies: Laboratory tests, and electrodiagnostic testing (EMG) [45]. Muscle biopsies are nonspecific and are not needed for confirming the diagnosis.

Genetic testing is recommended to confirm the diagnosis [4,6].

Treatment

Management Overview: Although there is no current available treatment to alter the course of MD1; management goals could be set to improve functioning, foster autonomy, preserve independence and minimize suffering. It is clinically recommended that patients receive annual visits within the framework of a multidisciplinary treatment team, composed of the primary care clinician, neurologist, physical therapist, speech therapist, pulmonologist, cardiologist, and genetic counselor and if warranted a neuropsychologist, .and a mental health professional [4,44].

Improving the quality of life and fostering physical independence: The following clinical intervention could alleviate and decrease symptoms intensity have been found helpful in some patients with MD1 [4]. Sodium channel blockers such as mexiletine, tricyclic antidepressants such as nortriptyline, and benzodiazepines such as clonazepam or calcium channel antagonists such as amlodipine could reduce sustained myotonia. Prompt and skilled cataract surgery could also minimize the degree of vision impairment. Stimulants such as methylphenidate could also decrease daytime sleepiness. Some patients with MD1 could also develop diabetes and would respond to antidiabetic medications such as metformin and other oral hypoglycemic medications. Patients with respiratory insufficiency who develop sleep apnea could also respond to CPAP machine treatment. The following targeted interventions could also be initiated with a clinical focus on the multi systems manifestation of MD1.

Muscle Weakness

Dehydroepiandrosterone (DHEA): Several studies have shown that MD1 could be associated with low level of circulating DHEA ,however there have been no evidence that replacement therapy with up to pharmacologic doses of (400 mg/day) of DHEA dehydroepiandrosterone improves muscle strength in MD1 [46].

Creatine: Short- and medium-term creatine treatment have been shown in several clinical trials to increases muscle strength to improves functional performance in MD1 [47]. Although creatine was well tolerated in most patients, further assessment of its potential beneficial effects need to be confirmed through the conduction of large double blind randomized trials prior to recommending the routine use of creatin in DM1treatment [48].

Insulin-like growth factor 1 (IGF1): Treatment with Insulin-like growth factor 1 (IGF1) was generally well tolerated in patients with MD1 and was reported to be associated with an increase in the lean body mass but not a noticeable increase in muscle strength or improvement of functioning thus, large randomized controlled trials would be needed to further evaluate the efficacy and safety of (IGF1 in patients with MD1) [49].

Gene Therapy: Interfering RNA and antisense oligo nucleotide compounds designed to silence the mutant DMPK transcripts and other genes modification agents have been recently investigated in clinical trials in patients with adult MD1 and in the foreseeable future could offer a glimpse of hope in reversing the disabling effects of this illness along with its associated multisystem manifestations.

Physical Exercise Training: Strength training or aerobic exercise programs could strengthen the muscles and improve cardiorespiratory functioning. These physical exercises could prevent muscle atrophy in patients who are living a sedentary life due to weakness and fatigue.

Conclusion

Myotonic dystrophy (DM1) is a multisystem disorder with a complex pathology and multiple organ systems involvement. Patients could develop muscle weakness, cardiac involvement, ocular Involvement with early cataracts, neuropsychiatric features, respiratory insufficiency, gastrointestinal symptoms, genitourinary complications, endocrine dysfunctions, and dermatological features. Although at the present, there is still no curative definitive treatment of MD1, the early diagnosis, genetic testing and general management strategies that focus on stabilizing its various medical manifestations with available symptomatic treatment, preventing its complications, and maintaining autonomy and independence, could preserve daily functioning with the hope that on-going research would lead to the discovery of effective treatment to reverse the agonizing suffering of this debilitating illness.

Conflict of Interest

The materials described in this article are those of the authors and do not reflect the views of the Department of Veterans Affairs, the VA Central California Health Care System, the VA Palo Alto Health Care System or the UCSF, Fresno Department of Psychiatry, California.

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