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Myotonic dystrophy type 1 – a multiorgan disorder

CLINICAL REVIEW

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Myotonic dystrophy type 1 is an autosomal dominant, inherited multiorgan disorder that can affect people of all ages. It is the most prevalent inherited muscular disease in adults. Late diagnosis points to limited knowledge among the medical community that symptoms other than typical muscular symptoms can dominate. The condition often worsens with each generation and some families are severely affected. Significantly delayed diagnosis means a risk of more serious development of the disorder and

inadequate symptomatic treatment. We hope that this clinical review article may lead to more rapid diagnosis and better follow-up of this patient group.

Myotonic dystrophy type 1, also known as Steinert disease, was first described in 1909 by Joseph Steinert. The prevalence varies considerably throughout the world, with an average of 9.3/100 000, according to a literature review (1). The prevalence in Norway is not certain, but a prevalence study from Northern Norway reports a rate of 13.4/100 000 (2). The main symptoms are often related to muscle stiffness and impaired relaxation of muscles (due to myotonia) and muscle weakness (due to dystrophy). Myotonia typically improves with activity (warm-up phenomenon). Myotonic dystrophy type 1 is a multiorgan disorder with symptoms and findings that may be more prominent than the muscular symptoms would suggest (Figure 1).

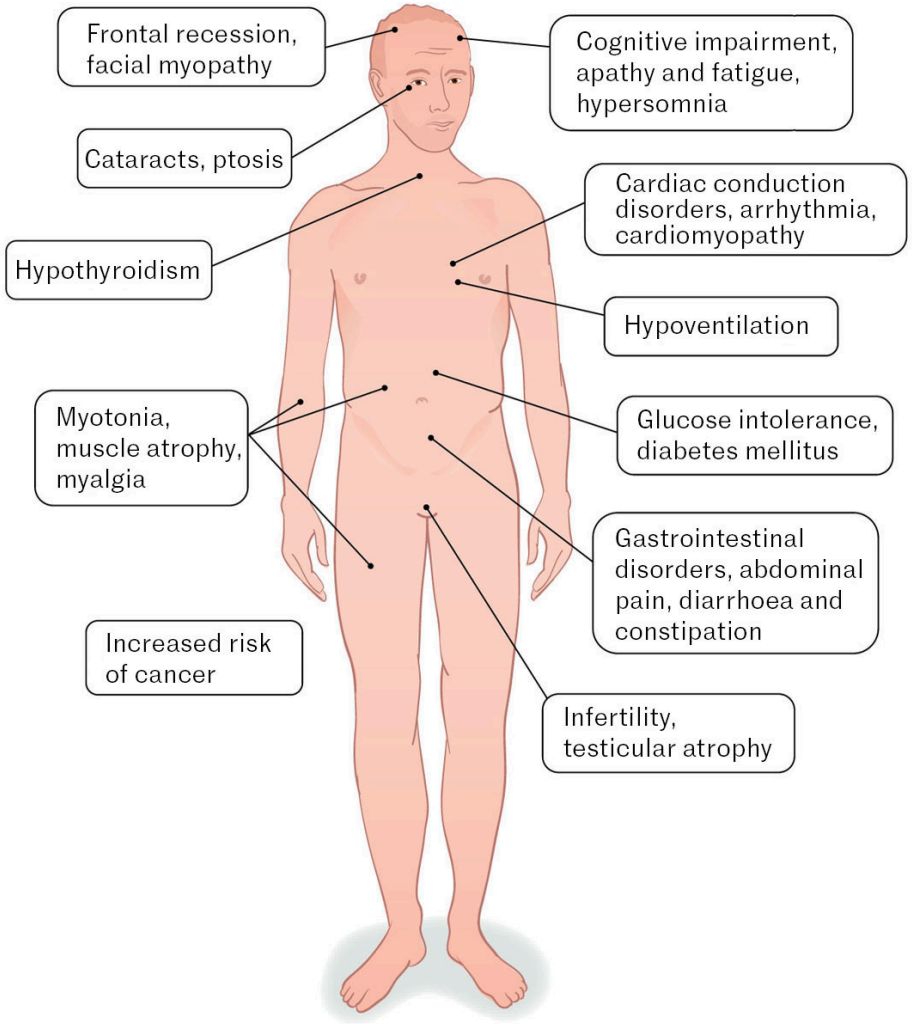

Figure 1 Myotonic dystrophy type 1 is a multiorgan disorder. The figure shows the organ systems that can be affected.

Differential diagnoses include myotonic dystrophy type 2, which is also dominantly inherited, presents with both myotonia and muscular dystrophy, and leads to an increased risk of cataracts and diabetes. However, there is currently no evidence that the condition worsens with each generation.

Symptoms typically start in adulthood, and proximal myopathy dominates. Myotonic dystrophy type 2 is rarer than type 1, with a prevalence of 2.3/100 000 (1). In this article, we focus on myotonic dystrophy type 1. Other important differential diagnoses are myotonia congenita, which presents with myotonia but not myopathy. In adolescents and adults, distal myopathies can also resemble myotonic dystrophy type 1, but these typically do not present with ptosis and facial myopathy as seen in myotonic dystrophy type 1.

This clinical review is based on a purposive sample of international literature, Scandinavian and international recommendations, and the authors' specialised knowledge of the patient group through clinical work, research and personal experiences as family members of a patient with myotonic dystrophy type 1. A review of this type does not cover the entire topic, but there are good international guidelines for diagnosis and follow-up that demonstrate the extent of this disorder (3–5).

Genetics

As described in 1992, myotonic dystrophy type 1 is caused by an unstable expansion of a CTG repeat in the dystrophia myotonica protein kinase (DMPK) gene (6), and is classified as a trinucleotide repeat disorder. Unaffected individuals have 5–37 repeats of the CTG complex. Repeats in the so-called premutation range (38–49 repeats) tend to slowly increase to the pathogenic range (more than 50) over generations. Repeats above 50 and up to more than several thousand are pathogenic. The instability and size of the repeat increases with age, and the number of repeats also typically increases when passed from parent to child, thus resulting in the disease phenotype becoming more severe in successive generations (anticipation) (7).

Subgroups

Myotonic dystrophy type 1 is divided into five subgroups depending on symptom onset (8). *Congenital* onset manifests at birth or during the neonatal period and is usually inherited from the mother. The child is hypotonic and often experiences difficulties with breathing and feeding. Some are born with clubfeet. Genetically, there are normally more than 750 repeats. Some of the children die during the neonatal period. Most others show motor improvement after the neonatal period but often have significant cognitive impairment. The motor difficulties gradually worsen again, as in classic myotonic dystrophy type 1.

Infantile onset presents before the age of ten. The initial symptoms are typically associated with delayed psychomotor development, learning or behavioural difficulties and mild motor symptoms (9). *Juvenile* onset presents between the ages of 10 and 18 years and typically involves social and learning difficulties, motor symptoms, myotonia and the development of muscle weakness (10). *Classic* adult onset presents after the age of 18, typically

involving motor symptoms but can also include abdominal pain, hypersomnia, cardiac symptoms or cataracts (8, 11). *Late* adult onset presents after the age of 40, and these individuals often have cataracts and possibly mild motor symptoms (11).

Diagnosis

Studies have shown considerable delays in the diagnosis of patients with myotonic dystrophy type 1. For patients with symptom onset before the age of 18, a US survey from 2013 revealed an average delay of 13 years between the first symptom and receiving a diagnosis (12).

Myotonic dystrophy type 1 is diagnosed by genetic testing. This test is not included in the gene panels used to diagnose neuromuscular disorders and must be ordered separately. Genetic testing should be considered as part of the investigation of behavioural, attentional and/or significant learning difficulties in children, including for those without other obvious symptoms and signs of myotonic dystrophy type 1. Motor symptoms can be subtle in children and young people with early cognitive impairment associated with the disorder. Adult patients with early bilateral cataracts, muscle stiffness or progressive daytime fatigue and lack of motivation should also be assessed, especially those with a positive family history. Muscle biopsy is not typically part of the diagnostic procedure, but if performed as part of a general investigation for myopathy, it can show characteristic findings. Creatine kinase (CK) levels can be normal or slightly elevated, while electromyography (EMG) can detect myotonia and myopathy even if this is not observed during clinical examination.

Myopathy and myotonia

In myotonic dystrophy type 1, there is typically muscle involvement, with distal atrophy of the extremities and the face, weakness in the hands and forearms, and many patients develop foot drop. Ptosis, reduced facial expression (myopathic facies) and atrophy of the temporal muscle are often observed in the face (8). Reduced facial expression can lead to misinterpretation of facial expressions. Early neck muscle involvement may be observed in adults, and a recent Norwegian study showed that this also applies to abdominal and back muscles in many cases (13). The muscles in the throat and around the mouth often become myopathic, resulting in slurred speech as well as problems with chewing and swallowing. These problems can also have a myotonic component.

Myotonia is otherwise typically observed in the hands in the form of problems releasing a grip or when shaking hands. Testing can entail asking the patient to clench their fist tightly and release it quickly, or thenar muscle percussion. Muscle weakness and poor balance often lead to falls. In neonates with the

congenital variant, hypotonia and delayed motor development are typically observed. Dysarthria and reduced facial expression can be typical features of myotonic dystrophy type 1 in children.

Cardiac and respiratory involvement

Patients with myotonic dystrophy type 1 have a reduced average life expectancy, with one literature review giving the average age of death as the mid-fifties (14). Respiratory dysfunction is considered the primary cause of death, but cardiac involvement also constitutes a significant risk factor for premature death (14). Cardiac involvement is described in up to 80 % of adults with myotonic dystrophy type 1 and can present as various arrhythmias, cardiomyopathy and sudden cardiac death (15). The international recommendation is annual electrocardiography (ECG) as well as Holter monitoring and echocardiography when symptoms occur (16).

Respiration can be affected in several ways (17). Patients may experience classic obstructive sleep apnoea due to weakness of the upper respiratory muscles. They may exhibit a restrictive pattern due to weakness of the diaphragm and accessory muscles, and centrally mediated respiratory involvement has also been described. Patients should be referred to a pulmonologist for assessment, and symptoms of hypoventilation, such as morning headaches and progressive daytime fatigue, should be specifically addressed at an annual check-up. Many patients need assisted ventilation at night. Even after successful treatment of nocturnal hypoventilation, some patients will still experience significant daytime fatigue, which may be centrally mediated.

Caution in relation to surgery and anaesthesia

Critical information about the condition should be entered in the summary care record for all patients with myotonic dystrophy type 1, and respiration and cardiac function should be assessed before surgery. Patients may have myotonia in the tongue/jaw, which can complicate intubation. They also have increased sensitivity to muscle relaxant medications, and depolarising muscle relaxants in particular should be avoided. Inhalation anaesthesia should be used with caution in patients with cardiomyopathy (18). Patients require close monitoring after anaesthesia, and a prolonged awakening time must be expected. Chronic respiratory failure is common in myotonic dystrophy type 1. If oxygen supplementation is needed, the patient must be monitored, and caution must be exercised as this can lead to CO_2 retention. A pulmonologist should be involved. Local anaesthetic and nitrous oxide are safe for minor procedures.

Endocrinology

Adult patients have an increased risk of type 2 diabetes mellitus, hypothyroidism and infertility. Monitoring of HbA1c and thyroid function tests are recommended annually for adults (4) and every three years or upon clinical suspicion for children (3).

Cognitive involvement

The cognitive profile varies from extensive impairment indicative of intellectual disability to few or no symptoms or findings. Impairment can manifest from early childhood but may not present until adulthood. Milder impairment is generally observed in individuals with a late onset phenotype, while those with onset in early childhood experience more severe symptoms. However, patients with a late onset phenotype can sometimes exhibit a relatively rapid decline in certain cognitive functions (4). Patients may have problems with memory, spatial and directional orientation, and concentration. Challenges with executive functions can also be seen, such as planning, abstract thinking, mental flexibility and impulse control (19). This often manifests as a lack of motivation and apathy, and many require considerable help to perform daily activities. Both research and clinical experience indicate that cognitive problems have a major impact on the quality of life of individuals facing such challenges (3).

Milder cognitive outcomes, such as executive function impairment, can also lead to difficulties in functioning in everyday life. There should be a low threshold for performing a neuropsychological investigation. A structured assessment of neuropsychological function and activities of daily living is a useful tool for patients and family members to better understand and manage the difficulties. Many people with myotonic dystrophy type 1 and cognitive problems have poor insight into their illness. This can lead to difficulties for healthcare personnel in obtaining accurate anamnestic information and to a lack of appointment follow-up and adherence to interventions. Regardless of why a patient lacks insight into their condition, it is important to recognise that this is not deliberate on their part. Family members and support services should be actively involved in the ongoing care and support, and it is recommended that patients have someone accompany them to medical appointments.

Other symptoms and findings

Cataracts with an unknown aetiology are a key warning symptom and often the only finding in those with late adult-onset myotonic dystrophy type 1 (4, 8, 20). In a Norwegian study of 50 adult patients, 84 % respondents reported chronic

pain (21). Many struggle with diarrhoea or constipation and abdominal pain, which can lead to pseudo-obstruction and repeated hospitalisation (22). A considerable proportion also experience urinary incontinence (22). Myotonic dystrophy type 1 also increases the risk of cancer, but there are so far no specific screening programmes (23).

Follow-up and treatment

There is no specific medication for myotonic dystrophy type 1, but trials are underway, including gene-modifying therapies such as antisense oligonucleotides (24).

Myotonic dystrophy type 1 is progressive, and regular follow-up in both the primary and specialist healthcare services is therefore crucial. Specific monitoring of the heart and respiratory system as described above is recommended. In cases of significant impairment and onset in childhood, patients should receive follow-up from the habilitation service. Many adult patients can benefit from in-patient rehabilitation. Physical activity and strength training are recommended to prevent deconditioning of unaffected muscles, preferably under the guidance of a physiotherapist familiar with the diagnosis. In cases of cardiac involvement, aerobic exercise should be carried out in consultation with a cardiologist.

Which type of strength training is effective is the subject of ongoing research. Cognitive therapy, in combination with an exercise programme where appropriate, has also been shown to be effective in reducing fatigue in this patient group (25). Affected patients, and parents of paediatric patients, should receive genetic counselling once the diagnosis is confirmed. It is important that the child is offered this again when they reach adulthood. Patients and family members in Norway can be advised to join the Muscular Dystrophy Association (*Foreningen for Muskelsyke*). The association also has a separate youth group.

Myotonic dystrophy type 1 presents challenges for healthy family members of a patient. In many families, the disease only comes to light when a severely affected child is born, but then several family members are often found to have the diagnosis, such as one of the parents of the child. Where the child experiences social challenges at school and a spouse with the diagnosis lacks motivation, experiences fatigue, and has a limited capacity to contribute, it places a particularly heavy burden on the healthy partner in the relationship. The Unit for Congenital and Inherited Neuromuscular Disorders at Oslo University Hospital has produced a handbook for family members of adult patients with myotonic dystrophy type 1 (26). This can be useful both for family members and for patients when dealing with support services.

The article has been peer-reviewed.

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