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Case study

Steinert's disease, from assumption to certainty in neurological practice

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Abstract

Steinert's disease, or myotonic dystrophy type 1 (MD1), is the most prevalent myopathy in adults. We report the case of a patient who was admitted to the Neurology Department for the progressive decrease in muscle strength in the lower limbs bilaterally. Symptoms began about 18 months before the presentation to the Neurology Department. On the electroneurographic examination, specific features for myotonic dystrophy type 1 were described, confirmed later by the genetic test.

Keywords: Steinert's disease, Paraparesis, Multisystemic Disease, Neurology.

1. Introduction

Myotonic dystrophy type 1 (DM1) is a multisystemic, hereditary disease affecting the muscular, central nervous, ocular, respiratory, cardiovascular, digestive, endocrine, and reproductive systems caused the expansion of a CTG triplet in the non-coding region of the DMPK gene, (protein kinase of myotonic dystrophy), located on the long arm of chromosome 19 (19q13.3)(1). Although Steinert's disease is the most common myopathy in adults, the diagnosis may be omitted, which is why the patient must be evaluated by a multidisciplinary team. This case report shows that even if the patient had a systemic clinical manifestation, the initial diagnosis did not include Steinert's disease. That is why practical knowledge about the disease is essential to offer patients the most suitable follow-up and treatment.

Case presentation

A 55-year-old man presented to the Neurology Department for a progressive decrease in muscle strength in the lower limbs bilaterally, preceded by muscle pain in the thighs and legs and subsequent associated with the reduction in distal muscle strength in the upper limbs. Symptoms began about 18 months before the presentation to the Neurology Department. In his medical history, we find atrial flutter ablated on 30.09.2019, appendicectomy, cataract of the right eye operated in 2011, cataract of the left eye operated in 2022. He smoked 15 pack-years, drank one coffee a day, denied consumption of alcohol. We also mention that he worked for 24 years in a toxic environment. There was no family history of malignancy, and his father had a mild form of the disease, manifested only by bilateral cataracts.

The general examination was regular. Neurological examination revealed motor impairment in all limbs. Muscle strength measured on a 5-point scale was 4/5 distal to the upper limbs, 3/5 distal to the lower limbs, and 4/5 proximal to the lower limbs, normo-

tonic with myotonic phenomenon highlighted on the bilateral upper limbs and more accentuated leg atrophies on the right side (Figure 2.) Orthostasis and gait are possible independently, with a stepped gait. Symmetrically diminished osteotendinous reflexes, plantar cutaneous reflex in bilateral flexion. The patient does not have disorders of exteroceptive and proprioceptive sensitivity and has no sphincter disturbances.

The cranial nerves were not affected, but on inspection, a facies characteristic of Steinert's disease with frontal hyperostosis, alopecia, and zygomaticus major muscle atrophies, was highlighted (Figure 1.) Laboratory investigations were modified for the following parameters: low folic acid levels-2,97 ng/ml (5,9-23,2 ng/ml), low vitamin B12-173 pg/ml (180-914 pg/ml), high uric acid-7,98 mg/dl (3,5-7,2 mg/dl), high total cholesterol-247 mg/dl (< 200 mg/dl), low total protein-6,22 g/dl (6,6-8,3 g/dl), high urea-53 mg/dl (17-43 mg/dl), high VEM-99,0 Fl (80-95 Fl) and HEM -32,6 pg (27-32 pg) , thrombocytopenia-128.000/L (150-400000/L). From the point of view of rhabdomyolysis, an increased value of CK creatine kinase-226 U/L (< 171 U/L) has been shown, and the valuea of CK-MB was normal. Renal, liver, and immunological markers were all normal. The patient underwent a lumbar puncture with the extraction of approximately 3 ml CSF, clear, colorless, the biochemical and cytological examination of the CSF without pathological changes.

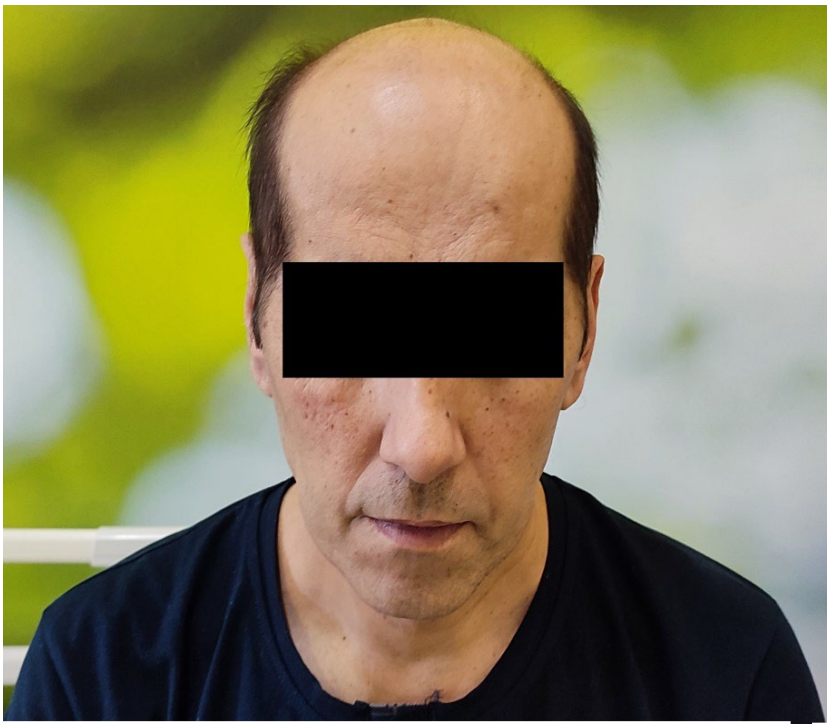

Figure 1. Patient's facies, with changes in Steinert's disease: alopecia, frontal hyperostosis, bilateral zygomaticus major muscle atrophy.

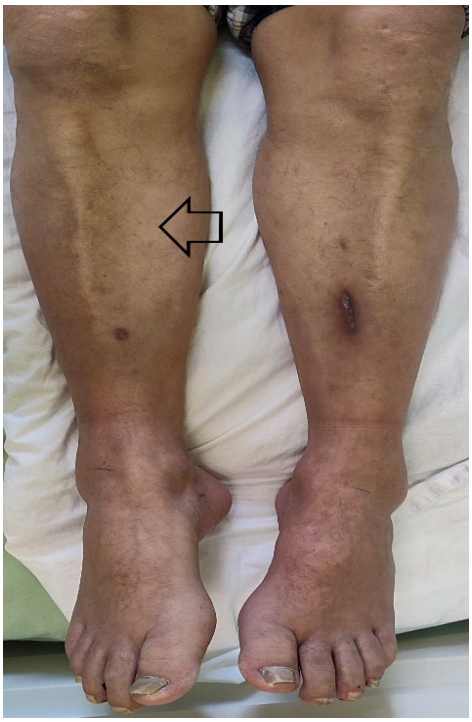

Figure 2. The arrow indicates a more pronounced leg muscle atrophy on the right side.

An electroneuromyographic examination was performed and revealed the following changes: peroneal nerve with amplitude of motor response and normal motor conduction velocities. Tibial nerve with diminished CMAP and diminished VCM. Sensitive response amplitude and typical sensitive driving speeds. EMG in muscles: anterior tibial, vastus lateralis right, and IOD I right. Series of myotonic discharges in all muscles examined, myogenic PUM with diminished duration and normal amplitude. Conclusions: clinical examination and ENMG specific for a type I myotonic dystrophy.

Following the anamnesis, the clinical examination, and the paraclinical investigations, the patient fulfilled the following criteria for diagnosing of myotonic dystrophy type I:1.The clinical examination: normotonic with myotinic phenomenon highlighted on the

bilateral upper limbs and more accentuated leg atrophies on the right side,2.Characteristic facies: alopecia, frontal hyperostosis, and zygomaticus major muscle atrophy,3.Rhabdomyolysis: CK creatine kinase-226U/L(< 171 U/L), 4. Electroneuromyographic examination: Series of myotonic discharges in all muscles examined, myogenic PUM with diminished duration and average amplitude, 5. Multisystemic damage to the body: Right eye cataract operated in 2011, left eye cataract operated on 01.04.2022, atrial flutter ablated on 30.09.2019, testicular atrophy, daytime sleepiness, gingivitis.

Based on these criteria, the diagnosis of type I myotonic dystrophy was made, and the patient was recommended to be genetically tested for the DMPK gene. After discharge, the patient was genetically tested, and the result was as follows: a significant expansion of CTG repetitions (> 80 repetitions) was detected by TP-PCR at the level of one allele. The second allele is normal, containing 5 +/- 1 CTG repetitions. Detection of more than 50 CTG repetitions is considered pathological.

After discharge, the patient performed an X-ray of the lumbar spine, which showed a lumbarization of the first sacral vertebra (L6), narrowing the intervertebral space. On 07.04.2022, the patient presents for genetic consultation for the interpretation of the genetic test performed due to the clinical suspicion of muscular dystrophy, the conclusions being the following: the test detects a significant expansion, of over 80 repetitions, in the DMPK gene, the disease being inherited from the paternal line, the patient's father showing a mild form of the disease. The patient's descendant, aged 25, has a 50% chance of inheriting the variant and, therefore, the disease.

Discussion

Myotonic muscular dystrophies are autosomal dominant disorders characterized by a clinical triad of progressive weakness, myotonia, and early-onset cataracts. The clinical features of myotonic dystrophy were initially described by Steinert in the early 1900s(2). Myotonic dystrophy type 1 (DM1) is inherited in an autosomal dominant pattern, caused by expansion of a cytosine–thymine–guanine (CTG) triplet repeat in the DMPK gene and represents the most common muscular dystrophy in adults with an estimated prevalence in Europe of between 10–18/100,000 (4). The age of onset for DM1 is birth to adulthood. DM1 causes distal weakness in the long finger flexors, facial muscles, and ankle dorsiflexion. Myotonia (delayed muscle relaxation) is a crucial element in the diagnosis of Steinert disease. The disease can cause multisystem manifestations, as presented in table 1. (7)

In muscular dystrophy type 1, there is a significant variation between the number of repetitions of the CTG triplet and the severity of the disease. The number of repeats of the CTG triplet varies from one organism to another, so it is currently considered that there is a weak correlation between the number of repetitions and the severity of the disease (5). The RNA messenger that is formed as a result of the transcription process of the CTG trinucleotide has a certain length depending on the number of repeats of the trinucleotide, and the CTG repeat is more stable in leukocytes than in skeletal muscle therefore the size of the RNA messenger chain and consequently the number of repetitions of the CTG trinucleotide may be smaller in genetic blood tests compared to the size of the messenger chain that is deposited in striated muscles (6). Along with the genetic diagnosis, the question arises as to whether there is a link between the number of repetitions and the severity of the disease. Larger repeat expansions are associated with a more severe course. Individuals with repeat expansions between 50 and 150 are likely to have late onset, also known as oligosymptomatic DM1 (2). Patients who fall into this category frequently develop symptoms after 50 years and have a milder form of the disease. Individuals with repeat lengths between 150 and 1000 are most likely to have adult-onset DM1, defined as symptom onset after age 18 (2). Whereas healthy individuals will have 5 to 30 CTG repeats, patients with myotonic dystrophy have 50 to 2,000 (8). In the case of our patient who has more than 80 repetitions of the CTG triplet, the neuro-muscular

symptoms began after the age of 50, preceded by ophthalmic symptoms: right eye cataract operated in 2011 and cardiological symptoms: atrial flutter ablated in 2019. Recent studies present new elements that can help us diagnose of Steinert disease. In the case of the RNA messenger chain is formed as a result of the transcription process, a very important element is the number of interruptions between CTG triplets. The studies demonstrating that disruption in the CTG repeat may modulate disease severity further hinder the ability to accurately predict the relationship between the repeat and clinical phenotype (6).

Table 1. Multisystem manifestations in Steinert's disease. (7)

Specialty	Disorder
Neurology	Myotonia, Fatigue, Hypersomnia, Cognitive deterioration, Weakness.
Cardiology	Rhythm disorders, Cardiomyopathy.
Pulmonology	Restrictive effect.
Endocrinology	Dysphagia, SAHS, Diabetes mellitus.
Ophthalmology	Cataracts, Eyelid ptosis.
Dermatology	Seborrhoeic dermatitis.
Gastroenterology	Delayed gastric emptying, Constipation, Diarrhoea (bacterial overgrowth syndrome), Cholelithiasis.
Stomatology	Caries, gingivitis.
Anesthesia	Respiratory complications.
Oncology	Increase in the incidence of cancer.

In the case of our patient, it falls into the oligosymptomatic form of DM1, which is a challenge to make a correct and timely diagnosis. Even though his symptoms started about 18 months before his presentation in our service, he received various diagnoses that did not allow the patient to follow a proper treatment plan, the neurological deficit being accentuated during all this time. Among the diagnoses with which the patient presented himself in our service are: acute motor axonal neuropathy and multiple motor neuropathy.

This case highlights the importance of performing electroneuromyographic and electromyographic examinations following a rigorous clinical examination. Also an anamnesis that includes as many details as possible, about the patient's history, is very important. Myotonic disorders can be detected by clinical neurological examination as appropriate: myotonic dystrophy type 2 (proximal myotonic myopathy), myotonia congenita, Schwartz–Jampel syndrome, or only by electroneuromyographic and electromyographic examination as appropriate: acid maltase deficiency.

Steinert's disease is not a single condition but is a systemic disease. In this case, until the presentation in our service, the heart, ophthalmological, dental, bone, and endocrinological damage of the patient was not taken into account. Differential diagnosis is a crucial element in the management of Steinert disease, the primary differential diagnoses in the case of myotonic diseases are presented in Table 2. (9)

From a treatment point of view, Steinert's disease must be treated by a multidisciplinary team. Recent studies make the following recommendations:1.Cardiological management- Annual evaluation, EPS study if PR > 200 ms, QRS > 100 ms or symptoms, cardiomyopathy echocardiogram every 3–5 years, 2. Pulmonary management- annual clinical assessment, annual spirometry, annual flu vaccination, pneumococcal vaccination, polysomnography, 3. Endocrinology control: annual EAT-10 test, dysphagia test, nutritional recommendations, 4. Ophthalmology control: intervene, eyelid ptosis blepharoplasty. (7) In the case of our patient, flutter ablation was performed in 2019, and an anual evaluation was recommended, two cataract surgeries were performed in 2011, and 2022. Endocrinological consultation was recommended to evaluate testicular atrophy, daily glycemic evaluation was established, spirometry and polysomnographic evaluation were advised to select an appropriate treatment for daytime sleepiness. From a neurological point of view, studies suggest: muscular exploration every 2 years, moderate aerobic exercise, Mexiletine 150–200 mg/8 h, and Neuropsychological evaluation (7). Although Mexiletine is recommended as a treatment in guidelines, recent studies have shown that it is less effective. In a randomized, double-blind, placebo-controlled trial, it has been demonstrated that mexiletine had a sustained positive effect on objectively measured hand grip myotonia, no benefit on six-minute walk distance at six months, and no impact on cardiac conduction parameters (10).

In our case, the patient received the recommendation of the annual neurological reassessment, hospitalization in a physical medicine and rehabilitation service and a program was prepared that includes the following types of physical exercises that the patient follows weekly at home: 1.Flexibility/ Stretching/ Range of Motion, 2. Aerobic/ Cardiovascular, 3. Resistive/ Strengthening, 4. Balance Training. For myalgia we recommended a low dose of pregabalin: 50 mg/day.

Table 2. Differential diagnosis of myotonic disorders. (9)

Clinical Myotonia and Electrical Myotonia	1. Myotonic dystrophy type 2 (proximal myotonic myopathy), 2. Myotonia congenita, 3. Schwartz–Jampel syndrome.
Clinical Paramyotonia and Electrical Myotonia	1. Hyperkalemic periodic paralysis 2. Paramyotonia congenita.
Electrical Myotonia without Clinical Myotonia	1. Acid maltase deficiency
Uncommon Causes of Myotonia	1. Myopathy, 2. Denervation, 3. Drug-induced hypothyroidism

From the point of view of prognosis, the younger the age of onset and the higher the number of repetitions of the CTG triplet, the more unfavorable the prognosis. As we mentioned, with new studies in the field of genomics, the hypotheses regarding the prognosis are changing, taking into account further elements such as the number of interruptions between the CTG triplet. That is why it is crucial to diagnose the disease quickly and quickly to provide the patient with quality care in a multidisciplinary team.

Patients whose disease begins after the age of 50 have the best prognosis compared to patients whose disease starts in the second or third decade of life. Up to 50 percent of adults become addicted to wheelchairs during the disease (11). The most common causes of death are pulmonary and cardiovascular complications, which is why Steinert's disease requires rigorous and continuous monitoring of patients.

Conclusions.

In conclusion, myotonic dystrophy type 1 is the most common form of muscular dystrophy. The variety of signs and symptoms shows the complexity of the disease, wich is why it is crucial the diagnosis needs to involve a clinical examination, neurophysiological examination, and finally, genetic examination. Steinert disease is a diagnosis that can be passed over, but the earlier the diagnosis is made, the more likely we are to give patients a chance to be treated and appropriately supervised.

In the case of neurodegenerative pathology, medical recovery is essential. Patients must have regular hospitalizations in the balneology and medical recovery departments, where they can carry out complete recovery programs aimed at keeping the person active as long as possible.

Conflict of interest

There is no conflict of interest for any of the authors regarding this article.

Informed consent

In this article was included an informed consent that was obtained from the patient.

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