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# MIOTONIČNE DISTROFIJE - MIŠIĆNE BOLESTI PO NAZIVU, SISTEMSKE U SUŠTINI

## MYOTONIC DYSTROPHIES - MUSCULAR DISEASES IN NAME, SISTEMIC IN ESSENCE

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## SAŽETAK

Uvod: Miotonične distrofije tipa 1 i 2 (MD1 i MD2) predstavljaju nasljedna, sporo progresivna, multisistemska oboljenja. Pored zahvaćenosti mišića, koja se klinički manifestuje slabošću, hipotrofijom i miotonijom, pogođeni su i brojni drugi organi i organski sistemi. Uprkos velikom napretku u razumijevanju patofizioloških procesa koji su u osnovi ovih oboljenja, još uvijek postoji niz nepoznanica koje otvaraju mogućnosti za dalja istraživanja. Između MD1 i MD2 postoje određene, prvenstveno etiopatogenetske, sličnosti, ali i značajne razlike, koje se najbolje oslikavaju kroz različitu kliničku prezentaciju bolesti (1).

Glavni dio rada: MD1 je najčešći oblik mišićne distrofije kod odraslih, nasljeđuje se autozomno-dominantno, a nastaje zbog ekspanzije trinukleotidnih CTG (citozin-timin-guanin) ponovaka na hromozomskom lokusu 19q13.3 u 3' nekodirajućoj sekvenci (3' untranslated region, 3'UTR) DMPK (engl. dystrophia myotonica protein kinasis) gena (2). Glavni patogenetski mehanizam bolesti predstavlja toksični učinak mutirane ribonukleinske kiseline (RNK) nastale prepisom izmjenjenog DMPK gena (3). MD2 je autozomno-dominantno nasljedna bolest uzrokovana mutacijom u intronu 1 CNBP gena (engl. CCHC-type zinc finger nucleic acid-binding protein). To je bolest ponovaka kao i MD1, ali kod MD2 postoji ekspanzija kvadripleta nukleotida CCTG (citozin-citozin-timin-guanin) u navedenom genu (4,5). Iako su genetički različite, MD1 i MD2 dijele zajedničke patogenetske mehanizme. Smatra se da je osnovni patofiziološki mehanizam u nastanku MD2, slično kao i kod MD1, stvaranje i akumulacija mutirane informacione RNK (iRNK).

MD1 je prava multisistemska bolest koja zahvata mnoge organe i organske sisteme, što je uslovljeno njenom patofiziologijom. Kardinalni znaci bolesti su mišićna slabost, miotonija i rana katarakta. Međutim, ovi pacijenti pate i od srčanih, respiratornih, gastroenteroloških i endokrinoloških poremećaja, a imaju i poremećaje centralnog i perifernog nervnog sistema i kože (6).

MD2 obično ima blažu kliničku sliku u odnosu na MD1, koja je često izrazito varijabilna, kasniji početak i bolju prognozu (7). Najčešće i najizraženije tegobe kod MD2 bolesnika jesu slabost i zamorljivost proksimalne muskulature nogu i bolovi u mišićima. Zbog navedene izražene fenotipske varijabilnosti i velikog broja pacijenata sa blagim tegobama, bolest često ostaje nedijagnostikovana (1). Ako se pacijenti i obrate ljekaru njihove tegobe se često pripišu „zamoru" mišića, „išijasu", drugim radikulopatijama, artritisu, fibromijalgiji ili neželjenim efektima statina (8).

Multisistemska afekcija u MD2 je prisutna, ali obično blažeg stepena u odnosu na MD1. Između MD1 i MD2 bolesnika postoji razlika u učestalosti i profilu metaboličkih i hemodinamskih poremećaja i sa njima povezanih komplikacija. Iako je mišićna slabost kod oboljelih od MD2 manje izražena u odnosu na one sa MD1, a samim tim sedentarni način života vjerovatno manje zastupljen, izgleda da bolesnici sa MD2 češće imaju metaboličke oštećenja (9).

Zaključak: Miotonične distrofije predstavljaju oboljenja koja zahvataju mnoge organske sisteme. Kauzalna terapija miotoničnih distrofija još uvijek ne postoji, te je od suštinske važnosti prevencija i liječenje komplikacija povezanih sa MD, što značajno poboljšava kvalitet života i produžava životni vijek oboljelih (6,10). Ipak, kliničke studije sa primjenom kauzalne, genske, terapije kod MD su u toku. Iz tog razloga neophodno je dobro poznavanje svih multisistemskih poremećaja u ovim bolestima kako bi se efikasno pratili efekti terapije i potencijalni razvoj njenih neželjenih dejstava (9).

Ključne riječi: Miotonične distrofije tipa 1 i 2, etiopatogeneza, klinička slika, multisistemska afekcija, metabolički poremećaji

## ABSTRACT

Introduction: Myotonic dystrophies type 1 and 2 (MD1 and MD2) are inherited, slowly progressive, multisystemic diseases. In addition to muscle involvement, which is clinically manifested by weakness, hypotrophy and myotonia, numerous other organs and organ systems are also affected. Despite great progress in understanding the pathophysiological processes underlying these diseases, there are still a number of unknowns that open up opportunities for further research. Between MD1 and MD2 there are certain, primarily etiopathogenetic, similarities, but also significant differences, which are best illustrated through the different clinical presentation of the disease (1).

Main part of the paper: MD1 is the most common form of muscular dystrophy in adults, inherited in an autosomal dominant manner, and is caused by the expansion of trinucleotide CTG (cytosine-thymine-guanine) repeats at chromosome locus 19q13.3 in the 3' untranslated region (3'UTR) of the DMPK (dystrophia myotonica protein kinase) gene (2). The main pathogenetic mechanism of the disease is the toxic effect of mutated ribonucleic acid (RNA) produced by transcription of the altered DMPK gene (3). MD2 is an autosomal dominant inherited disease caused by a mutation in intron 1 of the CNBP (CCHC-type zinc finger nucleic acid-binding protein) gene. It is a disease of repeats like MD1, but in MD2 there is an expansion of the quadruplet of nucleotides CCTG (cytosine-cytosine-thymine-guanine) in the aforementioned gene (4,5). Although genetically distinct, MD1 and MD2 share common pathogenetic mechanisms. The basic pathophysiological mechanism in the development of MD2, similar to MD1, is thought to be the formation and accumulation of mutated messenger RNA (mRNA).

MD1 is a true multisystem disease that affects many organs and organ systems, which is conditioned by its pathophysiology. The cardinal signs of the disease are muscle weakness, myotonia, and early cataracts. However, these patients also suffer from cardiac, respiratory, gastroenterological, and endocrine disorders, and also have disorders of the central and peripheral nervous systems and skin (6).

MD2 usually has a milder clinical picture compared to MD1, which is often highly variable, a later onset and a better prognosis (7). The most common and most pronounced complains in MD2 patients are weakness and fatigue of the proximal leg muscles and muscle pain. Due to the aforementioned pronounced phenotypic variability and the large number of patients with mild complaints, the disease often remains undiagnosed (1). If patients do seek medical attention, their complaints are often attributed to muscle "fatigue", "sciatica", other radiculopathies, arthritis, fibromyalgia or side effects of statins (8).

Multisystem involvement in MD2 is present, but usually of a milder degree compared to MD1. There is a difference between MD1 and MD2 patients in the frequency and profile of metabolic and hemodynamic disorders and their associated complications. Although muscle weakness is less pronounced in patients with MD2 compared to those with MD1, and therefore a sedentary lifestyle is probably less prevalent, it seems that patients with MD2 have more frequent metabolic impairments (9).

Conclusion: Myotonic dystrophies are diseases that affect many organ systems. Causal therapy for myotonic dystrophies does not yet exist, and prevention and treatment of complications associated with MD are of essential importance, which significantly improves the quality of life and prolongs the life expectancy of patients (6,10). However, clinical studies with the application of causal, gene, therapy in MD are ongoing. For this reason, a good knowledge of all multisystem disorders in these diseases is necessary in order to effectively monitor the effects of therapy and the potential development of its adverse effects (9).

Keywords: Myotonic dystrophies types 1 and 2, etiopathogenesis, clinical picture, multisystem affection, metabolic disorders