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Congenital myasthenic syndromes (CMS) a rare cause of uncommon fatigue

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Abstract:

Introduction and purpose:

Muscle weakness in newborns, infants and young children can be caused by disorders of the neuromuscular junction (NMJ). Congenital myasthenic syndromes (CMS) are a group of rare genetic diseases whose symptoms resemble the clinical picture of autoimmune myasthenia gravis. There are many mutations that can disrupt the neuromuscular transmission leading to pathology. The diagnosis of CMS is based on genetic testing. The aim of this study is to draw clinicians' attention to the symptoms and present current forms of CMS diagnosis and management.

State of knowledge:

An increasing number of genetic changes are associated with CMS pathology. They are divided, depending on the location in the NMJ of the encoded protein, into presynaptic, synaptic and postsynaptic. The most common disorder is the mutation of *CHRNE*, which is responsible for the expression of one of the subunits in the structure of the acetylcholine receptor. Regardless of the type of disease, the characteristic symptom is uncommon fatigue of skeletal muscles. It may present as ptosis of one or both eyelids or gait disturbance. The interview, laboratory tests and EMG are helpful in the diagnosis, but genetic tests play a key role. They can target specific mutations or cover the entire genome comprehensively. Currently used drugs alleviate the course of CMS by increasing the release of acetylcholine or increasing the concentration of acetylcholine in the synaptic cleft.

Conclusion:

Because of its rarity and variability, many CMS patients may be misdiagnosed. It is important to implement extensive genetic diagnostics and early implementation of treatment. There is a need for long-term studies of CMS cases and implementation of therapies targeted at specific mutations.

Keywords:

congenital myasthenic syndromes; myasthenia; neuromuscular disorders; muscle weakness

Introduction and purpose:

Congenital myasthenic syndromes are genetically heterogeneous diseases. At the root of the pathology is a mutation in one of the specific genes. This results in the loss of a protein or the production of an abnormal protein present in the presynaptic, synaptic or postsynaptic part of the neuromuscular junction (NMJ), which impairs the signal transmission from the nerve cells to the muscles. The most common CMS classification is based on the location of the protein from the mutated gene (presynaptic, synaptic, postsynaptic) [1].

CMS is a very rare disease. The prevalence of genetically confirmed CMS in Slovenia is 22.2 per million children under the age of 18 [2]. A similar study in Austria reported 3.1 cases of genetically confirmed CMS per million patients [3].

The severity and course of the disease are highly variable. The prognosis depends on the underlying genetic defect [4]. Regardless of the subtype, the symptoms result from significant muscle weakness [3].

There are effective forms of therapy to improve NMJ transmission, but it happens that patients are underdiagnosed. The aim of this review is to present the symptoms that should prompt us to undertake a genetic diagnosis for CMS and to summarize the current forms of therapy.

Description of the state of knowledge:

Etiology:

Mutations in the genes underlying CMS can be inherited autosomal recessive or dominant. The result of these changes are abnormalities that cause anomalies within the synapse, which is the junction between the neuron and the striated muscle cell [5].

In the presynaptic forms of CMS, the synthesis and recycling of acetylcholine (ACh) or the docking of vesicles and release of the transmitter from the nerve terminal may be impaired. The first group includes the *CHAT*, *SLC5A7* and *SLC18A3* genes [6]. A defect in choline acetyltransferase, encoded by *CHAT*, causes a deficiency in acetylcholine resynthesis after its reuptake in nerve terminals. *CHAT* disruption is the most common presynaptic etiology of CMS (5%). [7]. *SLC5A7* encodes high-affinity choline transporter-1 (CHT), which affects axonal transport. A mutation of this gene is a rare cause of CMS and, interestingly, may be linked to pediatric attention deficit-hyperactivity disorder (ADHD) [8,9]. Vesicular acetylcholine transporter (VAChT), encoded by *SLC18A3* and, like *SLC5A7*, participates in ACh recycling [10]. Impairment of docking, priming, fusion or exocytosis may result from mutations in one of the genes - *SNAP25*, *VAMP1*, *SYB1*, *SYT2*, *UNC13A1*, *PREPL*, however, this is a very rare cause of CMS [11-16].

Synaptic CMS may be associated with acetylcholinesterase (AChE) endplate deficiency or with defects in AChR clustering pathway. AChE is the enzyme responsible for breaking down ACh. It is attached to the basal lamina of the endplate by the collagen-like tail subunit (ColQ) of the asymmetric AChE [17]. It is composed of three subunits an N-terminal proline-rich attachment domain (PRAD), a collagenic central domain, bound to perlecan and a C-terminal domain enriched in charged residues and cysteines bound to muscle-specific tyrosine kinase (MuSK) [18]. Mutations in *COLQ* cause disturbances in the flow of the nerve impulse through different mechanisms [19]. Failure to break down and, as a result, prolonged residence time of ACh in the synaptic cleft may result in desensitization and loss of the ACh receptor (AChR). Another mechanism that interferes with signal transmission in NMJ is the change in interaction with MuSK and perlecan, affecting postsynaptic differentiation [20]. *COLQ*-associated CMS are the most common of the synaptic CMS (10-15%) and until recently were the only subtype in this category [5]. Single cases associated with homozygous mutations in laminin $\alpha 5$ (*LAMA5*) and laminin $\beta 2$ (*LAMB2*) have been described. They play a role in signaling and building the synapse [21,22]. Another gene whose mutation manifests as CMS is *COL13A1*, which encodes collagen type XIII alpha 1 (COL13A1). COL13A1 is a transmembrane protein located in the NMJ where it is responsible for the AChR clustering [23].

The postsynaptic forms are the most common and account for approximately 75–80% of CMS patients [24]. Mutations have been identified in some of the genes encoding the 4 subunits of the AChR (*CHRNA1*, *CHRNB1*, *CHRND* and *CHRNE*) and protein complex (*MuSK*, rapsyn (*RAPSN*), downstream of tyrosine kinase 7 (*Dok-7*), LDL-related protein 4 (*LRP4*)) that affect synthesis and clustering AChR [6]. Disturbances in the genes encoding AChR subunits are the most common cause of CMS (50%), of which abnormalities in *CHRNE* are the most repetitive [25]. Myasthenic symptoms result from reduced expression or kinetic defect of AChR (the slow-channel syndrome or the fast-channel syndrome) [26]. Rapsyn is essential for the development of the junctional folds where it also concentrates and anchors the AChR. Mutations in *RAPSN*, encoding rapsyn, are an important and quite common cause of postsynaptic CMS (15-20%) [27]. Another common cause of CMS is a

disorder in the *Dok-7* gene (10-20%). The disease-causing mutation truncates *DOK7* and leads to the loss of two tyrosine residues that are important for anchoring the AChRs in synapses [28]. Other postsynaptic pathomechanisms are much less common. CMS symptoms may also result from plectin deficiency or defect in skeletal muscle voltage-gated sodium channel [29].

There is also a group of rare mutations causing congenital glycosylation defects (*DAPGT1*, *GFPT1*). It combines the pre- and postsynaptic categories of CMS [29].

Clinical presentation:

The first symptoms of CMS usually appear immediately after birth or in the first years of life, but there are also less common forms with later onset. The clinical picture is the result of weakness of the skeletal, ocular, bulbar and limb muscles [1, 9, 30]. CMS sufferers show variable ptosis of one or both eyelids followed by restricted eye movement [31]. Facial and bulbar muscle weakness may occur with nasal speech and difficulty coughing and swallowing. Spinal deformities are also possible as a result of weakening or even atrophy of the back muscles [1,9]. A characteristic symptom of myopathy for limb-girdle CMS, in addition to eyelid ptosis, is an unusual gait - waddling or walking on the balls of their feet [32]. In its classic form, the disease does not involve the cardiac and smooth muscles. Clinical features such as distribution of weakness, age of onset, symptoms and response to treatment may vary depending on the genetic background. CMS can be very mild or, in more severe forms, lead to disability as a result of progressive weakness [33]. In some cases, conditions such as fever, infection, or overexcitement may cause sudden mild to severe myasthenic symptoms, including an episode of acute respiratory failure [34]. In the neonatal period, CMS is characterized by numerous joint contractures resulting from the lack of movement in fetal life. Weakness involves the palpebral, facial, bulbar or generalized muscles. This may promote crying and poor sucking. Characteristics of neonatal CMS are cyanotic apnea and stridor [35, 36]. Dysmorphic features such as a high-arched palate and a small jaw may also be observed. Motor milestones may be delayed [37].

Diagnosis:

A well-researched family history for CMS symptoms in the past and a review of past medical records, particularly genetic testing, are very important [5].

On examination, cognitive skills, coordination, sensation and tendon reflexes are normal. In laboratory tests, in contrast to autoimmune myasthenia (except for seronegative types), no specific antibodies are distinguished, which may be helpful in differentiation. Creatine kinase levels are mostly normal or slightly elevated [5].

Very often, NMJ abnormalities can be detected in electrophysiological studies by repetitive nerve stimulation or jitter analysis [38]. Single fiber EMG is a sensitive but low-specificity test for CMS. Abnormally increased variability in the time-locked firing of individual action potentials is an early indicator of a defect in neuromuscular conduction [39].

Most muscle biopsies show no abnormalities. The exception is the *GMPPB*-associated CMS, in which features of dystrophy are found. What is special for this type, the concentration of creatine kinase is also elevated [5].

The basis of CMS diagnosis are molecular genetic tests. The method can target specific genes that have been proven to be associated with CMS - a multigene panel, or comprehensive genomic testing such as whole-exome sequencing can be used [5].

Treatment:

The response to treatment depends on the CMS subtype and the underlying pathogenic molecular mechanism. A group of drugs that in one subtype gives good therapeutic effects in another category may cause an increase in symptoms. Therapy should be personalized and targeted. Most often, monotherapy is sufficient, but in some cases, it is necessary to add supportive drugs or use alternative therapy [40]. There is no indication for immunosuppression or immunomodulation, although treatment with prednisone or immunoglobulin may provide therapeutic benefits [41].

The main effect of CMS drugs is to increase the concentration of ACh. Potassium blockers (3,4-diaminopyridine) can be used as an alternative or supportive treatment. 3,4-diaminopyridine increases the release of ACh and prolongs the potential of presynaptic action [34].

The basic therapeutics used in the treatment of CMS are conducive to maintaining a high concentration of ACh in the synaptic cleft. The most commonly used group are AChE inhibitors, mainly pyridostigmine. Continuous monitoring of response to treatment by laboratory tests and observation of muscle weakness and clinical signs is required during therapy. AChE inhibitors are very clearly contraindicated in CMS associated with the *COLQ* mutation, due to the risk of exacerbation of symptoms [42]. Another group of drugs are β 2-adrenergic receptor agonists (ephedrine, salbutamol, albuterol). In addition to increasing the concentration of ACh, they can strengthen and stabilize the structure of NMJ. The use of this group has beneficial effects in the treatment of AChR clustering disorders [43]. In addition, in CMS patients responding to AChE inhibitors, it may mitigate the deleterious effects on endplate fine structure caused by long-term anticholinesterase therapy

[44]. Medications that increase the concentration of ACh by inhibiting open AChR (fluoxetine, quinidine) are mainly used in slow channel mutations [45].

Summary:

CMS is very rare and can often be overlooked by clinicians. The diagnosis is often made difficult by its similarity to autoimmune myasthenia gravis or congenital muscular dystrophy. It is important to consider extending the diagnostics with comprehensive molecular tests and genetic consultation. As many studies show, a growing number of disorders and congenital changes are involved in the pathomechanism of CMS. Early detection of the mutation allows for the efficient implementation of individually tailored therapy and the determination of the initial prognosis. Long-term follow-up in children is rare and urgently needed for counseling patients and their families.

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