Congenital Myasthenic Syndromes

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KEYWORDS

• Congenital myasthenic syndrome • Neuromuscular junction • Safety factor
• Acetylcholine receptor • Acetylcholinesterase

KEY POINTS

- Congenital myathenic syndromes refer to a growing list of rare genetic syndromes with abnormal neuromuscular transmission.
- Mutations within the acetylcholine receptor may result in early closure of the channel, prolonged closure of the channel, or a relative deficiency of the channel.
- Mutation in postsynaptic proteins may affect acetylcholine receptor distribution along the postsynaptic membrane.
- Mutations in the acetylcholinesterase proteins can result in prolonged acetylcholine receptor activation.
- Appropriate treatment depends on the specific genetic syndrome of the individual patient.

INTRODUCTION

The congenital myasthenic syndromes (CMS) constitute a growing list of rare genetic conditions that are characterized by abnormal neuromuscular transmission (reviewed in Ref.[1]). The functionally abnormal protein affects the physiology of neurotransmission that often results in fluctuating or fatiguable weakness. The most common forms of CMS are due to mutations in the genes coding for the different subunits of acetylcholine receptor (AChR); these were the first form of CMS to be described in the literature. Subsequently, other forms of CMS have been identified, including mutations coding for (1) proteins in postsynaptic terminal including AChR subunits and other proteins responsible for AChR development and maintenance (including AChR clustering)

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at the endplate, (2) proteins within the synaptic cleft, and (3) presynaptic terminal proteins. Fig. 1 illustrates this classification scheme. Several of these conditions affect the expression or function of the AChR, and thus the symptoms may be similar to myasthenia gravis. More recently, newer DNA sequencing techniques allow for massively parallel sequencing, resulting in the discovery of newer genetic entities that affect neuromuscular transmission. Some of these conditions affect multiple organ systems and may also affect proteins that span different sites within the neuromuscular junction.

The physiologic basis for most of these syndromes is the reduced response of the postsynaptic terminal to the signal that is entering the presynaptic terminal. The fidelity of this system is typically directly related to the severity of the symptoms the patients experience. In this review, the authors discuss some of the most common forms of CMS.

CLINICAL FEATURES

In most forms of CMS, the symptoms start at birth by definition, but some patients are evaluated later in childhood or early adult life because the symptoms are mild or not recognized. A positive family history is consistent with the diagnosis of CMS, but a negative family history does not exclude autosomal recessive CMS or even dominant inheritance. Most cases of CMS are inherited by an autosomal recessive pattern except one: the classic slow channel syndrome. On examination, the most important clue is increasing weakness on sustained exertion (myasthenic weakness) involving ocular, bulbar, and limb muscles. There are some findings suggestive of specific forms of CMS: scoliosis and delayed pupillary light reflex in acetylcholinesterase collagen tail (ColQ) syndrome, selective severe weakness of cervical muscles and of wrist and

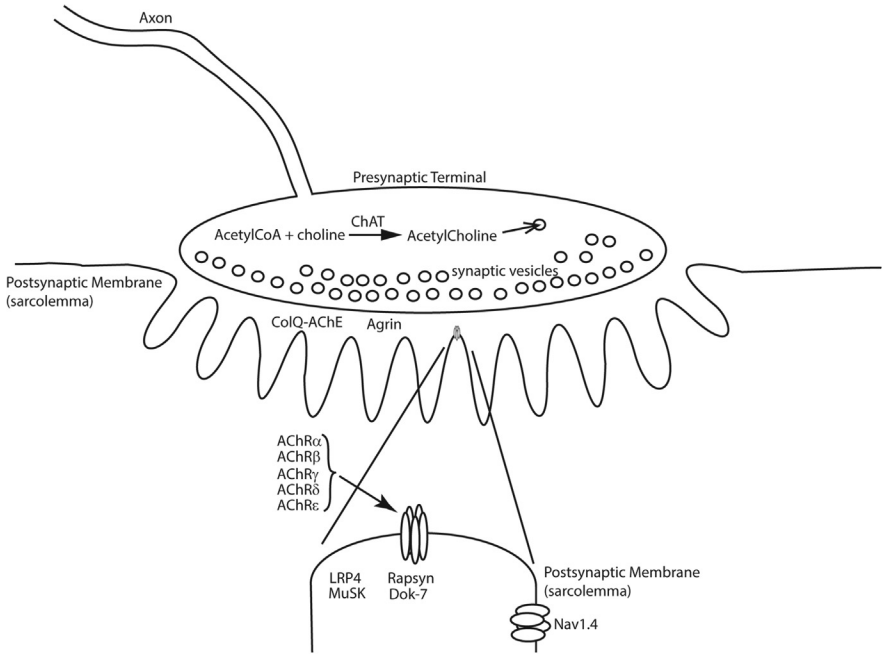

Fig. 1. CMS classified by location of the defective protein.

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