

Lesson 301: PreAnesthetic Assessment of the Patient With Amyotrophic Lateral Sclerosis

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Read this article, reflect on the information presented, then go online and complete the lesson post-test and course evaluation before the termination date below. (CME credit is not valid past this date.) You must achieve a score of 80% or better to earn CME credit.

TIME TO COMPLETE ACTIVITY: 2 hours

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Professional Gaps

Amyotrophic lateral sclerosis is one of the most commonly diagnosed neurodegenerative disorders and is encountered with significant frequency in anesthesia practice. Most anesthesiologists do not know when or which muscle relaxants are safe to use.

Learning Objectives

At the end of this activity, the participant should be able to:

1. Describe the basic pathophysiology of amyotrophic lateral sclerosis (ALS).
2. Identify changes at the neuromuscular junction occurring in ALS.
3. List the issues with depolarizing neuromuscular blockers (NMBs) in ALS.
4. Identify nondepolarizing NMBs that can be used for patients with ALS.
5. Identify hyperkalemic-associated electrocardiographic changes.
6. Outline the treatment strategies of hyperkalemia.
7. List appropriate reversal agents for patients with ALS.
8. Tabulate the respiratory issues in ALS.
9. Present a plan for general anesthesia for a patient with ALS.
10. Anticipate postoperative complications of anesthesia.

Case History

A 65-year-old man with progressive amyotrophic lateral sclerosis (ALS) presented for anesthesia evaluation for laparoscopic placement of a gastrostomy tube. His medical history was consistent with progressive neuromuscular disease, chronic obstructive pulmonary disease, congestive heart failure, hypertension, type 2 diabetes mellitus, and depression. He had significant pharyngeal weakness with extremely limited ability to swallow or clear secretions. Vital signs included a blood pressure of 132/88 mm Hg, pulse of 76 beats per minute with sinus rhythm, temperature 93.3 °F, respiratory rate of 16 breaths per minute, O₂ saturation of 93% on room air, height 175 cm, and weight 73.4 kg. The patient appeared cachectic and was trying to spit out his clear secretions. His mouth opening was extremely limited and 4 rotten teeth remained in the jaw. There were visible tongue fasciculations, and the Mallampati score was assessed as 3. The lungs had decreased air entrance bilaterally. There was significant weakness in all extremities. The patient had a 40-year 1- to 2-pack per day smoking history and was still smoking at the time of evaluation. He reported chronic clear sputum. The patient had multiple episodes of acute bronchitis, the last having cleared 2 weeks prior. He underwent distant open cholecystectomy under general anesthesia, which was reported to be uneventful. Chest x-ray showed flattening of the diaphragm, without significant abnormality. Computed tomographic scan of the chest was consistent with emphysematous changes and a stable pulmonary nodule. Pulmonary function tests dating 6 weeks prior revealed a forced expiratory volume in 1 second (FEV1) of 1.06 L or 58% of predicted, an FEV1/forced vital capacity of 0.78 L or 101% of predicted and forced expiratory flow 25% to 75% of 1.40 L per second or 59% of predicted, maximum voluntary ventilation of 53 L per minute or 57% predicted, and a residual volume/total lung capacity of 65 or 166% of predicted. Medications included lisinopril, aspirin, loratadine, paroxetine, riluzole, tiotropium, fluticasone propionate plus salmeterol, trihexyphenidyl, and metformin. The patient remained in a sitting position as the recumbent position caused significant secretion buildup in the pharynx because of the inability to swallow. General anesthesia was required for the procedure and the issue of neuromuscular relaxation was discussed.

ALS is a rapidly progressive neurodegenerative disease characterized by the degeneration and death of upper and lower motor neurons responsible for controlling voluntary muscles. Evidence suggests that this fatal disease is a proteinopathy secondary to accumulation of various aggregated proteins. It is one of the most common motor neuron diseases, affecting approximately 1.5 to 2.5 per 100,000 persons per year worldwide.¹

ALS most commonly affects adults between the ages of 40 and 60 years. Individuals of all races and ethnic backgrounds are affected, men more often than women. Although ALS is largely sporadic and of unknown etiology, a genetic basis has been linked to approximately 10% of cases (familial ALS).² Discovered in 1993 by Rozen and colleagues, mutation of the enzyme superoxide dismutase 1 is responsible for about 20% of familial cases. Since then, more than 10 genes have been linked to ALS and motor neuron diseases.³

Upper motor neurons (UMNs) originate in the brain (primary motor cortex), whereas lower motor neurons (LMNs) stem from the spinal cord to target muscles. In ALS, both UMNs and LMNs degenerate and cease to communicate properly with muscles. Ocular muscles and sensory neurons are never involved in ALS.

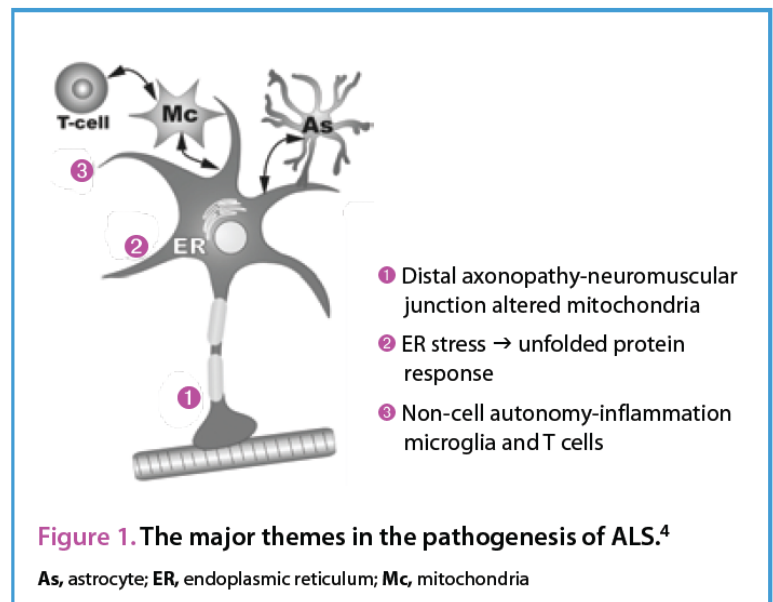
Signs of UMN involvement include motor weakness, spasticity, hyperreflexia, and extensor plantar response (Babinski's sign—or extension of toes to a plantar stimulus). Symptoms of LMN degeneration include muscle weakness, hypotonia, hyporeflexia, and muscle atrophy. Patients have impairments in walking, swallowing (dysphagia), speaking (dysarthria), and eventually breathing. Patients may feel twitches of muscles that can be seen under the skin (fasciculations).

In later stages of the disease, respiratory muscles are affected, necessitating the use of nocturnal ventilatory assistance such as positive airway pressure. Severe dysphagia eventually occurs requiring feeding tube placement. Within 3 to 5 years from the onset of symptoms, patients will usually lose the ability to breathe on their own and will need mechanical ventilation and support for survival. Unfortunately, no significant disease-modifying therapy is currently available.

The pathogenic processes underlying ALS are not fully understood. However, the interaction between non-neuronal cells and motor neurons play a key role in motor neuron degeneration. The current understanding of ALS pathophysiology suggests that the microglia, the innate immune cells of the central nervous system, maintain a balance between neuroprotection and cytotoxicity.⁴

Although motor neuron degeneration is the pathologic hallmark of ALS, a growing body of evidence suggests that the neuromuscular junction (NMJ) and the distal axons are early and important pathologic targets of ALS.⁴ Transgenic mice data suggest that the distal motor axons undergo a process called *dying back*, resulting in impaired synaptic function and axonal connectivity at the NMJ.⁵ Subsequently, faulty axonal transport hinders the clearance of newly synthesized proteins exerting stress on the endoplasmic reticulum and ultimately protein misfolding.

Once proteins are synthesized by amino acid building blocks during translation, they are converted into tightly folded and highly complex structures essential for proper solubility, functioning, and disposal. (Although 20 different amino acids occur in nature, the number of different protein configurations exceeds the number of atoms in the universe.) Molecular chaperones, including heat shock proteins, protect against misfolding and rescue already misfolded proteins. In a complex and apparently obligatory interaction between microglia and the motor neuron, a biochemical shift from survival-promoting to death-promoting signals initiates dying back (Figure 1).⁴



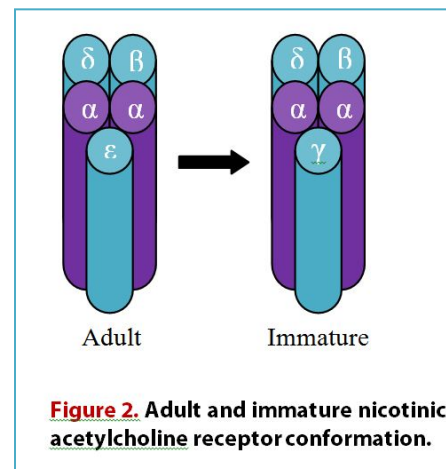
The Neuromuscular Junction

Neuromuscular blockers (NMBs; also called muscle relaxants) are commonly used in anesthesia, emergency medicine, and intensive care to facilitate conditions for tracheal intubation or to provide muscular relaxation for ventilation and surgery.⁶ These agents exert their effects by inhibition at acetylcholine receptors (ACh-Rs); the relaxant effects can be predictably altered by disease states

that interfere with the normal quantitative or qualitative properties of the receptors. States of increased quantity of ACh-R (upregulation) lead to exaggerated responses to depolarizing muscle relaxants (DMRs) and a resistance to nondepolarizing muscle relaxants (NDMRs).

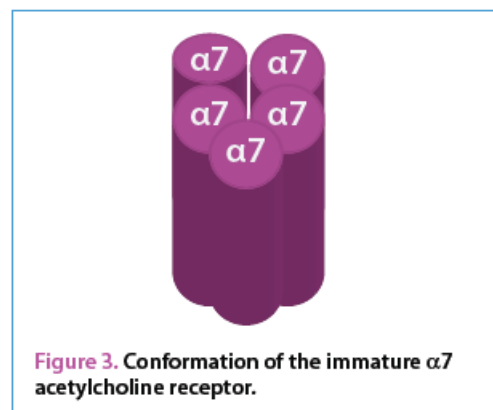
ACh-Rs at the NMJ are classified as nicotinic due to their ability to bind nicotine. Normal adult ACh-R, located on the muscle membrane, are pentameric, transmembrane channel-type receptors consisting of 5 subunits.⁷ The immature fetal ACh-R shares the same pentameric conformation observed with denervation states and has 5 subunits.⁷

In contrast with mature ACh-Rs, which are confined to the motor endplate of the NMJ, immature receptors can be found at aberrant locations throughout the muscle membrane.⁶ Most studies of ACh-R in the NMJ have occurred in burn patients or burn models. Following denervation injury, ACh-R undergoes conformational change from the adult subtype, with an ϵ -subunit to the immature, ACh-R subtype, containing a γ -subunit (Figure 2). The immature channels have a low channel conductance; low-amplitude currents, and a 2- to 10-fold longer mean open-channel time.⁸ Therefore, opening of the immature channels occurs with a far smaller dose of agonist and leads to larger potassium efflux, as the channels are slower to close.



Significantly lower concentrations of agonist drugs or native Ach are required to depolarize immature receptors.⁸ The conformational change most probably imparts the susceptibility to agonists, whereas the extra junctional locations are in part responsible for the increased resistance to the antagonist.

A separate nicotinic $\alpha 7$ ACh-R has been found to appear in times of skeletal muscle development and in denervation states (Figure 3). This homomeric receptor consists only of α receptors arranged in a pentameric configuration. Choline, a precursor to both Ach and succinylcholine, is a full agonist at this $\alpha 7$ ACh-R, and only a partial agonist at the mature $\alpha, \alpha, \beta, \epsilon, \delta$ receptors.⁷



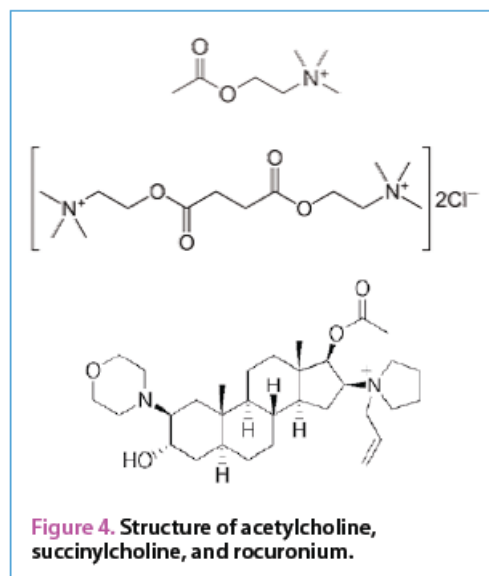
Muscle $\alpha 7$ ACh-Rs have a lower affinity for the NDMR, imparting resistance. In the normal $\alpha, \alpha, \beta, \epsilon, \delta$ receptors, binding of antagonists to either a subunit renders the receptors inactive, as Ach must bind both a receptors. In the $\alpha 7$ ACh-Rs, antagonist binding to fewer than 4 subunits will leave 2 remaining α subunits available. Therefore, even with significant antagonist presence, these receptors can still undergo depolarization—a mechanism suggested for resistance to NDMR.⁷

Succinylcholine, used since 1952, remains the only ACh-R agonist clinically available in the United States.⁹ Succinylcholine is formed by 2 molecules of Ach bonded by an ester linkage (Figure 4). It produces a fast and reliable onset of paralysis for intubation with a short duration of action. The NDMRs have more options classified mainly by duration of action and route of metabolism. They interact with the ACh-R, binding to the α subunit, rendering the channel incapable of participating in muscle contraction. Certain disease states lead to up- or downregulation, increasing and decreasing the number respectively, of ACh-Rs. In addition, prejunctional (neuronal), and postjunctional

(muscle-related) changes can occur simultaneously. Changes at the NMJ in denervation syndromes have been well studied.

The upregulation effect is not limited to ALS. It occurs in a variety of disease states such as disuse atrophy, burn trauma, direct muscle trauma, infection, and chronic use of NDMRs.⁸ Chronic occupation of ACh-Rs by NDMRs promotes upregulation, or increased receptor formation, leading to a larger number of ACh-Rs on the muscle membrane, which in turn imparts resistance. These changes arise following denervation of central or peripheral nerves from stroke or injury, respectively.

In patients experiencing central or one-sided denervation, the contralateral and unaffected side with respect to motor function exhibits a similar pattern of resistance to NDMRs suggesting a mechanism aside from classic receptor-ligand as a factor.⁸ Prolonged immobility is not a denervation state itself but rather lends the muscle to disuse atrophy. The ACh-Rs are stimulated less frequently causing a secondary upregulation. In such cases, increased response to depolarizing drugs and resistance to NDMR drugs may be observed, although patients with ALS may exhibit prolonged responses to NDMR.¹⁰ Prolonged immobility in patients with advancing neuromuscular degeneration can contribute mechanistically to the predictable response to NDMR.



Succinylcholine and Hyperkalemia

After denervation and prolonged immobilization, up-regulation of the ACh-R occurs at the NMJ and along the muscle membrane. Succinylcholine, when administered in such states, can lead to activation of a large quantity of receptors and subsequent depolarization of the entire muscle. This large-scale depolarization leads to massive efflux of potassium from both ACh-R and potassium channels resulting in an unpredictable elevation of serum potassium, often to cardiac arrhythmogenic levels. Generally, serum potassium levels rise after administration of 0.5 mEq/L of succinylcholine.¹¹

In patients with denervation injuries, the rise in serum potassium can be much greater, and more importantly unpredictable, as a larger number of channels are open to potassium flux. Neuromuscular changes can occur early in the disease course. In stroke patients, hyperkalemia can be demonstrated as early as 1 week following injury.¹² Thus, a patient presenting with clinical signs and symptoms of denervation may exhibit an unpredictable hyperkalemic response.

The risk for hyperkalemia in recoverable injuries such as burns and immobility can be reversible; however, the time frame to recovery of a safe margin for administration has not been determined. In patients with chronic and progressive motor neuron disorders, the risk for hyperkalemia after succinylcholine has been demonstrated years following onset of illness.¹³ The use of pretreatment, such as a small dose of NDMR, prior to the use of succinylcholine has not proven effective at abolishing the hyperkalemic response.¹²

Hyperkalemia interferes with the normal cardiac action potential, and can alter or halt the cardiac cycle at extreme levels. Hyperkalemia, whether induced by succinylcholine or other means, has a stereotypical electrocardiographic pattern correlating with serum potassium concentration. Initial influx causes a conduction delay. The first changes observed on electrocardiography (EKG) are increased amplitude of the T waves or *tenting* resulting from accelerated ventricular repolarization and may occur with a potassium level of 5.5 mEq/L.¹⁴

With further increases in serum potassium concentration, atrioventricular transmembrane potentials are reduced, and sodium channels become deactivated. With deactivation of membrane channels, atrial changes on EKG often are apparent, including flattening of the P wave and a lengthening of the PR interval, which typically occurs at potassium levels of approximately 6.5 mEq/L or greater. Eventually, the conduction through the sinoatrial and atrioventricular nodes becomes suppressed, and escape rhythms are generated with widening of the QRS on EKG. As the QRS progressively widens and fuses with the T wave, the classical sinusoidal pattern can be identified. Without treatment, ventricular fibrillation or asystole will occur.

Treatment is aimed at temporizing measures focusing on shifting potassium intracellularly. Calcium chloride (10-20 mg/kg) antagonizes the effect of potassium at the cellular membrane. Sodium bicarbonate (1-2 mEq/kg) will increase the pH and shift potassium intracellularly.¹⁵ Change of pH by 0.1 units will result in a 0.5 to 1.5 mEq change in serum potassium opposite to the direction of the pH. Insulin shifts potassium intracellularly; it requires co-administration of glucose to prevent hypoglycemia. Use of β agonists, such as epinephrine and inhaled albuterol, also promotes intracellular shifting of potassium. These treatments all have unpredictably short-lived effects on serum potassium levels as the intracellular shifting of potassium can reverse, requiring redosing according to the patient's responses. A potassium-binding agent (such as sodium polystyrene sulfonate) works in the intestinal lumen, exchanging 1 mEq of sodium ion for 1 mEq of potassium ion for each gram of agent given. Sodium polystyrene sulfonate has an onset of action of 1 to 2 hours and may be indicated if hemodialysis is to be delayed by more than 2 to 3 hours. Hemodialysis is the definitive and most effective treatment for hyperkalemia.¹⁶

Respiratory Issues in ALS

Respiratory complications are a major cause of morbidity and mortality in patients with ALS. In patients with bulbar ALS, early tongue fasciculation and pharyngeal muscle weakness may lead to an increased risk for aspiration.¹⁰ In classic ALS, muscles of the tongue, pharynx, larynx, and chest become weakened and eventually atrophy. These changes are associated with decreased vital capacity, maximum voluntary ventilation, and expiratory muscle reserve leading to respiratory failure and the need for ventilatory support.¹⁷

Inhalation anesthetics typically depress a multitude of respiratory parameters. In patients with ALS who have a limited pulmonary reserve, the need for postoperative ventilatory support following the use of inhalational agents is greater. In healthy individuals, twitch response is not reduced until more than 70% of the receptors are occupied by NDMRs, imparting a margin of safety. However, in patients with significant neuromuscular degeneration, a 10% ACh-R blockade by NDMRs can lead to significant weakness and respiratory compromise.¹⁸

Extubation criteria in such patients can be difficult to assess as a result of baseline muscle weakness and altered pulmonary physiology. Neuromuscular blockade can further depress already diminished ventilatory muscle action. As a result, the requirement for muscle relaxation should be weighed

against the potential increased likelihood of requiring postoperative ventilatory support. Case reports have identified alternative anesthetic techniques, such as epidural placement and avoidance of muscle relaxants.¹⁹

Reversal Agents

The use of reversal agents in patients with up-regulation should be administered with caution. Cholinesterase inhibitors reversibly bind to acetylcholinesterase, promoting the binding of native ACh to the ACh-R and displacement of the nondepolarizing agents from α sites. With the larger quantity of receptors, the use of reversal agents may lead to a greater than expected depolarization surge at the ACh-R. The effect is unpredictable.

Sugammadex

Unfortunately, no way of monitoring the depth of muscle relaxation has proven ideal. Thus, clinical judgment, and use of twitch monitoring should be applied in these patients. In the future, the newly developed drug, sugammadex, may allow for relatively safe use of the steroidal NDMR in ALS patients, by providing a quick reversal and avoidance of added respiratory weakness. Sugammadex is a selective relaxant-specific binding agent that encapsulates steroidal NDMRs and provides complete antagonism that is immediate and irrespective of the depth of blockade or time since the last dose of NDMR.²⁰ Sugammadex interferes with the binding ability of the NDMR with the ACh-R and allows avoidance of anticholinesterase, which would be ideal for such patients with advanced ALS. The clinical development stemmed from 30 clinical trials in 2,054 patients with excellent results and has led to its widespread use throughout the European Union.²¹ However, due to reports of hypersensitivity/allergic reactions occurring in approximately 1% of patients, the FDA in 2008 denied the request of Schering-Plough, then manufacturer of sugammadex, to market the drug in the United States. With promising safety results from its use in many countries worldwide, it is possible that sugammadex will gain FDA approval in the future. Until sugammadex arrives in the United States, the anesthesia provider must continue to remain cautious and creative in applying muscle relaxation to patients with ALS and other neurologic disorders.

Management of the Case Presented

In this case, induction of general anesthesia was accomplished using propofol, titrated to effect. Placement of an endotracheal tube without muscle relaxation proved impossible due to small mouth opening. Therefore, rocuronium 20 mg was administered to facilitate tracheal intubation without redosing. Train-of-four was checked until 4 of 4 twitches returned and a sustained tetanus could be observed at the orbicularis oculi muscle prior to administration of anticholinesterase agents. Neostigmine 2.5 mg (1 mg/cc) and glycopyrrolate 0.5 mg (0.2 mg/cc) were mixed and given at a rate of 1 cc per minute. Following oral suctioning, deep endotracheal suction was performed. Equipment was prepared and readily available for possible reintubation. The monitored patient was transferred to the postanesthesia care unit with face mask oxygen (6 L), sitting at 60 degrees. He made an uneventful recovery to his baseline and was discharged to the care of his daughter the following day. Subsequently, the patient's health progressively deteriorated; 4 months after discharge he was readmitted to the intensive care unit with pneumonia and underwent tracheostomy. He is now at home under hospice care.

Summary

Although ALS is encountered with significant frequency in anesthesiology practice, anecdotal case reports recommend avoidance of NMBs. However, if skeletal relaxation is necessary, cisatracurium among other NDMRs may prove useful adjuncts. However, it is likely that a greater initial dose of NDMRs will be required due to resistance, although even minimal occupation of ACh-R by NDMRs can result in significant weakness, potentiating the possibility for postoperative respiratory complications. Sugammadex may allow safer use in the future. Unfortunately, no means of monitoring the depth of muscle relaxation has proven ideal. Thus, clinical judgment and use of twitch monitoring should be applied.

Dr. Elizabeth A.M. Frost, who is the editor of this continuing medical education series, is clinical professor of anesthesiology at The Mount Sinai School of Medicine in New York City. She is the author of Clinical Anesthesia in Neurosurgery (Butterworth-Heinemann, Boston) and numerous articles. Dr. Frost is past president of the Anesthesia History Association and former editor of the journal of the New York State Society of Anesthesiologists, Sphere. She is also editor of the book series based on this CME program, Preanesthetic Assessment, Volumes 1 through 3 (Birkhäuser, Boston) and 4 through 6 (McMahon Publishing, New York City).

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Post-test

1. Which of the following statements regarding ALS is false?
 - a. ALS affects approximately 1.5 to 2.5 per 100,000 people worldwide.
 - b. People aged 40 to 60 years are most commonly affected.
 - c. A cause can be identified in about 10% of patients.
 - d. The prevalence of ALS among men and women is equal.
2. Which of the following statements regarding symptoms in ALS patients is false?
 - a. ALS affects upper motor and lower motor neurons.
 - b. ALS can have an effect on sensory neurons.
 - c. Ocular function is well preserved in ALS.
 - d. Ventilation and feeding issues may occur 3 to 5 years from onset.
3. In denervation states, the correct ACh-R conformational change is _____.
 - a. $(\alpha, \alpha, \beta, \epsilon, \delta)$ to $(\alpha, \alpha, \beta, \gamma, \delta)$
 - b. $(\alpha, \alpha, \beta, \epsilon, \delta)$ to $(\alpha, \alpha, \alpha, \gamma, \delta)$
 - c. $(\alpha, \alpha, \beta, \epsilon, \delta)$ to $(\alpha, \beta, \beta, \gamma, \delta)$
 - d. $(\alpha, \alpha, \beta, \epsilon, \delta)$ to $(\alpha, \alpha, \gamma, \gamma, \delta)$
4. With regard to immature ACh-R channels, which of the following is false?
 - a. Immature channels are found only at the neuromuscular junction.
 - b. They have a lower channel conductance compared with adult-type channels.
 - c. They have a 2- to 10-fold longer channel opening time compared with the adult ACh-R.
 - d. Less agonist drug will cause more depolarization in immature ACh-R.
5. Which of the following statements about the $\alpha 7$ ACh-R is false?
 - a. The precursor to Ach and succinylcholine, choline, is a full agonist at the $\alpha 7$ ACh-R.
 - b. The $\alpha 7$ ACh-R has a lower affinity for NDMR.
 - c. The $\alpha 7$ ACh-R is present only during denervation states.
 - d. The additional α subunits impart the resistance to NDMR.

- 6. In patients experiencing denervation (such as after stroke or immobilization), which of the following effects are observed with respect to DMR and NDMR?**
- a. Sensitivity to DMR and resistance to NDMR
 - b. Sensitivity to DMR and NDMR
 - c. Resistance to DMR and NDMR
 - d. Resistance to DMR and sensitivity to NDMR
- 7. Which of the following statements regarding hyperkalemia is false?**
- a. The use of an NDMR at preinduction doses will reliably prevent a hyperkalemic response to Ach.
 - b. Under normal circumstances, the serum potassium may rise 0.5 mEq/L after ACh administration.
 - c. Receptor changes following denervation states may occur only hours following denervation.
 - d. Tenting of T waves can be an early sign of hyperkalemia on EKGs.
- 8. Which of the following statements regarding sugammadex is correct?**
- a. It binds nonselectively to DMR.
 - b. The effect is irrespective of the time since last NDMR dose.
 - c. It does not work on steroidal NDMRs.
 - d. It provides an incomplete antagonism.
- 9. Which of the following treatments/mechanisms for hyperkalemia is incorrect?**
- a. Use calcium chloride for cellular membrane stabilization.
 - b. Use sodium bicarbonate—pH change and intracellular potassium shift.
 - c. Use insulin—potassium binding and excretion.
 - d. Use sodium polystyrene sulfonate—potassium binding and excretion.
- 10. With respect to the respiratory changes in ALS, which of the following choices is false?**
- a. Respiratory complications are the leading cause of death in ALS patients.
 - b. A nerve twitch monitor can be used reliably to assess muscle weakness in ALS patients.
 - c. Patients with bulbar-type ALS have an increased risk for aspiration.
 - d. ALS is associated with weakness of the tongue, pharynx, larynx, and chest wall.