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Infant Botulism Effect of Clostridium and the Involvement of Sudden Infant Death Syndrome (SIDS): Review

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Abstract:

Infant botulism is a rare disease that affects infants under one year of age. The case of this disease has been reported in many countries except Africa. The higher incidents occur in United States up to 90% of the total world's cases. Infant botulism is caused by the absorption of the neurotoxins that produced by genus Clostridium that temporarily colonize the GI tract of the human. Mostly, it is produced by C. botulinum, C. butyricum, and C. baratii. They will lead the flaccid paralysis. Honey, corn syrup, dust and dirt are the most of common vectors that inpact with infant to lead to botulism. This review summarizes etiological agents, habitat and source of Clostridium; pathogenic mechanism; clinical symptom and diagnosis; and prevention and treatment of infant botulism. We also explain about the recent vector of C. botulinum by infant milk formula and the involvement of infant botulism that will link with sudden infant death syndrome (SIDS).

Key words: Clostridium, infant, toxin, sudden infant death syndrome, infant milk formula

Introduction

Clostridium produces the highest number of toxins of any type of bacteria. It represents a heterogeneous group of anaerobic spore-forming bacteria, comprising prominent toxin-producing species, such as *C. difficile*, *C. botulinum*, *C. tetani* and *C.*

perfringens. *C. tetani* and *C. botulinum* produce the most potent biological toxins known to affect humans. One type of those toxins product involves a neuro-paralytic disease in human and animal. It will lead to the disruption of the signaling that allows neurons to communicate effectively. Generally, neurotoxins will achieve this by interrupting ion channels and also inhibit some signaling molecules that lead propagation of the action potential from one neuron to other neuron. In this case toxins will block evoked quantal acetylcholine release from motor ending at peripheral cholinergic synapses, producing a profound but transient muscle flaccid paralyses (Simpson 1986). There are three types of neuroparalytic diseases caused by clostridium, such as: *foodborne botulism* that is induced by ingestion of food containing botulinum toxins; wound botulism that is caused by growth and toxins production in vivo at the site of wound by infection of intravenous drug users; and *infant botulism* that is led by the absorption of the toxins produced by neurotoxigenic clostridia that temporarily colonize the gastrointestinal tract (GI) of human infant under one year of age.

Infant botulism is categorized in USA as a rare disease that was recognized as a distinct clinically entity in 1976. Infant ingest botulinum spore that germinates in the GI and produces toxin in situ. The case of infant botulism has been documented in many countries except Africa. The large number of these cases occur in USA, Canada, Argentina, Italia, Canada and Japan but 90% of the world's cases of infant botulism are diagnosed in the USA, mostly because of physician awareness. More than 250 cases of infant botulism occur in the USA each year, but many go unrecognized. It contributes above 71% of botulism compared with foodborne and wound botulism (Saphiro et al. 1998). California, Utah and Pennsylvania have the highest incidence; nearly 50 percent of all cases are reported in California.

Etiological Agent

Infant botulism is a serious paralytic condition that can lead to human death. It is caused by botulinum toxin that is mostly produced by *C. botulinum*. It is determined as gram-positive, spore-forming, and anaerobic obligate. The vegetative cells are straight to slightly curved motile rods with oval subterminal spore. The seven toxigenic types have been assigned (A through G) and usually serve as convenient clinical and epidemiological marker. Each of the seven serotypes of this bacterium produce a unique form of botulinum toxins. Toxin type of A, B, E, and F are well-established causes of human botulism, while C and D primarily cause illness in animals. Type G has not been fully established as a cause of either human or animal disease. Usually, the case of infant botulism occurs by toxin type A or B and special toxins of type C are found in Japan. Unusual clostridial bacteria such as *Clostridium butyricum* and *C. baratii* have been reported as likely to lead to infant botulism by produced toxins-like E and F. Healthy adults and children over one year of age have a more mature digestive system that prevents the *Clostridium* bacteria from surviving.

Habitat and Source of Clostridium

C. botulinum is ubiquitous in nature (water and soils) as the dust on which it may travel, hence, its spores commonly are present on the surface of fresh fruits, vegetables, and other agricultural products such as honey. In the case of foodborne botulism, mostly *C. botulinum* is present on home canned product especially low acid food product. Almost all food products with a low pH (less than 4.6) can support the growth of *C. botulism* and the subsequent production of toxin. Many canned food that are commonly associated with botulism are fermented meats, smoked fish, luncheon meats, tuna, salad dressing, sausage, corns, garlic oils, ripe olives, asparagus, and

green beans. Spores have also been found in the surface of fruits or vegetables.

In the case of infant botulism, the major source of Clostridium spores are honey (Nevas et al. 2006; Kuplulu et al. 2006), soil contaminant or dust, and many type of syrup (Lilly et al. 1991). The presence of *C. botulinum* spores in honey does not originate from honey bee, but is accidental contaminant that was carried into the hive on dust, water, or pollen from the environment. Honey has high antimicrobial properties and osmotic effect that will prevent germinating and rendering the spore dormant in various length of time. The consumption of honey is typically in the raw material without processing such as heated, pasteurized, sterilized, or irradiated and honey can contain dormant bacterial spores.

Pathogenic Mechanism

Infant botulism occurs when the *C. botulinum* heat-resistant spores are consumed and germinate within the human intestine. The spores will multiple and generate the deadly toxins. The risk of infant botulism comes from consumption of honey or syrup. Usually, it happens in infant less than one year old with undeveloped gut or lacking of microflora in intestines. About 90 percent of infants with botulism are younger than six months (Ferrary and Weisse 1995). Mostly, the infant's intestine is free of bacteria but bacteria start to colonize within the intestine quickly after birth. The lack condition of microflora or undeveloped gut in infant's intestine make newborn unprotected when encountering foreign bacteria such as *C. botulinum*. The spores will germinate, multiple, produce neurotoxins that can block nerve impulse transmissions causing paralysis and, in extreme cases, death. It will activate when it enters in contact with the environment of intestine. The typical of infant botulism is descending flaccid paralysis that may lead to death upon respiratory muscle. It also appears

on cases of wound botulism and foodborne botulism.

The paralysis effect is different from tetanus that is also caused by Clostridium that will lead to spastic paralysis. Flaccid and spastic paralysis are both forms of muscle control loss but their causes and symptoms are highly different. Flaccid paralysis is a weakness or lack of muscle tone which has no obvious causes. Spastic paralysis is a stiffness of the muscles and muscular spasms caused by a specific nervous condition. Although flaccid paralysis has a less deadly effect than spastic paralysis, the exposure of high amount of botulinum toxin will lead to death. Botulinum toxins are absorbed from the GI tract and are carried via the lymph to the bloodstream until neuromuscular terminal. Toxin type of A that is produced by *C. botulinum* has higher affinity for nerve tissue than other type of toxins. Botulinum toxin acts by blocking the releasing of acetylcholine at the neomuscular junction. Firstly, the toxin molecule will irreversibly bind to presynaptic cholinergic receptor of the motor nerve terminal, then all of the toxin molecule or some portion of it will internalize. Finally the toxin interferes with the release of acetylcholine that needed to excite the human muscle. Montecucco and Schiavo (1994) has elucidated the mechanism of blocking the acetylcholine production. The active part of neurotoxin that will enter to the nerve ending has peptidase activity. It is specific for proteins that will form the vesicle structures that contain the neurotransmitter and contributes in exocytosis. It happens when the intracellular vesicle or membrane bound sphere moves to the plasma membrane and subsequent fusion of the vesicular membrane and plasma membrane ensues. The botulinum toxins will disrupt exocytosis and inhibit the release of acetylcholine neurotransmitter that needed to excite muscle.

Clinical Symptoms and Diagnosis

Symptoms of infant botulism appear between 3 to 30 days after

an infant consumes the spores. It may be difficult to recognize it in its early stage. Diagnoses considered for patients whose illnesses were subsequently confirmed as infant botulism include sepsis, pneumonia, failure to thrive, myasthenia gravis, poliomyelitis, brain stem encephalitis, meningitis, hypothyroidism, and disorders of amino acid metabolism. The main clinical features of infant botulism are constipation (mainly), flat facial expression, breathing problem, listlessness, lethargy, difficulty in sucking (poor feeding), trouble swallowing, weak cry, pooled oral secretions, hypotonia, general muscle weakness, and loss of head control. Neurologic findings can include apoptosis, ophthalmoplegia, sluggish pupillary reaction to light, flaccid expression, dysphagia, weak gag reflex, and poor anal sphincter tone.

Recently, electromyogram (EMG) can be performed for an early diagnostic of *C. botulinum* by isolation from the stool. Arnon (2004) found a physical method that is also helpful in the early diagnosis of infant botulism. Firstly, take the infant patient to dark room then give bright light into the eye for finding the initial brisk pupillary constriction may become sluggish and unable to constrict maximally. Also, constrictor muscle fatigability may yield a pseudo gibbus. Secondly, shine a bright light onto fovea for 1-3 minute to find if latent ophthalmoplegia may be elicited or purposeful efforts to avoid the light may diminish, because fatigability with repetitive muscle activity is the clinical hallmark of botulism. The third is place a clean fifth finger in the infant's mouth, taking care not to obstruct the airway to find the suck is weak and poorly sustained. The gag reflex strength also may be quickly checked.

Prevention and Treatment

The spores of *C. botulinum* could be found everywhere because it is ubiquitous in nature. They're in dust and dirt, and even in the air. One method to reduce the risk of botulism is not to give

infants honey or any processed foods containing honey before their first birthday. Honey is a proven source of the bacteria and has led to botulism in infants who have ingested it (Nevas et al. 2006; Kuplulu et al. 2006). The corn syrups was thought to be a source of spores, but no proven cases of infant botulism have been attributed to ingesting them (Lilly et al. 1991).

Infant with botulism should be treated in the hospital with intensive care unit due to the fact that they frequently require airway management, nasogastric tube feeding, and physical and occupational therapy. It can limit the problem of toxin in infant body. The botulinum toxin could affect the breathing muscle so infant needs ventilator. The infant also needs intravenous fluids to provide nourishment because the toxin can affect the swallowing muscles. An antitoxin is now available for the treatment of infant botulism called Botulism Immune Globulin Intravenous (BIG-IV), a human-derived antitoxin. It will neutralize the toxin so it should be given as early in illness as possible. BIG-IV has successfully reduced the time spent in the hospital and the need for mechanical ventilation and tube feeding. Prompt treatment of infant botulism type A or type B with BIG-IV was safe and effective in shortening the length and cost of the hospital stay and the severity of illness (Arnon et al. 2006)

Link to Sudden Infant Death Syndrome (SIDS)

Sudden infant dead syndrome (SIDS) is the sudden death of an infant under one year of age that could not be predicted by medical history and is unexplained by forensic autopsy and detailed death scene investigation. It mostly occurs during infant sleep. Infant botulism was thought to contribute to SIDS by paralysis of the respiratory musculature that leads to rapid hypoxemia and respiratory arrest. It has been proposed that SIDS due to intestinal infection with *Clostridium botulinum* may mimic the clinic-pathological features of sudden infant

death syndrome. Botulism bacteria or toxin were found in up to 20% of case SIDS (Bartram and Singer 2004). A recent 10-year prospective study did not find occult botulism to be a significant factor for SIDS. A link between the fulminant type of infant botulism and sudden infant death syndrome (SIDS) was noted in California because of a similarity between the sudden respiratory arrest of an infant botulism patient and SIDS. In some of the specimens, the toxin types were very unusual, in that type C and type G were detected. In a study conducted in Australia over a 10-year period from 1981 to 1990, both small and large intestine specimens from 248 SIDS cases were cultured specifically for *C. botulinum* (Byard et al. 2008). Although infant botulism was not associated with SIDS in Southern Australia, it can explain a small number of SIDS cases in Europe and North America.

Concluding Comment

The purpose of this article is to present the diversity of vectors that could lead to infant botulism, pathogenic mechanism, and dynamics of clinical symptom, diagnosis development, prevention and treatment therapy after more than 30 year since recognition in 1976. Infant botulism occurs in infant under one year of age that results by the absorption of botulinum toxin produced by genus of clostridium that will colonize the GI tract. Honey, corn syrup, dust and dirt are many types of spore vector of Clostridium for Infant botulism that occurs by accidental contamination. Recently, infant milk formula has been reported as new vector of Costridium. In 2013, Fronterra, the biggest dairy export from New Zealand, found the contamination of *C. botulinum* in that infant milk formula product. It happened by the contamination of a dirty pipe at the processing plant of whey protein concentrate. They also exported the contamination of whey protein concentrate to China, Malaysia, Vietnam, Thailand, and Saudi Arabia

(Anonim 2013). The major aspect of pathogenic mechanism of infant botulism is flaccid paralyze. The clinical symptom of this disease is mainly constipation that will take place 3-30 days after spores exposure. Recently, electromyogram (EMF) of stool and physical method have been reported as early diagnostic methods. Respiratory care in intensive-care setting in hospital is priority to treat infant botulism, and followed by BIG-IV antitoxin. However we can prevent the disease by not giving infants honey or any processed foods containing honey before their 1st birthday. We also suggested to give breastfeeding to infant before first birthday to prohibit contamination of Clostridium from infant formula milk because in that condition the intestine of infant is still undeveloped with lack condition of microflora. It will make infant become unprotected and foreign bacteria encountering the GI tract, easily. Infant botulism also could lead to SIDS by paralysis of the respiratory musculature that leads to rapid hypoxemia and respiratory arrest.

In the near future some of the aspects that could lead to successful control, prevention, and treatment of infant botulism are: effective educational programs to increase physician awareness of the disease; the modern technology usage for development rapid and sensitive laboratory to detect toxin detection or spore; and the ready availability of antitoxin that is distributed in many hospitals, such as BIG-IV.

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