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(REVIEW ARTICLE)

Autoimmune diseases in children and anesthesia

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Abstract

Autoimmune diseases in children may be linked to genetic, environmental, and hormonal factors. It's estimated that 5% of children worldwide have at least one autoimmune condition, with many experiencing multiple autoimmune challenges. Around 80 autoimmune diseases are present. However, autoimmune diseases in children are rare. When they occur they can be challenging to diagnose and difficult to treat. Advances in our knowledge of the immune system are uncovering connections between inflammation and many different diseases. All autoimmune diseases have relapsing and remitting tendencies. Autoimmune diseases can affect almost any part of the body, though they often target connective tissues (skin, muscle and joints). Symptoms can range from fatigue and mild rashes to rare, serious side effects, like seizures. Diagnosis can be difficult, because many symptoms tend to come and go and are frequently nonspecific. They occur in different kinds of autoimmune diseases as well as other types of illnesses, like infection and cancer. Autoimmune diseases occur most often in females by a 3-to-1 margin over males. Organ-specific disorders (also called localized) focus on one organ or a specific type of tissue: Addison's disease affects the adrenal glands; Autoimmune hepatitis affects the liver; Crohn's disease affects the gastrointestinal tract; Multiple sclerosis (MS) affects the central nervous system; Type 1 diabetes affects the pancreas; Ulcerative colitis affects the gastrointestinal tract. Non-organ-specific disorders (also called systemic) cause problems throughout the body: Juvenile dermatomyositis affects the skin and muscles; Juvenile idiopathic arthritis affects the joints and sometimes the skin and lungs; Lupus affects the joints, skin, liver, kidneys, heart, brain, and other organs; Scleroderma affects the skin, joints, intestine, and sometimes the lungs. Pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections (PANDAS) are rare neurobehavioral disorders in children. Affected children may have a diverse array of perioperative manifestations including compulsive behavior, agitation, and abnormal movements. Intravenous anesthetics have anti-inflammatory properties, which in most septic cases are useful for patients. The anti-inflammatory effects of ketamine may be related to the suppression of TNF production by macrophage in the presence of bacteria. Propofol inhibits the phagocytosis and chemotaxis of human monocytes through GABAA receptors. Inhalational anesthetics, in a dose-dependent manner, suppress cytokine release, reduces lymphocyte proliferation, induce apoptosis of the lymphocytes, and inhibits the function of neutrophils. lnhalational anesthetics influence the endocrine response from the hypothalamus-pituitary-adrenal axis and indirectly through the secretions of hormones, such as glucocorticoids and catecholamines. Long-term administration of general anesthesia drugs, due to their effects on cytokines, can lead to disease progression in patients with immune deficiency.

Keywords: Autoimmune diseases; General anesthesia; Children; Immune system; PANDAS; OCD

1. Introduction

The production of antibodies to streptococcal antigens associated with the M-protein of Group A beta hemolytic streptococcus (GABHS) has been shown to cross-react with epitopes on neuronal tissue It has been postulated that the pathogenesis of Sydenham's chorea results from immune complex disease produced by nondestructive anti-streptococcal antibodies that localize to the basal ganglia and striatal areas of the brain. Structural and functional

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neuroimaging studies have demonstrated abnormalities of the basal ganglia structures and their related corticostriato-thalamocortical circuitry in the pathobiology of obsessive compulsive disorder (OCD). The PANDAS subgroup is identified by five clinical criteria: presence of OCD and/or tic disorder; prepubertal symptom onset; episodic course characterized by acute, severe onset and dramatic symptom exacerbations; neurological abnormalities (e.g., choreiform movements) present during symptom exacerbations; temporal relation between GABHS infections and symptom exacerbations. The major distinguishing feature of the PANDAS subgroup is the temporal association between neuropsychiatric symptom exacerbations and GABHS infections. Anesthetic Implications: PANDAS are rare and affected children have significant anesthetic implications. The abnormal behavior and movement of children with PANDAS are real challenge to anesthesiologists. We have described the first case in anesthesia literature of a patient with PANDAS who required anesthesia for a series of therapeutic plasmapheresis. The children usually have motor or vocal tics, obsessions, and/or compulsions. Often communication with them is a major problem. In addition to these symptoms, children may also become moody, irritable or show concerns about separating from parents. In our patient, premedication with oral ketamine and midazolam worked well to separate the patient from his parents and gain an intravenous access. Propofol infusion at usual doses provided optimum sedation during plasmapheresis and the recovery from propofol was favorable. With frequent plasmapheresis, there is a potential for coagulopathy from washout/dilution of plasma clotting factors. Evaluating coagulation status, especially after the first few plasmaphereses may identify patients at risk of bleeding. In conclusion, we described our anesthetic management of a case of PANDAS in a young boy who underwent a series of therapeutic plasmapheresis. Anesthesiologists should be aware of the abnormal behavior and movements with this disorder and potential anesthetic implications. Atopic dermatitis is one of the most common skin disorders in childhood, and general anaesthesia has a risk of developing potential complications in various organs and anaphylaxis and allergies. However, the relationship between exposure to general anaesthesia and atopic dermatitis remains unknown. General anaesthesia (GA) has a risk of developing potential complications in various organs and anaphylaxis and allergies. General anaesthesia could affect various immune responses, including Th1 and Th2 immunity, which might also affect cells that play an important role in the pathogenesis of atopic dermatitis. The number of patients undergoing GA in the paediatric population is increasing and thus interest in whether GA could be a risk factor for various diseases has increased. In particular, previous studies revealed that exposure to GA in early childhood and multiple exposures increased the risk of developmental delay and attention deficit hyperactivity disorder. Conversely, autistic disorders or learning disabilities were not associated with a single exposure to GA. Also, it has been reported that exposure to GA in early life reduced the risk of asthma, allergic rhinitis, and AD. Congential myasthenic syndromes are genetically, mainly recessive, transmitted disorders. This group is clinically very heterogeneous, children present shortly after birth with a feeding problem and muscular hypotonia. As a severe symptom is respiratory insufficiency is well described and children often need artificial ventilation. A few children respond to therapy with acetycholinesterase-blockers. The defect could be located presynaptic (eg. CholinacetylTransferase Defect CHAT), synaptic (eg. mutations in the gene encoding for Collagen Q COLQ) and postsynaptic (eg. disturbances in fast or slow channels in acetylcolinrezeptors or mutations in the gene encoding for the Rapsyn gene). A special feature in CHAT defects are recurrent apnea in children suffering from simple infectious diseases. These children require fast intubation and artificial ventilation. Transient Neonatal Myasthenia gravis occurs in approximately 12% of the newborns of mothers with MG and improves within the first weeks of life as the antibody concentration decreases. The first signs are often muscular hypotonia, feeding problems and respiratory [1-24].

2. Autoimmune diseases

The exact causes of autoimmune conditions in children are not fully understood. Research suggests there may be a complex interplay between environmental factors, genetics, and increased intestinal permeability. A disease is defined as autoimmune if the tissue injury is caused by an adaptive immune response to self-antigen. Development of the disease by transferring the active component of the immune response to an appropriate recipient (usually an animal model, or in some instances materno-fetal transfer of autoantibody) is the best proof that a disease is caused by autoimmunity. Autoimmune diseases can be considered on a continuum between those which are organ specific, and those which are non-organ specific. There are over 100 identified autoimmune conditions. Some commonly known in children include: Type 1 diabetes, the immune system affects the beta cells of the pancreas, impacting insulin production; Celiac disease, the immune system reacts to gliadin, a protein in gluten-containing foods, affecting the small intestine lining; Juvenile idiopathic arthritis, the immune system produces markers that primarily affect the joints; Pediatric lupus, the immune system targets various tissues, including the lungs, skin, and kidneys. Autoantibodies are commonly regarded as being intrinsically involved in the tissue injury associated with autoimmune diseases. Whilst this may be true in a number of important examples (e.g. systemic lupus erythematosus (SLE), Goodpasture's disease, and myasthenia gravis), this is not true of all autoimmune diseases. For example, autoantibodies may form secondary to the tissue damage associated with the underlying disease (e.g. cardiac antibodies produced after myocardial infarction). Corticosteroids, cytotoxic drugs and other immunosuppressant agents are an important part of the therapeutic approach to many non-malignant autoimmune disorders. Thus, treatment protocols for these diseases in pediatrics are often based on adult practice, but

despite the similarities in disease processes, the most widely used treatments have different effects in children. Some of the side effects of chronic steroid use, including linear growth deceleration, bone demineralization, and chronic weight issues, are more consequential in children than in adults. Although steroids remain a cornerstone of therapy in JDM and are useful in many cases of CIDP and JMG, other immunomodulatory therapies with similar efficacy may be used more frequently. Early treatment with intravenous immunoglobulin (IVIG) or plasma exchange (PE) is recommended for any child with Guillain-Barré syndrome who has difficulty ambulating. Azathioprine is the most widely used steroid-sparing therapy in childhood CIDP (Chronic inflammatory demyelinating polyradiculoneuropathy). Patients with juvenile myasthenia gravis (JMG) can be offered three main categories of disease-modifying therapy: acetylcholinesterase inhibitors (AChE-I), medical immunomodulation or immunosuppression, and surgical intervention (thymectomy). Corticosteroids (prednisone, prednisolone, methylprednisolone) are effective immunosuppressants with good evidence for their efficacy in MG. Methotrexate is often used as an alternative immunosuppressant agent in adults with MG who are unable to tolerate azathioprine. Cyclophosphamide therapy has been used for severe, treatment-resistant adult MG. Rituximab has been used with promising results in adults with severe, refractory MG. Plasma exchange (PE) is an alternative to IVIG for treating acute exacerbations. The immune system relies on a large number of genes for its normal development. In children affected by combined immunodeficiency (CID), a defect in one or more of these genes results in the absence or malfunction of a protein necessary for normal functioning of the immune system. Different types of CID are named based on the particular protein or gene that is affected. Some of the better-known types include Wiskott-Aldrich syndrome, DOCK8 deficiency and recombination activating gene (RAG) deficiency. Some live vaccines might need to be avoided, particularly BCG, rotavirus, measles/mumps/rubella (MMR) and chickenpox (VZV). Haematopoietic stem cell transplantation In some cases, haematopoietic stem cell transplant (HSCT) (including bone marrow transplant, BMT) offers the potential for long-term cure of CID. This treatment is most well-established for defined types of CID that are known to be life-limiting because of predictably severe complications. Gene therapy aims to correct the underlying genetic abnormality by replacing the faulty gene in immune cells with a normal copy. The commonest condition affecting thymus development is called 22q11 deletion syndrome (also known as DiGeorge syndrome). In the small fraction (<1%) of DiGeorge patients whose thymus is completely missing, thymic transplant may need to be considered [25-63].

3. Anesthesia - Anesthetic Drugs and immune system

General anesthesia, which is a drug-induced deliberated state, is the most commonly used strategy in anesthesia care. There are various drugs to ensure unconsciousness, analgesia, amnesia, and loss of reflexes of the autonomic nervous system. General anesthesia usually induces using intravenous anesthetics, inhalational (volatile) anesthetics or a combination of both. Also, opioids and benzodiazepines are often used as adjuvants in general anesthesia. In some cases, ventilation of the patients should be controlled. Anesthesia and drugs that administer to induce the anesthesia, affect the immune system, mainly immune cells, during the perioperative period. The effects of anesthesia on B-lymphocytes, T-lymphocytes, NK cells, macrophages, erythrocytes, and leukocytes is well documented. Anesthesia affects the pro-inflammatory and anti-inflammatory cytokines' secretion. The main Pro-inflammatory cytokines include IL-6, Il-8, IL-1, and tumor necrosis factor-a (TNF-α). The main anti-inflammatory cytokine includes IL-10. The levels of interferon Gamma (IFN-γ) and TNF are changed by general anesthesia. Evaluation of the effects of general anesthesia agents on the immune system helps to improve the management of anesthesia. The most common method to produce general anesthesia is the intravenous anesthesia (IV anesthesia). Sodium thiopental, propofol, and ketamine are examples of drugs which commonly use in IV anesthesia. Ketamine and sodium thiopental reduce the number of T-helper cells and NK cell activities and increase the T-inhibiting cells. Sodium thiopental and ketamine inhibit the release of IL-1, IL-6, TNF-α, and IL-8. It is well-documented that low dose ketamine, as an N methyl-D-aspartate (NMDA) receptors antagonist, reduces the lifetime of IL-6. In addition, these drugs increase the level of IL-10. However, according to the results reported by Song et al., ketamine inhibits the production of anti-inflammatory cytokines. Sodium thiopental is a rapid induction intravenous anesthetic agent which affects the GABA- A receptors that their presence in immune cells is confirmed. In a study, the effect of propofol and sodium thiopental on Th1/Th2 balance is compared by measuring the levels of IFN-γ, IL-4, and IL-2. Compared to propofol, sodium thiopental reduce the concentration of IFN-γ and IL-4 without affecting the concentration of IL-2. Propofol (2,6-diisopropylphenol) is a commonly used intravenous anesthetic agent. Besides, it uses for maintenance of general anesthesia and sedation in the intensive care unit. Propofol causes rapid induction of and recovery from anesthesia. This drug has anti-oxidant and anti-inflammatory characteristics. Information about whether anesthesia with propofol increases or decreases the IL-6 levels is controversial. Propofol in vitro inhibits IL-6 production by stimulated lipoproteins. The study conducted by Gonzalez-Correa et al. reported that propofol decreased the concentration of IL-1, TNF-α, and IL-6 cytokines. Propofol increases the concentration of IL-10. A higher concentration of anti-inflammatory cytokines in patients who received propofol is the reason for its anti-inflammatory properties. Jin et al. reported that Injection of high dose propofol increased the ratio of IFN-γ/IL-4, while low dose propofol did not change the concentration of the cytokine. Volatile anesthetics can inhibit the release of IFN in animals, reduce the number of NK cells, and the production of cytokines in the human body.

Desflurane increases the number of neutrophil cell and pro-inflammatory cytokines expression in alveolar macrophages. Desflurane produces more pro-inflammatory responses compared to sevoflurane.Evidence suggests that opioids affect the immune system, although the results are contradictory. Both the suppressive and stimulant effects of the opioids on the immune system are reported by various studies. Opioids cause a significant reduction in the concentration of TNF-α, IL-1, and IL-6. Morphine produces TGF-β by stimulating lymphocytes, monocytes, and macrophages. These effects are mainly the result of long-term treatment, which leads to an increase in the concentration of IL-4 and IL-5 as well as the reduction of IL-2 and IFN-γ. Fentanyl exhibited cytotoxicity against NK cells. It is found that morphine, remifentanil, fentanyl, methadone, and codeine alter the immune system more than oxycodone, hydrocodone, and tramadol. Remifentanil decreases IFN-γ concentrations. IL-6, TNF, IL-10, and IL-2 concentrations do not change during treatments with remifentanil or fentanyl. Midazolam is more common than other benzodiazepines, because if administered intravenously causes less pain, and it's a short-acting drug compared to others. Midazolam can inhibit the production of IL-2 and IL-8 and produces an immunosuppression effect. Midazolam can inhibit the activity of TNF-α [64-81].

4. Discussion

One of the ventilation methods during general anesthesia is controlled ventilation. Controlled ventilation, through damaging alveolar cells and mechanical stress, suppresses the stability of the ventilation/perfusion ratio, which results in the release of inflammatory mediators and worsening of the gas exchange during the postoperative period. The other factor that causes lung tissue damage and increases the release of cytokines is hypoxia during surgeries. Sevoflurane reduces the inflammatory response during one-lung ventilation in chest surgery and may be preferable in patients who the level of their pro-inflammatory cytokines is more than expected. Treatment of childhood autoimmune disorders is based upon published prospective and retrospective cohort studies, expert opinion, pediatric randomized controlled trials (particularly for Guillain-Barré syndrome and dermatomyositis), and extrapolation of results from adult studies. Early diagnosis and initiation of treatment can significantly reduce long-term morbidity for these diseases. In addition to affecting quality of life, pediatric autoimmune conditions may increase the risk of various health issues, including cardiometabolic concerns, cancer, and mental health challenges. Conventional treatments can provide some relief but may not address all underlying factors of autoimmunity.

5. Conclusion

Autoimmune neuromuscular disorders in childhood include Guillain-Barré syndrome and its variants, chronic inflammatory demyelinating polyradiculoneuropathy (CIDP), juvenile myasthenia gravis (JMG), and juvenile dermatomyositis (JDM), along with other disorders rarely seen in childhood. Intravenous anesthetics have anti-inflammatory properties, which in most septic cases are useful for patients. The anti-inflammatory effects of ketamine may be related to the suppression of TNF production by macrophage in the presence of bacteria. Propofol inhibits the phagocytosis and chemotaxis of human monocytes through GABAA receptors. Inhalational anesthetics, in a dose-dependent manner, suppress cytokine release, reduces lymphocyte proliferation, induce apoptosis of the lymphocytes, and inhibits the function of neutrophils. lnhalational anesthetics influence the endocrine response from the hypothalamus-pituitary-adrenal axis and indirectly through the secretions of hormones, such as glucocorticoids and catecholamines. Long-term administration of general anesthesia drugs, due to their effects on cytokines, can lead to disease progression in patients with immune deficiency. Many autoimmune diseases share common pathogenic mechanisms. However, there are limited studies quantifying the coexistence of autoimmune diseases.

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