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HYPERSENSITIVITY REACTIONS IN PAEDIATRIC DENTISTRY

Dentistry

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ABSTRACT

An antigen, or foreign substance, triggers an allergic reaction in the immune system. One form of detrimental allergic immunological response is the hypersensitivity response that causes injury to tissues with deleterious effects. This immune reaction could be from an exogenous source like pollens resulting in hay fever or a pathogen or it could be endogenous. Patients seeking dental care may have underlying sensitivities that are known to them or that they are unaware of. Certain dental materials have the potential to trigger an allergic reaction right away or later on. Consequently, in order to prevent and control undesirable occurrences in practise, it is critical for a dental professional to possess a comprehensive grasp of the various hypersensitive reactions. The present review is about types of Hypersensitivity Reactions, disorders and syndromes associated with dental materials used in Paediatric Dentistry.

KEYWORDS

Hypersensitivity, Allergens, Paediatric Dentistry.

INTRODUCTION:

Hypersensitivity is the term used to describe the overabundance of unwanted (painful, uncomfortable, and occasionally fatal) reactions that the immune system typically produces. Pre-sensitized (immune) states are necessary for hypersensitivity reactions to occur. An antigen is eventually eliminated by the immune response, which enlists and mobilises a number of effector molecules to cause a localised inflammatory response.[1] The host tissues are typically not severely damaged by this inflammatory response. However, under specific circumstances, the inflammatory response can have detrimental effects that lead to severe tissue damage or even death; this is known as hypersensitivity.[2]

Definition

The hypersensitivity syndromes represent a diverse group of illnesses that are caused by immunological mechanisms reacting to foreign proteins—most frequently, medications and infectious agents.[3]

Hypersensitivity is an immunological state in which the immune system "over-reacts" to foreign antigen such that the immune response itself is more harmful than the antigen.[4]

Types of Hypersensitivity Reactions

Hypersensitivity reactions are of four types depending upon the mechanism involved and time taken for the reaction: immunoglobulin E-mediated (type I), cytotoxic or antibody-mediated (type II), immune complex-mediated (type III), and delayed-type (type IV).[3]

Type I or Anaphylactic Response

IgE antibodies are generated by the immune system in reaction to environmental proteins (allergens), which include dust mites, pollens, and animal dander. These antibodies mediate the anaphylactic reaction. These antibodies (IgE) bind to mast cells and basophils, which contain histamine granules that are released in the reaction and cause inflammation. In bronchial asthma, allergic rhinitis, allergic dermatitis, food allergy, allergic conjunctivitis, and anaphylactic shock, type I hypersensitivity reactions can be observed.[5,6]

Type II or Cytotoxic-Mediated Response

Cells are destroyed by antibodies in a type II hypersensitivity reaction. Another name for it is cytotoxic reaction. In this hypersensitivity reaction, specific antibody (IgG or IgM) bound to cell surface antigen and destroy the cell. If the cell is microorganism, killing of cell is beneficial to host. However, in Type II hypersensitivity, the cells are own RBC. In autoimmune haemolytic anaemia, autoimmune neutropenia, and immune thrombocytopenia, type II hypersensitivity reactions can occur.[7]

Type III or Immunocomplex Reactions

It is also known as immune complex hypersensitivity. Following antigen exposure, the reaction could occur three to ten hours later. Type III hypersensitivities are mediated by IgG and IgM antibodies. Unlike a Type II response, Type III hypersensitivity is associated with responses to soluble antigens that are not combined with host tissues but with antibodies in the blood which can then lead to inflammatory responses. Under normal conditions circulating Ag/Ab complex is cleared by monocytes / microphages but excessive amount of antigen leads to overwhelming amount and deposition of immune complex (Ag-Ab) that monocytes fail to remove.[8]

Type IV Hypersensitivity

Delayed or type IV hypersensitivity was originally characterized by its time course in which the reactions took 12-24 hours to develop and persisted for 2-3 days. The best-known examples are reactions induced by injecting tuberculin protein into the skin of animals infected by Mycobacterium tuberculosis and the contact hypersensitivity induced by exposure to reactive hapten such as Dinitrofluorobenzene (DNFB). Type IV hypersensitivity reactions also cause the skin lesions in viral diseases such as smallpox and measles.[9]

Common Hypersensitivity Reactions in Dentistry

1. Hypersensitivity Reactions Due to Drugs

a. Antibiotics

Antibiotics are among the drugs most likely to cause anaphylaxis. Amoxicillin, and metronidazole commonly used antibiotics in Paediatric Dentistry. Amoxicillin is probably the one most commonly associated with anaphylaxis. Deaths from anaphylactic reactions to amoxicillin have been reported.[10-12]

b. NSAIDS

Ibuprofen is the most commonly used nonsteroidal anti-inflammatory drug (NSAID) at all age ranges. Ibuprofen-H was found to be prevalent in 22.73% in a paediatric study.[13]

Paracetamol intoxication also seen in some children. Marano M, et al (2023) reported that nausea and vomiting were most commonly reported adverse drug reactions with paracetamol in children.[14]

Overdosing on mefenamic acid is frequently linked to dose-related central nervous system toxicity, particularly convulsions, which are much more common.[15]

2. Anaesthetic Agents

Local Anaesthetics

Although they are extremely uncommon, anaphylactic reactions to local anaesthetic (LA) given in a dental setting[16] have been documented [17-19]. The incidence of negative impacts from LA is about 0.1-1%, with 1% of these cases being confirmed allergic reactions. Actual allergic reactions to LAs are either immediate hypersensitivity reactions (type I: systemic signs) or delayed hypersensitivity reactions

(type IV: confined response at the injection location, contact dermatitis).[16] Since ester LA agents are metabolised to the known allergenic compound para-aminobenzoic acid, allergic reactions are more common with them. The only ester LA utilised in dentistry is benzocaine used as topical application before administration of LA.[16] Because of its low water solubility, benzocaine is not well absorbed by the cardiovascular system and leaves residues on the applied surface for a considerable amount of time.[17] Allergies can be triggered by excipients like antioxidants (metabisulphites in LA solutions containing adrenaline) and preservatives (benzoates used in multi-dose vials)[18,21,22]

General Anaesthesia

Anaphylaxis to general anesthetic drugs is not uncommon. Some of these drugs have been reported to cause direct mast cell activation (MC activation), whereas others are frequently involved in IgE immediate hypersensitivity reactions (IHR). Propofol, thiopental, and ketamine may cause different histamine releases in cutaneous and pulmonary microglia (MCs), according to in vitro research. IgE-dependent IHR are rare, despite reports of positive skin tests for thiopental. Anaphylaxis to ketamine and etomidate is considered rare, and has not been reported on recent studies. Benzodiazepines (BZPs), including midazolam, are generally regarded as safe medications under effects of direct MC activation, and are even indicated on the premedication of patients with MC disorders.[23]

3.Dental Materials

a. Latex

Global data indicates that healthcare workers, susceptible patients, and the general public continue to have average prevalence rates of 9.7%, 7.2%, and 4.3% of latex allergy, respectively.24 Patients with spina bifida (67% chance of latex allergy), medical professionals, and those with a history of food allergies or Elastoplast allergy are among the at-risk groups.[25,26]

b. Toothpastes

There have been reports of toothpaste allergies, including anaphylaxis[27] and even fatal anaphylaxis.[28] A young person in the US who had a documented allergy to dairy products used toothpaste recommended by her dentist that contained Recaldent, a protein derived from milk, and suffered anaphylaxis before passing away.[29]

c. Chlorhexidine

Since it works well as an antiseptic, chlorhexidine is a common ingredient in many dental products, such as toothpaste, varnishes, gels, and mouthwashes.[30] But anaphylaxis to chlorhexidine is becoming more and more common around the world. There have been two cases in the UK where mouthwash containing chlorhexidine was used to irrigate tooth sockets after a recent tooth extraction; sadly, both patients died from the anaphylaxis that followed.[31,32]

d. Iodoform

Alvogyl is one of the endodontic products that contains iodoform. According to the product information for Alvogyl, patients with known allergies to iodine, procaine (novocaine)-type anaesthetics, or compounds related to iodine should not use this medication.[30]

e. Resin Materials Composites

Dental professionals frequently report meth-acrylate-induced asthma attacks and contact dermatitis. Allergies resulting from occupational contact are caused by 2-hydroxyethyl methacrylate (HEMA), ethylene glycol Di methacrylate (EGDMA), and tri-ethylene glycol Di methacrylate (TEG-DMA).[33] According to a study, patients in this study experienced lip reactions resembling lichenoid reactions, and patch testing indicated a positive response to composite materials.[34] Resin-based restorative materials are thought to be safe, but as one patient with mild gingivitis and buccal mucosa reported, their ingredients can leak out and cause allergic contact stomatitis.[35,36]

f. Fissure Sealants

In 1993, Hallstrom U. described a single instance in which the implantation of a fissure sealant caused allergic reactions such as urticaria and asthma, which subsided once the sealant was removed.[37]

g. Mercury Allergy Associated with Amalgam Restoration

The oral mucosa and the skin on the face and neck can develop erythematous, itchy lesions as a result of delayed hypersensitivity reactions to amalgam restorations.[38] Oral lichenoid lesions (OLL) are a common sign of these reactions.[38] Burning mouth syndrome is another sign of a mercury allergy (BMS).[39] A patient with BMS showed positive patch test results in a study by Pigatto PD et al. (2004), and after the mercury filling was replaced, the patient experienced complete remission.[39]

h. Metals

Nickel-Chromium

The first instance of nickel dermatitis, which is characterised by sensitivity to nickel compounds, was documented by Goldman in 1889. Allergies to nickel are 0.1-0.2% common. Forty In general, women are more likely than men to be sensitive to nickel (4–10 times more frequently), while chromium allergies are rare (10% in men and 3% in women).[42] The burning sensation, gingival hyperplasia, and numbness on the tongue's sides are clinical signs and symptoms of nickel allergy. A patch test utilising 5% nickel sulphate in petroleum jelly is used to confirm the diagnosis.[43]Exposure to nickel in sensitised individuals causes systemic allergic contact dermatitis.[44] The Ni-Ti arch wire should be changed to titanium molybdenum alloy (TMA) or stainless steel wire if nickel hypersensitivity is determined to be the cause of the symptoms.44 When children treated with older generation SSCs (72% nickel) had their nickel sensitivity assessed, there was no nickel sensitivity observed when the children were treated with newer generation SSCs (9–12% nickel).45,46 Within the first week, there is a peak and a subsequent decrease in in vitro nickel leaching from orthodontic materials, space maintainers, and arch wires.46 Reactivity to cobalt and chromium is often linked to nickel allergy. In a 2005 patch test of 1208 patients with contact dermatitis, Duarte I et al. discovered that 18.5% of them had positive reactions to two or three metals.[48]

Titanium

With a low prevalence rate of 0.6%49, urticaria, eczema, and mucosal redness are the common symptoms of titanium allergy.[50,51] In 2006, 56 patients who had endoprostheses, orthodontic braces, or titanium dental implants experienced severe health complications (chronic fatigue syndrome, pain in the muscles and joints).[52] It has been noted that certain elements, such as beryllium (Be), cobalt (Co), and chromium (Cr), in titanium alloys may induce allergic reactions in people receiving dental implants.[53,54]

i. Impression materials

Polyether impression materials have been linked to allergic reactions, which present as swelling, itching, and redness. During patch testing, it was discovered that a catalyst paste component was the source of the allergy; when this component was replaced, no allergic reactions were seen.[55,56]

There is only one documented instance of an allergic reaction, wherein a patient experienced redness, itching, and oedema after receiving a secondary impression for both upper and lower complete dentures. The patient recovered after receiving topical corticosteroids (Betamethasone valerate ointment, 0.1%).[57]There is also a recorded case study of a fatal anaphylactic shock due to alginate impression material.[58]

Root Canal Sealers and Obturating Materials

Zinc Oxide Eugenol

Allergies to zinc oxide are generally uncommon, and there is only one documented instance of a patient with zinc oxide allergy receiving a successful root canal treatment.[59]

Gutta-percha is biocompatible, according to studies by Munaco et al. (1978) and Pascon & Spangberg (1990); nevertheless, its high zinc oxide content may make it toxicity. Therefore, as an alternative to gutta-percha, a resin-based filling material called Resilon (Pentron Clinical Technologies, Wallingford, CT, USA) has recently been introduced. It is made of polyester, difunctional methacrylate resin, bioactive glass, and a resin sealer. According to studies, resilon is a biocompatible substitute for patients who are allergic to dental materials based on zinc oxide and ethanol.[59]

Eugenol causes type IV hypersensitivity reactions, generalised anaphylactic symptoms, and acts as a contact irritant. In addition, a patient with gingival inflammation in the mucosal region next to the metal-ceramic bridge was reported to have experienced an allergic reaction to eugenol.[60] There have also been reports of allergic contact stomatitis following the use of eugenol as a temporary restorative material, which healed when replaced with glass inomer.[61]

Ledermix Paste
No allergy to ledermix paste is reported except for a single case in which a female experienced type I allergy in the form of urticaria, general malaise and fever when a mixture of ledermix paste and calcium hydroxide was used as an intracanal medicament and her symptoms subsided following flushing out of the ledermix paste and re-dressing the canal with $Ca(OH)_2$.[62]

Formaldehyde
One common cause of allergic contact dermatitis is formaldehyde. It was stated that formaldehyde was the cause of 40%–60% of the reactions.[63]The dental literature describes 28 patients who experienced immediate symptoms after receiving root canal compounds containing formaldehyde.[64] Generalised urticaria and anaphylactic reaction or shock are the hallmarks of formaldehyde allergy.[64,65]

Sodium Hypochlorite
There is also a case report of a sodium hypochlorite allergy. The patient experienced breathing difficulties and a burning sensation after the canals were irrigated with the same. Corticosteroids, antibiotics, antihistamines, and analgesics were given to treat the symptoms. A positive skin scratch test resulted after 15 days, confirming the presence of 1% sodium hypochlorite allergy.[66]

Syndromes/Disorders Associated with Hypersensitivity
Erythema Multiforme Exudative (MEE)
It is an acute disease of the skin and mucous membranes that rarely recurs. It is distinguished by a rash that combines many of the main components (spots, papules, blisters, vesicles, blisters).[67] Both medications and infections may be the cause. Sulfonamides, pyrazolone derivatives, barbiturates, tetracyclines, acetylsalicylic acid, diuretics, progesterone, streptomycin, etc. are the most frequently occurring MEE inducers.[67]

STEVENS-JOHNSON SYNDROME (SSD)
It is an acute mucocutaneous-ocular syndrome, or severe malignant exudative erythema. During medication therapy, skin lesions are brought on by focal infections and hypothermia. This illness can be brought on by sulfonamides, antipyretics, penicillin, tetracycline, and other medications. The herpes simplex virus and early acyclovir and prednisolone therapy are involved in the etiopathogenesis.[68]

A case of Ibuprofen-Induced Hypersensitivity Reaction in a Young Child was reported by Kumar N in 2021. The main complaint of a 7-year-old girl and her father when they arrived at the outpatient department was tooth decay. According to the medical history, the child experienced a severe Stevens-Johnson reaction as a result of an ibuprofen allergic reaction. The event occurred a year ago, when the child received ibuprofen to relieve pain. The child received no other medication, not even antibiotics. Upon extraoral examination, the face, hands, abdomen, and legs showed healed rashes' scars. In addition to visual impairment, the child also had cicatricial entropion, trichiasis, dry eyes, and symblepharon formation. The child's finger and toenail malformations are another issue. The child could understand the spoken instructions and exhibited good cognitive development. The child received gentle, loving care, and an intraoral examination was conducted. Multiple carious teeth with hypomineralized molars and mucosal adhesions in the buccal vestibule were found during an intraoral examination. There were whitish grey patches all over the tongue, and its dorsum was smooth and devoid of papillae. [69]

Lyell's Syndrome
Bullous necro epidermolysis, scorched skin syndrome, toxic epidermal necrolysis (TEN), and bullous erythroderma are other names for Lyell's syndrome that were first reported in 1956. Multi-etiological processes are involved. The illness appears 10 hours to 21 days after the medication is taken, most commonly sulfa drugs (e.g., sulfanamides), antiepileptic drugs, and non-steroidal anti-inflammatory drugs that are derived from oxicam. The condition frequently starts out as urticaria. It starts suddenly and sharply. There's a sore throat, headache, diarrhoea, chills, and sore muscles and joints. It gets up to 39–40 °C in a matter of hours. Following skin soreness and burning, a rash of erythematous, painful, and slightly swollen spots of varying sizes appears. These spots are localised to the skin of the face, trunk, limbs, and mucous membranes, and they frequently merge with one another. Blisters that are shaped irregularly and have flabby walls with serous or serosanguineous contents appear. A pronouncedly positive Nikolsky sign is present. Skinless areas are similar to II–III-degree burns. The epidermis that has not shed resembles corrugated paper. There is severe hyperesthesia, a yellowish-dirty coating on the tongue, swelling, difficulty opening the mouth, and numerous pharyngeal erosions. lips with dried crusts. The tongue and oral cavity together constitute a single wound surface. There is hyperaemia of the conjunctiva, an increase in headaches, internal organ damage, and loss of consciousness. Death can happen in a serious way.[6]

Immune Thrombocytopenia (ITP)
ITP, an autoimmune disease, can strike anyone at any age and is frequently brought on by the medications penicillin, NSAIDS, and furosemide. In peripheral blood, phagocytes degrade sensitised platelets. Petechiae with sudden onset and bleeding from the nose, intestines, gums, and urinary tract happen. Bleeding can occur in conjunction with malignancy, infections, drug reactions, and other autoimmune conditions like systemic lupus erythematosus and thyroid disease.[68]

Autoimmune Haemolytic Anaemia (AIHA)
Immunoglobulin G-mediated (warm AIHA) and IgM-mediated (cold AIHA) immune haemolytic anaemia are the two forms. The warm variety could be secondary to other illnesses like cancer that affects the lymphoid tissues or idiopathic autoimmune. Idiopathic colds and infections like the Epstein-Barr virus can also cause colds. Jaundice is the main clinical symptom of the two. A positive Coombs test, which detects immunoglobulins and C3 on red blood cells, leads to the laboratory diagnosis. Often brought on by medications like NSAIDS and cephalosporins.[7]

Autoimmune Neutropenia
Infections (bacterial and fungal), autoimmune diseases (systemic lupus erythematosus, rheumatoid arthritis, autoimmune hepatitis), infections, and lymphoma can all coexist with autoimmune neutropenia. Clozapine and Penicillin G are the causal factors.[71]

Haemolytic Disease of Foetus and The Newborn (ERYTHROBLASTOSIS FETALIS)
At birth, when the placenta tears away, the mother's immune system becomes initially sensitised to the foetal Rh+ red blood cells. After becoming sensitised, the mother can trigger a haemolytic reaction against a second Rh+ foetus, resulting in anaemia and jaundice once the maternal IgG crosses the placenta. The first child survives the disease.[72]

Myasthenia Gravis
An autoimmune condition known as myasthenia gravis is brought on by antibodies that obstruct post-synaptic acetylcholine receptors, preventing neuromuscular transmission. Severe muscular exhaustion, bilateral ptosis, double vision, deconjugate eye movements, dysphagia, and upper limb weakness are its hallmarks. Pathogenic IgG antibodies that cross the placenta can cause temporary muscle weakness in babies born to mothers with myasthenia gravis. frequently brought on by D-penicillamine.[73]

Goodpasture Syndrome
The weed killer Paraquat is the cause of Goodpasture syndrome, a type II hypersensitivity reaction characterised by nephritis and lung haemorrhage. Cross-reactive autoantigens found in the kidney and lung basement membranes are the primary cause in the majority of patients. Numerous patients with this issue have antibodies against type IV collagen, a crucial component of basement membranes.[74]

Pemphigus
A severe blistering disease called pemphigus affects the skin and mucous membranes. It is brought on by ether thiol compounds like captopril or drugs like piroxicam that are metabolised into thiols. Antibodies against desmoglein-1 and desmoglein-3, which are parts of desmosomes, which create connections between epidermal cells, are present in the sera of pemphigus patients. HLA-DR4 (DRB1*0402), a molecule that presents one of the autoantigens involved in the immunopathogenesis of this disease (desmoglein-3), is strongly associated with pemphigus.[75,76]

CONCLUSION:
In Paediatric Dentistry, the patients are exposed to allergens through oral cavity as they are constantly exposed to sensitizing substances and dental staff is also exposed to allergens like latex, acrylates and

formaldehyde that cause allergic reactions and cause severe outcomes. In order to prevent allergic manifestations in the dental clinic, a dentist must establish a diagnosis through a thorough history of allergies, clinical examination, and confirmatory tests such as enzyme-linked immunosorbent assay (ELISA) and patch tests.

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