INDIAN JOURNAL OF PRACTICAL PEDIATRICS

IJPP

• **IJPP is a quarterly subscription journal of the Indian Academy of Pediatrics committed to presenting practical pediatric issues and management updates in a simple and clear manner**

• **Indexed in Excerpta Medica, CABI Publishing.**

Vol.15 No.3	**JUL.- AUG. 2013**
Dr.K.Nedunchelian Editor-in-Chief	**Dr.S.Thangavelu** Executive Editor

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TOPIC OF INTEREST - "ALLERGIC DISORDERS"

GENERAL ARTICLES

Journal Office and address for communications: Dr. K.Nedunchelian, Editor-in-Chief, Indian Journal of Practical Pediatrics, 1A, Block II, Krsna Apartments, 50, Halls Road, Egmore, Chennai - 600 008. Tamil Nadu, India. Tel.No. : 044-28190032 E.mail : ijpp_iap@rediffmail.com

Published by Dr.K.Nedunchelian, Editor-in-Chief, IJPP, on behalf of Indian Academy of Pediatrics, from 1A, Block II, Krsna Apartments, 50, Halls Road, Egmore, Chennai - 600 008. Tamil Nadu, India and printed by Mr. D.Ramanathan, at Alamu Printing Works, 9, Iyyah Street, Royapettah, Chennai-14.

51ST ANNUAL NATIONAL CONFERENCE OF INDIAN ACADEMY OF PEDIATRICS

Venue: 5, Brilliant Convention Centre, Scheme 78, Part II, Indore (M.P.)

Achieving MDG-4: Strategies & Action

PEDICON 8–12 JANUARY 2014 INDORE

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1st May-31st July,13	9,500	9,500	12,000	12,000	7,000	7,000	850 USD	850 USD	12,500	50%
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16th Oct-15th Dec,13	13,000	13,000	15,000	15,000	10,000	10,000	1200 USD	1200 USD	15,500	NIL
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Registration Fee Inclusions

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Venue: 5, Brilliant Convention Centre, Scheme 78, Part II, Indore (M.P.)

Workshop Codes	WORKSHOP DETAILS	Academic Coordinator	Fee for Indian Delegates
1	Growth Monitoring	Dr. Vaman Khadilakar	1,000
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3	Asthma for Clinicians	Dr. Shishir Modak	1,000
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5	Advanced Mechanical Ventilation	Dr. Anil Sachdev / Anchor - Dr. Krishen Chug	1,000
6	Bed side Ultrasound in emergency & Critical Care	Dr. Dhireen Gupta	1,000
7	a) Art & Science of writing article in Journal b) Professional Social Responsibility*	Dr Harish Pemade Dr.Naveen Thacker	1,000
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13	Infant & Young child feeding	Dr. Satish Tiwari	500
14	IAP-BLS Course for Health Care Providers	Dr LN Taneja / Dr.Sukhmeet Singh	1,000
15	Pediatric Gastroenterology workshop: What, When & How?	Dr. Neelam Mohan	1,000
16	Pediatric Hematology Oncology in office practice	Dr. Anupam Sachdev	1,000
17	Comprehensive Pediatric Infectious disease course (Two Days)	Dr. Abhay K Shah	2,000
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19	Medico legal Issues in Paediatric Practice	Dr. Mukul Tiwari	1,000
20	Practice Cardiology in Paediatrics	Dr. Smita Mishra	1,000
21	Pals recertification course*	Dr. Arif Ahmad	2,000
22	Dialysis in Children	Dr Siddharth Sethi	1,000
23	Pediatric Emergency and acute care in office practice	Dr.Suresh Gupta / Dr. Indumati Sanathanam	1,000
24	Newborn Hearing Screening Programme	Dr. Abraham K Paul	500

*Special attraction for interested participants: 1.5 to 2 hours session on Professional Social Responsibility, this will cover How to write bestselling self-help health books for the use of general public and empowering patients to obtain optimal health care from health providers, Publication in newspapers, magazines and electronic media during Art & Science of writing article in Journal

Important Notes

- Registration is mandatory for attending the workshop.
- Workshop no. 4 & 17 are two days duration on 7th & 8th January 2014 while remaining is one day on 8th January.
- Details of the faculties shall be announced in due course of time.
- One can participate in one workshop only. However you can give up to 3 choices in order of preference.
- Maximum seats for all the delegates are 50 in each workshop. It is on first come first serve basis.
- For Indian delegates Fee structure of workshops is as per table.
- For SAARC/International Delegates workshop 4, 17 & 21 fee is 200 USD while remaining it is 100 USD.

Bird's eye view of CME programme

Thursday : 9th January

8.30 - 9.00 am	**Inaugural Function for CMEs**
09.00 - 10.00 am	Guest Lectures (1-2)
10.00 - 11.00 am	Panel discussion
11.00 - 12.00 Noon	Guest Lectures (3-4)
12.00 - 01.00 pm	Case based discussion
01.00 - 02.00 pm	Guest Lectures (5-6)
02.00 - 03.00 pm	Symposia
03.00 - 04.00 pm	Guest Lectures (7-8)
04.00 - 05.00 pm	Clinical quiz/Keypad
06.00 pm onwards	Inaugural function of Pedicon 2014

Scientific Programme - Bird's eye view

- Most sessions would run concurrently in six different halls
- Orations would be non concurrent & conducted in main hall

Time	Friday : 10th January	Saturday : 11th January	Sunday : 12th January
7.30 – 8.30 am	Meet the Expert	Meet the Expert	Meet the Expert
8.30 – 10.00 am	Sp. Chapters	Sp. Chapters	Sp. Chapters
10.00 – 10.30 am	Guest Lecture	Guest Lecture	Guest Lecture
10.30 – 11.30 am	S. C. Oration	Plenary I	Plenary II
11.30 – 12.30 pm	Dialogue session	Dialogue session	IAP Quiz/Awards
12.30 – 1.00 pm	Guest Lecture	Guest Lecture	Pictorial Quiz
1.00 – 1.30 pm	Free Papers	Free Papers	Free Papers
1.30 – 2.00 pm	Therapeutic Dilemma	Therapeutic Dilemma	Free Papers
2.00 – 2.30 pm	Diagnostic Difficulties	Diagnostic Difficulties	-
2.30 – 3.15 pm	Symposia	Symposia	-
3.15 – 3.45 pm	Challenges in Practice	Challenges in Practice	-
3.45 – 4.30 pm	Panel Discussion	Panel Discussion	-
4.30 – 5.00 pm	Hot topics	Clinical Quiz	-
5.00 – 6.00 pm	Sponsored Activity	Sponsored Activity	-

INSTRUCTIONS TO AUTHORS

General

Print the manuscript on one side of standard size A4, white bond paper, with margins of at least 2.5 cm (1") in double space typescript on each side. Use American English using Times New Roman font 12 size. Submit four complete sets of the manuscript.

They are considered for publication on the understanding that they are contributed to this journal solely.

All pages are numbered at the top of the right corner, beginning with the title page.

All manuscripts should be sent to: The Editor-in-Chief, Indian Journal of Practical Pediatrics

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1st Page –

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Word count

No. of figures (colour / black and white)

No. of references

Authors contribution

2nd Page –

Abstract (unstructured, not exceeding 100 words) with key words (not exceeding 4)

3rd Page -

Acknowledgement

Points to remember (not more than 5 points)

Text

References

Tables

Legends

Figures – should be good quality, 4 copies black & white / colour,*

(4 x 6 inches – Maxi size) Glossy print

* Each colour image will be charged Rs. 1,000./- separately, with effect from January 2006 (Except for invited articles).

Text

Only generic names should be used

Measurements must be in metric units with System International (SI) Equivalents given in parentheses.

References

Recent and relevant references only

Strictly adhere to Vancouver style

Should be identified in the text by Arabic numerals as superscript.

Type double-space on separate sheets and number consecutively as they appear in the text.

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All manuscripts, which are rejected will not be returned to author. Those submitting articles should therefore ensure that they retain at least one copy and the illustration, if any.

Article Categories

Review article

Article should be informative covering the recent and practical aspects in that field. Main articles can be in 1500 – 2000 words with 12 – 15 recent references and abstract not exceeding 100 words.

Case report (covering practical importance)

250 – 600 words, 8 – 10 recent references

Clinical spotters section

150 – 200 words write up

With 1 or 2 images of clinically recognizable condition

(of which one could be in the form of clinical photograph / specimen photograph / investigation)

Letters to the Editor

200 – 250 words pertaining to the articles published in the journal or practical viewpoints with scientific backing and appropriate references in Vancouver style.

Check List

Covering letter by corresponding author

Declaration (as enclosed) signed by all authors **

Manuscript (4 copies)

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ALLERGIC DISORDERS

FOOD ALLERGY IN CHILDREN

***Ganesh R**
****Sathiyasekeran M**

Abstract: *Food allergy (FA) is a common cause of morbidity in children and young adults especially in developed countries with a prevalence of 6 to 8 %. FA is also an emerging problem in children from developing countries including India. True food allergy is an immunologically mediated reaction which may be IgE mediated, non IgE mediated or mixed and can range in its severity from mild to life threatening event. The task faced by the pediatrician is to recognize the clinical features of food allergy and differentiate it from a wide spectrum of non immunologic adverse food reactions. FA continues to pose a therapeutic challenge to the pediatrician since no definite therapy exists to prevent or cure FA and the best option available is dietary elimination of the specific food allergen. This article highlights the gastrointestinal manifestations of food allergies in children.*

Key words: *Food allergy, Children, IgE, Elimination diet*

Food allergy (FA) is an adverse immune response to food proteins.[1] Although 25% to 30% of the general population believe that they have FA it may not be true. The incidence of FA in the United States confirmed by history and food challenges suggest a prevalence rate of 6% in children and 3.5% in adults.[2] FA is also being reported from developing countries though robust data is not available.[3] FA could be transient or permanent, immediate or late in reaction, early age of onset or late age of onset. The mortality rate from FAs is 0.006 individuals per 100 000 children in the UK while 150-200 individuals die from FAs every year in the USA. Since there is no definite therapy except to avoid the food allergen, this problem poses a great challenge to the parent and the pediatrician.

* Consultant in Pediatrics

** Senior Consultant Pediatric Gastroenterologist
Kanchi Kamakoti CHILDS Trust Hospital
Chennai.

Definitions and terminologies[2]

An adverse food reaction is an abnormal response to an ingested food, regardless of the pathophysiology. This may be divided into toxic and nontoxic adverse reactions. Toxic reactions (eg. food poisoning) may occur in any individual if a sufficient dose of the toxin is ingested. Non-toxic reactions are more individual based and may be immune reactions (allergy/hypersensitivity) or non-immune (intolerance) reactions (eg. carbohydrate malabsorption).

Food intolerance is an abnormal physiological response to an agent which is non immune mediated. Thus there are several adverse food reactions which could be toxic or due to intolerance. These are non immunologic adverse food reactions and are not food allergies (Table I).

Food allergy or food hypersensitivity is defined as a reproducible adverse immune reaction to a food protein antigen.

Immune Reactions: The three broad categories of FA based on the underlying immunopathology are IgE mediated, non-IgE (T cell) mediated and mixed (IgE and T cell mediated). IgE mediated reaction occurs within minutes to 2 hours of ingestion of food. Non – IgE mediated reactions (T cell-mediated) are typically delayed in onset (i.e., 4 to 48 hours) and most frequently involve the gastrointestinal tract. FA may also present with a mixed pattern of both IgE and cell mediated response (Table II).

Incidence: 6% to 8% of children younger than 3 years experience documented adverse reactions to foods. In adults it is less than 3- 4 %, though the perceived FA in adults may be as high as 25- 30 %. The peak incidence is seen around 1- 2 years of age since most of FA is acquired at this age. The incidence falls progressively until late childhood and then remains stable. The reasons hypothesized for the increase in incidence in infants are the immature gut barrier, damage to the gut mucosa following diarrhea and early introduction of food by over enthusiastic parents.

FA to specific Foods: The common food allergens in infancy are cow's milk, egg, peanuts and soy. In younger children the common food allergens are cow's milk, egg, peanuts, soy, wheat, tree nuts (cashew nut, wallnut), fish and shell fish which is referred as the "Allergy wheel".

Table.I Non-immunologic adverse food reactions which are NOT food allergies

I. Toxic reactions	Shell fish : saxitoxin Fish:Ciguatera poisoning Bacterial & Fungal toxin: Cl.botulinum, ergot, aflatoxin Flavoring and preservatives: sodium metabisulphite Dyes: tartrazine Contaminants: heavy metals, pesticides
II. Metabolic:	Carbohydrate malabsorption (e.g. lactase deficiency, sucrose- isomaltase deficiency), Pancreatic insufficiency: cystic fibrosis,Galactosemia Phenylketonuria
III. Pharmacologically active food component:	Scombroid poisoning(fish:tuna,mackerel,sardines) Tyramine(cheese, pickled fish) Theobromine, caffeine
IV. Infections	Parasitic: Giardia Bacterial : Salmonella Viral: hepatitis
V. Neurological	Auriculo-temporal syndrome Gustatory rhinitis

Table.II Food allergies based on immunopathology

Immunopathology	Disorder	Typical Age
I.IgE mediated	Urticaria, Angioedema	Children > adults
	Rhinoconjunctivitis/Asthma	Infant/child > adult
	Anaphylaxis	Any age
	Food dependent, exercise -induced anaphylaxis	Onset in late childhood/ adulthood
	Oral allergy syndrome	Onset after pollen allergy established(adult > young child)
II.Mixed IgE and cell mediated	Atopic Disorders	Infant > child > adult
	Eosinophilic gastrointestinal disorders	Any age
III.Cell mediated	Dietaryprotein-induced proctitis/proctocolitis	Infancy
	Food protein-induced enterocolitis syndrome	Infancy
	Celiac Disease	Children and adults

FA in older children and adults is primarily caused by peanut, tree nuts and seafood. Allergy to fruits and vegetables may be significant but usually are not severe. Population-based studies in children have documented cow's milk allergy at a prevalence rate of 2.5%, egg allergy in 1.5% and peanut allergy in 1 %.[4] FA is no longer a health problem confined to the West but also reported from Asia and depends on the culture and food habits. In Japan, the most common allergens causing FA were milk, egg, wheat, peanut and soy beans followed by sesame and buckwheat.[5] In Singapore, cow's milk and egg white are an important cause of anaphylaxis.[6] A report from Hyderabad has stated that beans, mustard, cardamom and cashewnut as causative allergens in patients with urticaria.[7] An unpublished data from Chennai has identified cow's milk protein as the leading allergen in young infants.

Cow's milk allergy/cow's milk protein allergy (CMA/CMPA)

CMPA is the most common food allergy in children with a documented prevalence of 0.3-3.5% in children less than 5 years of age and 1% in older children.[8] Its incidence in breast fed infants is 0.5%. In India of 137 children with chronic diarrhea CMPA was seen in 6% and in children <2 yrs it was 13%.[9] CMPA can be IgE mediated or T cell mediated or both. The clinical manifestations that result from IgE mediated reactions are systemic anaphylaxis, urticaria, angioedema, nausea, vomiting, diarrhea, abdominal pain, rhinoconjunctivitis, wheeze and those from (IgE and T cell mediated) are Heiner syndrome, atopic dermatitis, proctitis, enteropathy, proctocolitis, enterocolitis, eosinophilic esophagitis and gastroenteritis. The other GI manifestations are reflux like vomiting, FTT in infants, abdominal pain, constipation in older child-refractory to usual medications but responsive to milk withdrawal. High index of suspicion and a positive challenge helps in diagnosis. Endoscopy with biopsy may help. The majority of children with CMPA will tolerate cow's milk by the age of 1 year.

Pathophysiology of food allergy[2,10]

The average intake of protein by an individual is about 1gram per kg which is derived from a variety of animals, birds, plants and fungi. Oral tolerance is the active antigen-specific non response to antigens administered orally. Most of the food that is ingested does not cause any allergy because of "oral tolerance". Food represented in the allergy wheel accounts for nearly 90% of positive food challenges. These share common characteristics such as small molecular weight less than 70 KD, abundant source of the relevant antigen, glycosylation residues, water solubililty and resistance to heat and digestion.

Delivery of antigen to the small intestine: The dietary proteins undergo digestion by the enzymes in the saliva and gastric acid which reduces the immunogenicity. However proteins with the above physiochemical features may retain the allergenic potential when they reach the small intestine.

Gastrointestinal Complex Barrier: The gastrointestinal mucosal barrier uses both physiologic and immunologic barriers to prevent the penetration of foreign proteins. The physiologic barrier comprises of the intestinal epithelial cells (IEC), glycocalyx, intestinal microvillous membrane, tight junctions which block the penetration of antigens and the salivary amylases, gastric acid, pepsin, pancreatic and intestinal enzymes and epithelial lysozymes which break down the ingested antigens. The immunologic barrier comprises of antigen specific SIgA (secretory IgA) and IgG which blocks and clears the penetration of ingested antigens.

Fate of food antigens that cross the barrier: The mature "gut associated lymphoid tissue (GALT)" therefore functions as a very complex integrated network of tissues and cells performing the daunting task of protection. Developmental immaturity of various components of the intestinal barrier and immune system reduces the efficacy of the complex barrier and plays a role in the high prevalence of FA seen in the first few years of life. About 2% of ingested food antigens are absorbed and transported throughout the body in an "immunologically" intact form or recognizable antigen even through the normal mature intestine. However tolerance is the dominant response of GALT and is maintained by various antigen presenting cells (APC) such as IEC, dendritic cells and regulatory T cells. Commensal bowel flora and Langerhans cells in the oral mucosa also plays a role in oral tolerance. In young infants the physiologic and immunologic barriers may not be efficient and therefore allow increased penetration of food antigen. The GALT appears less capable of "tolerizing" compared with the mature system and therefore food allergy or hypersensitivity occurs during this susceptible age.

Immunopathogenesis of food allergies[2]

IgE-mediated reactions: IgE-mediated response has been well characterized. The sensitivity to antigens is usually due to a glycoprotein and the reaction results as a series of molecular and cellular interactions involving antigen-presenting cells (APCs), T cells and B cells.

i. APCs present the antigen as small peptide fragments (T cell epitopes) in conjunction with major histocompatibility complex (MHC) class II molecules to T cells.

ii. T cells bearing the appropriate complementary T-cell receptor (TCR) bind to the peptide MHC complex.

iii. This interactive first signal leads to T-cell proliferation and cytokine generation and generation of a second signal (IL-4).

iv. IL-4 promotes an Ig E response(Th2-like cell activation).These cells and their products in turn interact with B cells bearing appropriate antigen specific receptors leading to isotype switching and generation of antigen specific IgE.

v. The antigen specific IgE then binds to the surface receptors of mast cells, basophils, eosinophils and macrophages, causing intracellular signalling and the release of histamine, prostaglandins, leukotrienes and cytokines on the next encounter with the specific antigen.

In children the first exposure can occur in utero or in post natal period through breast milk. Subsequent exposure in the sensitized host can lead to an immediate hypersensitivity reaction in various target organs. A breakdown in mucosal integrity caused by infection or inflammation can also cause sensitization due to increased permeability.

Non IgE-mediated (T cell – mediated) reactions: Food specific T cell mediated reactions are currently not well understood. The APCS and or/T cells are activated to secrete TNF-á or IL-4 and/or IL-5 and other cytokines attracting eosinophils and inducing the inflammatory response leading to the delayed onset of symptoms.

Clinical features of food allergies[2,11]

The common clinical manifestations of FA are cutaneous, respiratory and gastrointestinal (Table III). The GI manifestations of FA are detailed below.

I. Immediate gastrointestinal hypersensitivity

Type of reaction: IgE mediated

Age of presentation: Infants and children.

Clinical features: The symptoms are acute in onset occurring usually within minutes or up to 1 to 2 hours. Nausea, vomiting and abdominal pain usually occurs within minutes of ingestion whereas diarrhea may follow several hours after the initial symptoms. Although immediate IgE mediated gastrointestinal reactions may occur without other systemic symptoms; they are more commonly associated with reactions in other organ systems.

Usual offenders: milk, egg, peanut, soy, wheat and seafood.

Diagnosis: allergy prick skin tests and RASTs to the causal protein will be positive.

II. Oral allergy syndrome (pollen food syndrome)

Type of reaction: IgE mediated disorder

Age of presentation: older children and adults

Clinical features: Oral pruritus and sometimes angioedema of the lips, tongue and palate when ingesting certain fresh fruits and vegetables may occur. The expression of this allergic response requires initial sensitization via the respiratory route to pollens that contain proteins which are homologous to those found in particular fruits and vegetables. Since these proteins are easily digested, cooked forms of these fruits and vegetables generally do not induce symptoms. However 10% of individuals experience systemic symptoms and 1% to 2% experience anaphylaxis.

Usual offenders: Reactions to melons or bananas in individuals with ragweed allergy and to apples, potato, carrot, kiwi and cherries in those with birch pollen allergy.

Diagnosis: Allergy skin tests of the implicated food are positive.

III. Eosinophilic gastroenteropathies (Eosinophilic esophagitis, gastroenterocolitis, and gastritis)

Type of reaction: **Mixed IgE and T cell mediated**

Age of presentation: Any age including preterm

Clinical features: This heterogeneous group of eosinophilic gastroenteropathies has in common an eosinophilic inflammation of the gut. The symptoms include postprandial nausea, dysphagia, abdominal pain, vomiting, diarrhea and rarely obstruction. Small bowel involvement may result in protein-losing enteropathy and weight loss. Serosal involvement can cause eosinophilic ascites.

Offending allergens: Role of allergens is debatable. A subset may be due to milk, egg, wheat, soy.

Diagnosis: Endoscopy and biopsy shows eosinophilic infiltration of the gut mucosa (>15 eosinophils/HPF in the esophageal mucosa. However there is no consensus regarding the number of eosinophils in the gastric/small intestinal mucosa). Peripheral eosinophilia is sometimes observed (50% of patients).

IV. Dietary protein-induced proctitis/proctocolitis

Type of reaction: T cell mediated

Age of presentation: Infants

Table.III Clinical manifestations of food allergy

System	IgE mediated Acute/onset	Cell mediated Chronic/delayed	Mixed Chronic/Delayed
Cutaneous	Urticaria,angioedema, morbiliform rash, flushing	Contact dermatitis, dermatitis herpetiformis	
Respiratory	Acute rhinoconjuctivitis bronchospasm	Food induced Pulmonary hemosiderosis	Asthma
Gastrointestinal	Oral allergy syndrome. GI anaphylaxis	Food protein induced proctitis,enterocolitis, enteropathy syndrome	Eosinophilic oesophagitis/ gastroenteritis

Clinical features: Infants with dietary protein-induced proctitis/proctocolitis are generally healthy but have visible specks or streaks of blood mixed with mucus in the stool. Blood loss is usually minimal and anemia is rare. The disorder manifests in the first several months of life, with a mean age at diagnosis of 2 months. The lack of systemic symptoms, vomiting, diarrhea and growth failure help to differentiate this disorder from other gastrointestinal food allergies with colitis. Most infants present while being breastfed and are symptomatic as a result of maternally ingested proteins excreted in breast milk. The disorder has also been noted in infants who take casein hydrolysates. The prognosis for this condition is good and 25% of these children have other atopic diseases.

Offending allergens: Cow milk protein and less commonly, soy protein

Diagnosis: Endoscopic examination is often deferred but may show focal to diffuse colitis with edema and erosions. Biopsy reveals an eosinophilic infiltration and occasionally lymphonodular hyperplasia (Fig.1).

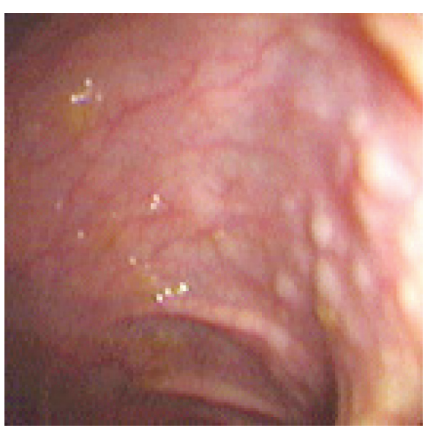

Fig.1. Colonoscopy showing lymphonodular hyperplasia

V. Dietary protein enteropathy

Type of reaction: T cell mediated

Age of presentation: Infancy

Clinical Features: Dietary protein enteropathy is characterized by protracted diarrhea and vomiting (60%) with resulting malabsorption and failure to thrive. Protein-losing enteropathy may lead to edema, abdominal distension and sometimes anemia. Though some features are similar to Celiac disease, resolution generally occurs by 1-2 years and there is no increased incidence of malignancy. Dietary protein enteropathy may persist into later childhood, but the frequency of persistence into adulthood is unknown.

Offending allergens: Cow milk protein, soy, cereal grains, egg and seafood.

Diagnosis: Endoscopy/biopsy, allergen elimination and challenge. Biopsy reveals villus injury, increased crypt length, intraepithelial lymphocytes, and few eosinophils.

VI. Dietary protein enterocolitis

Type of reaction: T cell mediated

Age of presentation: Infancy and usually resolves by 2 years of age

Clinical features: The symptoms of vomiting usually begins within 2 to 4 hours, of ingestion. The reaction seems similar to but more severe than those observed in protein enteropathy. The term "enterocolitis" implies both small and large bowel involvement. The symptoms of "food protein-induced enterocolitis syndrome (FPIES)" include vomiting and diarrhea and can progress into a severe shock like state.

Offending allergens: Cow's milk and soy protein are the most common antigens. Egg, wheat, rice, oat and peas, have been reported to trigger symptoms in older children.

Diagnosis: In FPIES, an increase in peripheral blood neutrophil counts during a positive challenge is the only positive finding. Skin tests are negative for the offending antigen, No specific diagnostic test for FPIES currently exists and diagnosis is based on history.

VII. Celiac disease (CD)

Type of reaction: T cell mediated

Age: Any age, usually beyond infancy

Clinical features: CD is a T-lymphocytic mediated small intestinal enteropathy induced by gluten in individuals with a genetic predisposition. Vomiting, diarrhea, growth failure, anemia are common features. Management is lifelong gluten free diet.

Diagnosis: Presence of anti gliadin, antiendomysial and tissue tranglutaminase antibodies along with duodenal mucosa showing scalloping of the mucosal folds and villous atrophy suggests celiac disease (Fig.2&3).

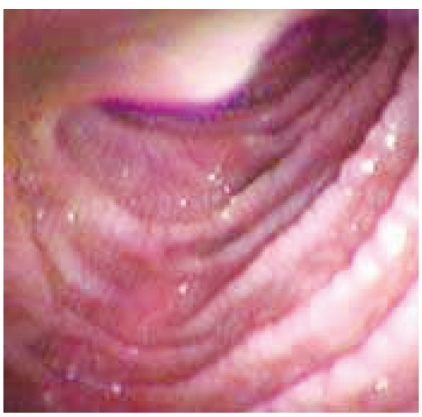

Fig.2. Duodenal mucosa showing scalloping

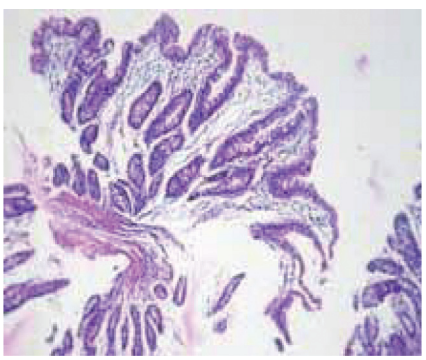

Fig.3. Duodenal mucosa showing villous atrophy

Natural history of food allergy

Childhood food allergies are dynamic with spontaneous resolution of many (IgE mediated) but not all food allergies (allergy march). Allergy to milk and egg usually resolves by third year of life whereas allergy to peanuts, seafood and tree nuts are not lost over time and may persist into adulthood.[4] Clinical reactivity is lost more quickly than the loss of food specific IgE measured by prick skin testing or RAST. Children who begin with one allergy eg. Ig E mediated may develop other allergies. The process of outgrowing food allergies varies among individuals and with different foods. Children with food allergy need to be followed up at regular intervals with appropriate oral challenges to determine when they outgrow their food sensitivity. Strict avoidance may help in development of tolerance

Diagnosis of FA presenting with gastrointestinal manifestations

I. History is still the most important tool for the diagnosis of FA. The characteristics of food allergy are persistent symptoms occurring in relation to food involving two or more different organs and an allergic predisposition. Symptoms should follow contact with a food substance that is innocuous to most people. Immune mechanisms should be evident in the pathogenesis, other pathogenic mechanisms should be absent and lesions or functional abnormalities of the gut should be demonstrable.

Clinical scenarios which would raise suspicion of FA[12]

i. Oral pruritus, vomiting, diarrhea immediately after ingestion of a particular food
ii. Mucoid/bloody stools in an infant
iii. Malabsorption/failure to thrive
iv. Chronic vomiting/diarrhea/dysphagia
v. Gastro esophageal reflux disease/chronic constipation recalcitrant to typical therapy
vi. Infantile colic not responding to behavioral interventions.
vii. Gastrointestinal symptoms in a patient with atopy.

II. Laboratory tests[12]

Peripheral eosinophilia and elevated total IgE levels may be present in children with FA but are not diagnostic. The tests which are included in the diagnostic panel are:

1. Immunologic tests: Specific IgE antibody to particular foods and RAST (Radio allegro sorbent test) are used as indicators of sensitization and quantitative measurement of IgE antibody is preferred. RAST has a high false positivity

especially in young infants. Though measurement of specific IgG and IgG4 has been marketed, it is not indicated in a suspected or proven FA.

2. Skin tests: Skin prick tests (SPTs), Prick prick test, scratch test and patch test: These skin tests evaluate sensitization by re-exposing the individual to a minute quantity of antigen. These tests though widely used, are not universally accepted. Children with IgE mediated FA are likely to have positive results however false negativity may be seen in children <3 years. Defined and standardized food antigens should be used for testing to avoid non specific reactions.

3. Adjunctive tests: Endoscopy with biopsy, absorption studies and stool analysis (RBC, leukocytes and eosinophils) help in the diagnosis of the non IgE mediated and mixed forms of FA and also to differentiate it from other causes of esophagitis, enterocolitis, enteropathy and colitis.

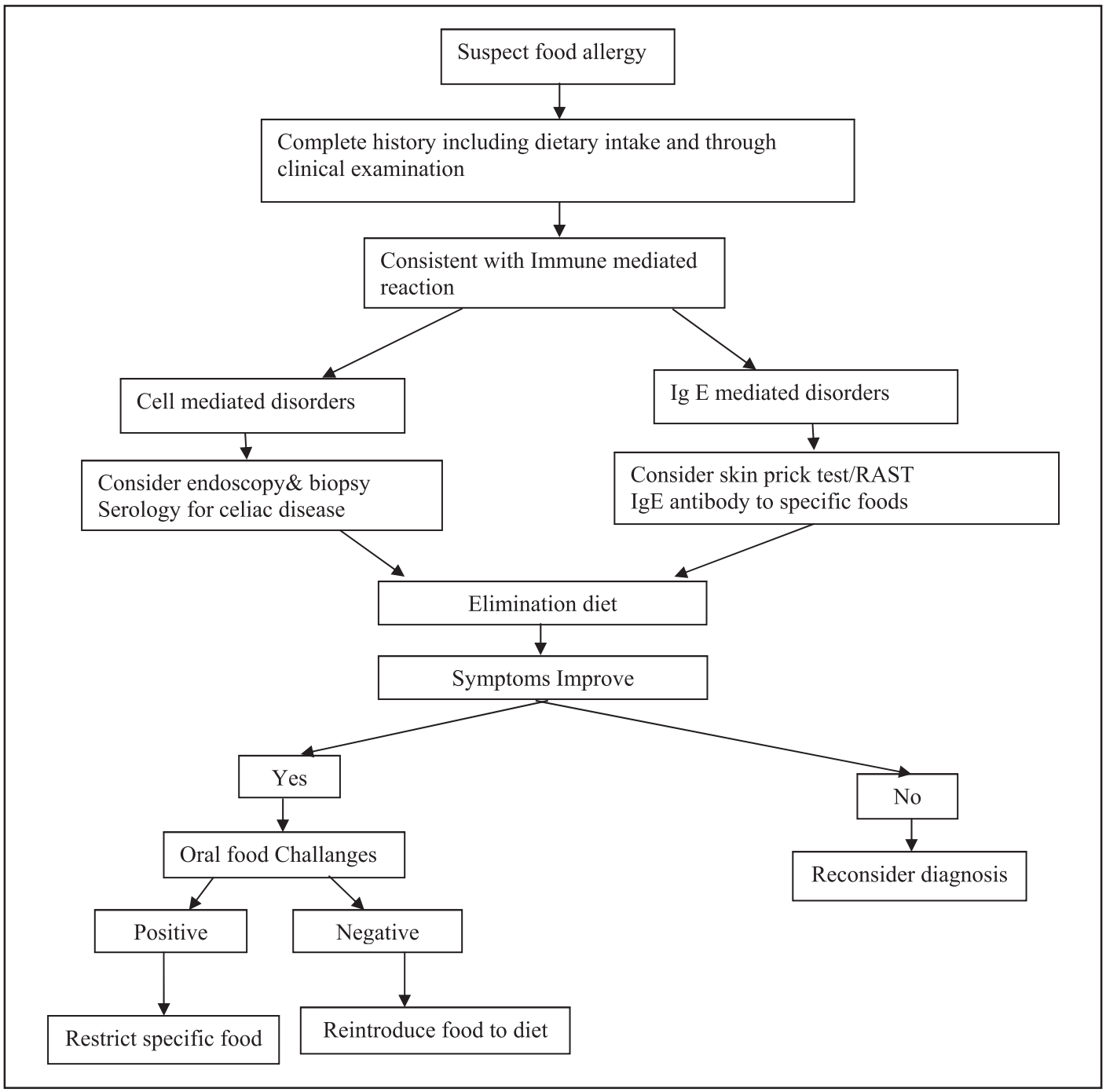

Fig.4. Algorithm for management of food allergy

A practical and simple diagnostic approach to gastrointestinal allergy is

- If an IgE mediated disorder is suspected, selected prick tests or quantification of food specific IgE antibodies followed by an appropriate elimination diet and blinded oral food challenge (OFC) are warranted.
- If a non Ig E mediated GI hypersensitivity disorder is suspected laboratory and endoscopic studies (with or without OFC) are required for diagnosis.

Management[2,12]

Strict dietary elimination of the offending allergen is the only proven therapy. Growth of the child should be properly monitored. In young infants with cow's milk protein allergy hypo allergenic formula may be necessary to maintain proper nutrition. Educating and instructing parents and children regarding reading of labels and introduction of a new food forms an important protocol of therapy. In children with documented FA it is preferable to delay the introduction of one new solid food every 5-7 days. Drugs such as H_1 and H_2 antihistamines and glucocorticoids modify symptoms to FA but overall have minimal efficacy or unacceptable side effects. Knowledge of the natural history of FA helps in selecting the time of challenging or eliminating the specific allergen in the diet. The rule of 1,2,3 is a simple guideline where the least allergenic food is introduced at 6 months of age, cow's milk at 1 year, egg at 2 years, fish, nuts and peanuts at 3 years of age. New immune modulatory therapies such as anti IL-5 have shown promise in eosinophilic disorders. The emerging modalities are food allergen nonspecific and food allergen-specific therapies which are indicated in those with severe anaphylaxis and those who are unlikely to outgrow the allergy. Food allergen nonspecific therapy under evaluation includes monoclonal anti IgE antibodies. The food allergen specific therapies include oral immunotherapy (OIT), sublingual immunotherapy (SLIT) and epicutaneous immunotherapy (EPIT) with native allergens and mutated recombinant proteins. The overall algorithm for management of food allergy is shown in (Fig.4).

Prevention of food allergy

Primary prevention: This strategy is to prevent the onset of IgE sensitization in high risk infants with a significant positive family history. Exclusive breast feeding offers some protection against eczema and asthma but not food allergy when compared with cow's milk protein formulas. Wherever possible exclusive breast feeding should be encouraged till the age of 6 months. Complementary feeds with hydrolysed infant formula may protect high risk infants when breast milk is not sufficient. There is little evidence to suggest that manipulation of the maternal diet during pregnancy and/or lactation has any protective effective on FA. Observational studies suggest that early complementary feeding of solids may increase the risk of allergic diseases but not FA. Dietary interventions such as long chain poly unsaturated fatty acids , antioxidants, prebiotics, probiotics and vitamin supplementation have shown inconsistent results and not broadly recommended.

Secondary prevention: This step is necessary to interrupt the development of food allergy in IgE sensitized children and prevent progression of "Atopy march".

Tertiary prevention: This important step is to reduce the expression of end organ allergic disease in children with food allergy by avoiding allergens and prescribing medications.

Points to Remember

- ***Food allergy should be considered in children with reproducible signs and symptoms in relation to specific food allergen.***
- ***In many children the symptoms may be transient, mild and may be lost with age but in some the reaction is severe and permanent.***
- ***Elimination of the specific allergen without compromising the nutrition is the best therapeutic option.***
- ***History is still an excellent tool in the IgE mediated disorders.***
- ***Endoscopy and histology are useful in a select group of children with FA and should be recommended.***

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BOOK REVIEW

Child abuse and Neglect – Challenges and Opportunities, Edited by Srivatsava R N, Rajeev Seth, Joan Van Niekerk, published in 2013 by Jaypee Brothers Medical Publishers (p) limited, New Delhi, with Foreword by Jenny Gray.

The increasing prevalence and incidence of diverse forms of child abuse and neglect across the globe and more so in India necessitates the publication of this book titled "Child Abuse and Neglect – Challenges and Opportunities" in this year 2013.

The objective of bringing out this book to highlight the challenges in addressing Child Abuse and Neglect has been brought out well by the Indian contributors. The second objective of learning the opportunities in dealing with the same from other countries where systems are in place to address the menace of child abuse with legal as well as political support has also been achieved by including the contributions from many active workers across the globe.

The contents of the book have been appropriately divided into four areas with introduction to the topic by the key crusaders of prevention of child abuse and neglect from National and International Societies.

Section two gives factual details about the extent and forms of child abuse and neglect across the globe including India. Section three describes the currently available protection and prevention strategies keeping the rights of the child in perspective. Section four describes the judicial aspects of the existing acts in India and section five addresses the social and cultural aspects of child abuse and neglect.

The book has rightly brought out the existing challenges that one embarks while addressing the needs of a child who has been abused or neglected with utmost clarity stating the existing situation of helplessness in view of the lack of protocols to proceed. Inclusion of experiences from other countries enables in learning the multiple opportunities from which the new roads can be created to focus on this subject of public health importance.

This book is more a book of social relevance than a medical approach to child abuse and neglect; can be read not only by practitioners of child health but all others who are involved with child welfare.

Absence of bibliography in some of the chapters prevents the readers and researchers from accessing the original works. English language editing would help the book to achieve a flawless status.

This book can be recommended as an introductory book for all those who wish to help children who may be suspected to be subjected to abuse and neglect by adults around them.

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ALLERGIC DISORDERS

COW'S MILK PROTEIN ALLERGY

*Sumathi B

Abstract: *In recent times food allergy is being increasingly recognized in children. Cow's milk protein allergy (CMPA) is an important cause of food allergy in infants and young children due to immunological reactions to one or more milk proteins. The clinical signs and symptoms of CMPA vary from subtle features to frank anaphylactic reactions. Symptoms involving skin, respiratory, gastro intestinal tract can be the presenters feature. Early recognition and prompt intervention is necessary to restore normal growth and development in infants. Response to elimination diet and reappearance of signs and symptoms on reintroduction remains the gold standard test in the diagnosis of CMPA in a clinical setting.*

Key words: *Cow's milk protein allergy, Food allergy, Hypo allergenic formula, Children*

Food allergy has become a health care concern nowadays and cow's milk is a leading cause of food allergy in infants and children. Food allergy is defined as an adverse health effect arising from a specific immune response that occurs reproducibly following exposure to a given food.[1] Cow's milk protein allergy (CMPA) is a disease of infancy which is due to allergy against lactoglobulin, or one or more milk proteins contained in cow's milk. Antigenic stimulation from goat and buffalo milk can also produce symptoms that are indistinguishable from CMPA. Though the management of CMPA is generally straightforward, mismanagement may result in significant morbidity, nutritional deficiencies and rarely anaphylaxis as well. Early recognition of signs and symptoms is important to prevent growth retardation in young infants.

Epidemiology

Between 5% and 15% of infants show symptoms suggesting adverse reactions to cow's milk protein with the highest prevalence during the first year of age.[2] This prevalence then falls to <1% in children 6 years of age and older.[3] Childhood CMPA is more prevalent in boys than girls.[4] Most children with non-IgE mediated CMPA will develop tolerance by 5 years of age, whereas only 42–85% of children with IgE-mediated CMPA outgrow their allergy by 8 years.[5,6] In a study of chronic diarrhea with malabsorption among children from Chandigarh, India, 13% of them had CMPA and most of them were below 2 years.[7] The incidence of CMPA is about 0.5% in exclusively breast fed infants, lower compared to formula fed or infants fed with mixed feeds and symptoms are mild to moderate and severe forms of CMPA is extremely rare in them.[8] Soy protein, is not hypo-allergenic and the incidence of soy allergy in soy formula-fed infants is comparable to that of CMPA in cow's milk formula-fed babies.[9]

Pathogenesis

CMPA results from an immunological reaction to one or more milk proteins.[10] The immune reaction may be immunoglobulin (Ig)E mediated, non-IgE mediated or mixed. Adverse events can be immune mediated resulting in CMPA or non immune mediated like cow's milk protein intolerance (CMPI). This immunological basis distinguishes CMP allergy from other adverse reactions to cow's milk such as lactose intolerance.[11, 12]

Symptoms

Symptoms of CMPA occur often, but not always, within the first weeks after the introduction of cows milk protein. Most of the children develop symptoms in at least two of the following organ systems: gastrointestinal (50-60%), skin (50-60%) and respiratory tract (20-30%).[2] The symptoms associated with CMPA can range from mild, moderate to severe. The GI symptoms of CMPA may be non specific at times. The clinical manifestations can be early or late. Early reactions usually manifest as urticaria, angioedema, vomiting or an acute flare of atopic dermatitis and late reaction may present either with atopic dermatitis or with the gastrointestinal tract involvement. GI involvement may be clinically manifested as gastroesophageal reflux disease (GERD), eosinophilic esophagitis, enteropathy with hypoprotenemia, anemia, allergic proctitis, food protein induced enterocolitis like syndrome. In young infants GERD may be indistinguishable from CMPA. A subset of older children can present with

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GERD, dyspepsia or bloat due to lactose intolerance. Infantile colic in association with CMPA is a subject of controversy, however a subset of infants are likely to be benefited from elimination diet. Although extremely rare, severe anaphylactic reactions to cow's milk protein may also occur following contact with the mouth or lips and clinical features include coughing, wheezing, severe distress, pallor, floppiness and/or collapse.Infants with early reaction are more likely to have a positive skin prick test (SPT; wheal size ≥3 mm) or test positive for specific IgE than those with later reactions.

Food protein-induced enterocolitis syndrome (FPIES)

This is an uncommon non IgE mediated disorder due to cow milk protein, soy, rarely to cereals and meat presenting in infants and characterised by acute onset of repeated projectile vomiting, hypotonia, pallor and sometimes diarrhea 1 to 3 hours after ingestion of cows milk protein and FPIES may be mistaken for acute gastroenteritis, sepsis or intestinal obstruction, This is rare in exclusively breastfed infants. Remission usually occurs by third year of life. Treatment consists of strict elimination of cow milk, substitution with extensively hydrolysed formula (eHF).[13]

Food protein-induced enteropathy

Infants with allergic enteropathy due to cow's milk protein may present with persistent diarrhea, perianal excoriation, abdominal pain, failure to thrive and various degrees of vomiting. Edema and ascites may be present in severe cases due to enteric protein loss.[14]

Food protein-induced proctocolitis

Infants with allergic proctocolitis due to cow's milk protein allergy usually present with mild diarrhea and low-grade rectal bleeding. In infants with exclusively breast feeding, symptoms may be caused by protein transferred via the breast milk. The bleeding is usually observed as stools containing mucus and flecks of blood rather than as frank rectal bleeding. Other systemic features like failure to thrive, anemia are usually absent, and the infants generally appear well.[15]

Role of cow's milk protein in constipation, GERD and infantile colic are controversial. About 40% of infants with symptoms of gastroesophageal reflux disease have allergy to cow's milk protein and are typically not IgE mediated.[16] Constipation may resolve in a proportion of children on withdrawal of cow's milk and cows milk protein-induced constipation is often associated with anal fissures and rectal eosinophilia.[17]

Atopic eczema

Atopic eczema is a chronic, relapsing, pruritic inflammatory disease of the skin, and can be a manifestation of cow milk protein allergy and most often IgE mediated.[18]

Heiner syndrome

This syndrome is a rare food hypersensitivity pulmonary disease that primarily affects infants. It is mostly caused by cow milk. The symptoms include cough, wheezing, hemoptysis, nasal congestion, dyspnea, recurrent otitis media, recurrent fever, anorexia, vomiting, colic, diarrhea, hematochezia and failure to thrive.[19]

Table.I Alarm symptoms and findings indicating severe CMPA as the possible cause[8]

Organ involvement	Symptoms and findings
Gastrointestinal tract	Failure to thrive due to chronic diarrhea and/or refusal of feed and/or vomiting
	Iron deficiency anemia due to occult or macroscopic blood loss
	Hypoalbuminemia
	Endoscopic/histologically confirmed enteropathy or severe colitis
Skin	Exudative or severe atopic dermatitis with hypoalbuminemia or failure to thrive or iron deficiency anemia
Respiratory tract (unrelated to infection)	Acute laryngeal edema or bronchial obstruction with difficult breathing
General	Anaphylaxis

Alarm symptoms as in Table.I, need referral to a specialist for further evaluation and management.

Diagnosis

Diagnosis of cow's milk allergy is difficult due to the wide range of possible symptoms that may occur and in a clinical context diagnosis of CMPI is based either on repeated withdrawal of and challenge with cow's milk, or by demonstration of histological changes on repeated endoscopic biopsies. The double-blind, placebo controlled food challenge is the best way to diagnose but it is difficult to perform and interpret. The gold standard in the diagnosis of CMPI have been the 'Goldman criteria'.[20]

According to these, symptoms should subside following withdrawal of cow's milk and should recur within 48 hours of its reintroduction. Re-challenge is a cumbersome process and in view of risk of serious reaction during repeated challenge in a subset of infants more objective diagnostic criteria, have been suggested i.e. improvement in symptoms on withdrawal of cow's milk, normal or mildly abnormal intestinal histology 6-8 weeks after improvement in symptoms and histologic relapse with or without clinical relapse after 24 hours of re-exposure to cow's milk.[21]

Sigmoidoscopy showing aphthous ulcers is seen in 82% of cases and rectal biopsy is positive in 97% of infants with allergic colitis which provide an initial clue in diagnosis and further confirmed by clinical improvement on elimination diet.[22]

Skin tests

The value of this test is limited since it measures only IgE mediated reactions and thus will yield negative results in patients with non-IgE mediated responses. Patch tests measure non-IgE responses and may be of some value in patients with skin problems resulting from the handling of a particular food but lacks standardization and hence may not be useful in clinical practice.

The RAST (radioallergosorbent) test: This is the best known laboratory test used for detecting circulating IgE

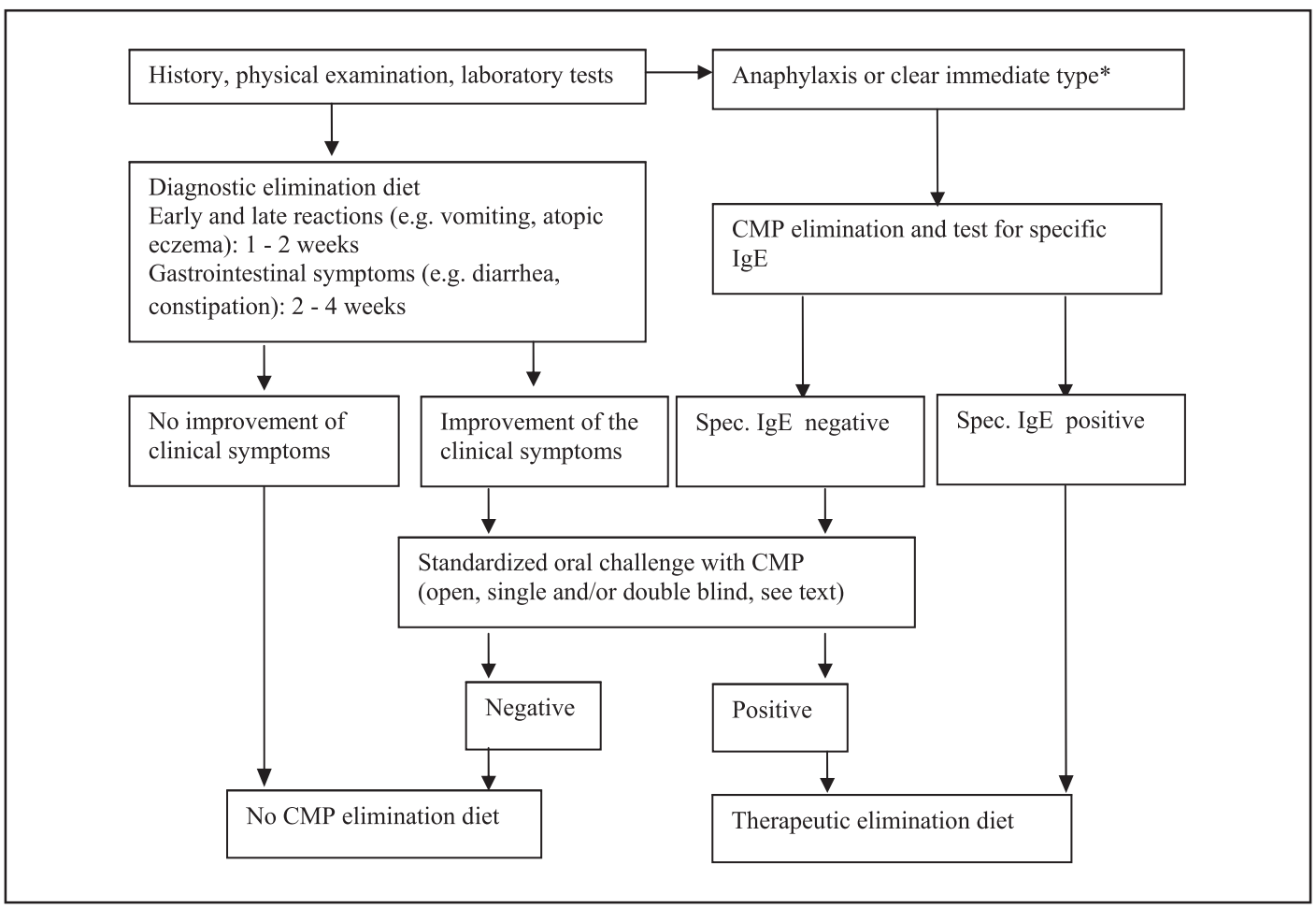

Fig.1. Algorithm for infants and children with symptoms suggestive of cow's-milk protein allergy

antibodies. RAST tests have a number of limitations, for example, they are expensive, can give false positive results, cannot identify individual food triggers in non-IgE mediated food intolerances and a patient with a history of reactions to a food, such as a type of nut, cannot be assessed for intolerance to related foods such as to other nuts.

Measurement of IgG anti-lactoglobulin antibody is not useful in diagnosing CMPI in the Indian setting.[23]

Elimination diet

All suspected foods need to be eliminated for approximately 2 weeks prior to dietary challenge and if symptoms disappear during the elimination period, suspected food items are to be added to the diet, one by one, in small amounts, gradually increasing the dose daily until normal portion size is achieved under medical supervision. The elimination diet should be continued for a minimum of at least 2 weeks, and up to 4 weeks in cases of atopic dermatitis or allergic colitis. The mother will require calcium supplements 1000 mg per day in divided doses during the elimination diet. If the elimination diet fails to improve the symptoms, the mother should resume her normal diet and a referral to a specialist should be considered, depending on the type and severity of the infant's symptoms.

Food challenges

Very small amounts of the suspect food are given orally and then symptoms are observed and this test should only be performed under medical supervision where medical facilities are available.

General guidelines[24]

Currently, the only treatment is strict avoidance; however, a hypoallergenic substitute is necessary at this young age.

Elimination diet is recommended. Currently 3 types of infant formula (soy, extensively hydrolysed formula and amino acid) are available. Selection of the formula depends on the allergy syndrome to be treated, age of the infant. As most of the formula are costly, rice based feeds can be used in infants above six months, along with continuation of breast feeding in our set up. eHF is recommended as first choice for infants under 6 months of age for treating immediate cows milk allergy (non-anaphylactic), food protein-induced enterocolitis syndrome, atopic eczema, gastrointestinal symptoms and food protein-induced proctocolitis.

- Soy formula is recommended as first choice for infants over 6 months of age with immediate food reactions, and for those with gastrointestinal symptoms or atopic dermatitis in the absence of failure to thrive.
- Amino acid formula is recommended as first choice in anaphylaxis and eosinophilic oesophagitis. Amino acid-based formula (AAF) is therefore suggested as the first-line treatment choice in infants with previous cow's milk anaphylaxis unless exposure to soy, eHF have been done under medical supervision.
- If treatment with the initial formula is not successful, use of an alternative formula is recommended

The strict avoidance of CMP is presently the safest strategy for managing CMPA.

The best choice of a formula depends mostly on the age of the patient and the presence of other food allergies. Children with CMPA that continues beyond the first 12 months of age need individualized nutritional advice with adequate supply of nutrients especially proteins, calcium, vitamin D and vitamin A. Those infants with an immediate allergic reaction presenting with generalized urticaria, angioedema or acute vomiting without cardio respiratory involvement should be managed with strict avoidance of CMP and replaced with an extensively hydrolysed formula (eHF) especially in infants less than 6 months of age. A soy based formula may be considered in infants above 6 months of age. Mothers should be encouraged to continue breastfeeding and about 10% of infants do not tolerate eHF and require transition to an amino acid-based formula (AAF). Approach to infants and children with symptoms suggestive of cow's milk protein allergy is summarised in (Fig.1). [25]

Points to Remember

- ***Cow's milk protein allergy is an important cause of food allergy in infants and young children.***
- ***More than two organ system can be involved and the reactions may be IgE or non IgE mediated one.***
- ***Clinical symptoms may vary in severity and may be non specific at times.***
- ***Early recognition of signs and symptoms is essential to have a favourable outcome.***
- ***High index of suspicion, clinical improvement on milk withdrawl and reappearance of symptoms on challenge remain the gold standard test in diagnosis.***
- ***Exclusive breast feeding, avoidance of early introduction of allergenic items are likely to reduce the condition.***

- ***Soy based formula, extensively hydrolysed formula, aminoacid formula are currently available to tackle CMPA.***

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ALLERGIC DISORDERS

DRUG ALLERGY – AN OVERVIEW

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Abstract: *Drug allergy is an immunologically mediated adverse drug reaction. It is classified based on the type of hypersensitivity reaction and timing of onset of reaction. Immediate reactions are IgE mediated and delayed reactions are non IgE mediated. A detailed history, review of records and clinical examination are necessary but not sufficient to confirm drug allergy. Skin testing is helpful in diagnosing type I drug hypersensitivity reactions but it is standardized only for few drugs. Treatment of drug allergy includes withdrawal of the offending drug and timely management of anaphylaxis and other life threatening conditions. Options for continuing treatment include use of alternative drug or desensitization.*

Keywords: *Drug allergy, Drug hypersensitivity, Graded challenge, Desensitization.*

Drug allergy is over reported by patients but after careful evaluation only a small proportion of these patients have true drug allergy. Misdiagnosis could lead to escalation of treatment cost, exposure to potentially toxic drugs and risk of developing drug resistance.

Adverse drug reaction is an undesirable effect of a drug beyond its intended or beneficial effects. Most adverse drug reactions are predictable that includes side effects, drug interactions and overdose. Adverse drug reactions that are not predictable and occurs in a smaller subset of population includes drug allergy, drug intolerance and idiosyncrasy (Fig.1).

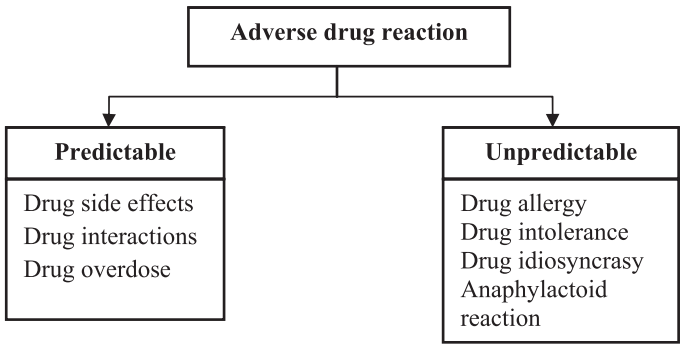

Fig.1.Types of adverse drug reactions

Drug allergy[1] is defined as an immunologically mediated response to a pharmaceutical agent in a sensitized person. Allergic drug reactions accounts for 6 to 10 percent of all adverse drug reactions but up to 10 percent of fatal reactions.[2]

Drug intolerance is defined as an undesirable pharmacologic effect that may occur at low or usual doses of the drug, eg., aspirin induced tinnitus at low doses. This putatively reflects altered drug metabolism or increased end organ sensitivity.[3]

Drug idiosyncrasy is an abnormal and unexpected effect that is unrelated to the intended pharmacologic action of a drug and has an unknown mechanism. These reactions can arise from genetic differences in the patient such as primaquine causing hemolysis in G6PD deficiency.[4]

Classification of drug allergy

1. Classification based on type of Immunological reaction

Immunologic mechanisms of drug allergy can be stratified according to the Gell and Coombs classification of hypersensitivity.

Type I (IgE mediated or immediate hypersensitivity eg., anaphylaxis) The time course is usually seconds to minutes for drugs administered parenterally and up to 1 hour for drugs taken orally.

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Type II (antibody dependent cytotoxic hypersensitivity) is typified by hemolytic anemia due to antibodies formed against cell bound drug such as erythrocyte bound penicillin.

Type III (Immune complex mediated hypersensitivity) is typified by serum sickness syndrome. Clinical manifestations appear 1 to 2 weeks after administration of the drug in the form of fever, rash, arthralgia and lymphadenopathy. Usually prognosis is good and the condition may require treatment with steroids and antihistamines.

Type IV (T-cell mediated delayed hypersensitivity reaction) is often mediated by activated T cells and in some cases other cell types like eosinophils, neutrophils and macrophages are also involved. Hence type IV reactions were further sub-classified into IVa to IVd reactions depending upon the cell type involved.[5] Type IV reactions are implicated in the pathogenesis of the following diseases with prominent skin manifestations.

Contact dermatitis occurs primarily in relation to cutaneous exposure and hence is seen only with topically applied drugs, eg. Neomycin.

Stevens Johnson Syndrome is characterized by fever, mucous membrane involvement and sloughing of epidermis up to 10% of body surface area.

Toxic Epidermal Necrolysis (TEN) is a life threatening febrile illness characterized by diffuse necrosis and sloughing of cutaneous and mucosal epithelial surfaces involving >30% of body surface area. Visceral involvement accounts for a mortality rate of up to 40%.

DRESS (Drug Rash with Eosinophilia and Systemic Symptoms) is a severe drug hypersensitivity reaction involving skin rash, fever and multi organ failure[6] Several antiepileptic medications have been implicated in causing DRESS syndrome.

Morbilliform eruptions are common and may arise from type IV immunologic reactions as well as from other mechanisms.

Other types of reactions

Anaphylactoid reactions are clinically indistinguishable from anaphylactic reactions but are not IgE mediated, eg. radio-contrasts used for imaging studies.

Fixed drug eruptions are macular, non pruritic, violaceous skin eruptions that occur at the same location on the body with each exposure to a given drug. Common offending drugs are analgesics, barbiturates, beta-lactam antibiotics, sulphonamides and tetracycline.

2. Classification based upon timing of symptom onset

The World Allergy Organization (WAO) has recommended dividing immunologic drug reactions into a) immediate reactions, i.e., onset within one hour of exposure and delayed reactions, i.e., onset after one hour based upon the timing of the appearance of symptoms.[7] The distinction between immediate and delayed drug reactions is intended to differentiate IgE-mediated type I reactions from other types.

Risk factors for drug allergy In a given individual it is difficult to predict the likelihood of developing drug allergy. But there are some factors which are known to increase the risk. These factors may be drug related or host (patient) related.

Drug factors

Nature of the drug: Although numerous drugs have been implicated in the production of allergic reactions, penicillins, aspirin, and sulphonamides account for over 80 percent of allergic drug reactions.

Degree of exposure (dose, duration, frequency: Risk of drug allergy is more likely in patients receiving intermittent courses compared to patients receiving continuous course of the same drug. During a single course of treatment, the likelihood of a reaction is greater during the first two or three weeks of therapy.

Route of Administration: Topical application of a drug is associated with a high incidence of sensitization and should be avoided with certain drugs like neomycin. Oral administration of a drug is generally safer than any type of parenteral administration. However, severe reactions have been reported following this mode of administration.

Cross-Sensitization: Once sensitization to a drug has occurred, there is a possibility of reactivity either to drugs with a close structural chemical relationship or to immunochemically similar metabolites. Classical example is cross-reactivity between penicillins and cephalosporins.

Host Factors

Age and sex: Some allergic reactions to drugs are probably less frequent in children and elderly patients, possibly owing to immaturity or involution of the immune response. Women are at greater risk than men for allergic reactions to some drugs for reasons that are not well-defined.

HLA type: There is evidence for a familial propensity to develop immunologic drug reactions.[8] Data on a variety of drugs and severe drug allergies demonstrated that certain HLA-B alleles represent highly significant risk factors for severe side effects to a particular drug.

Previous drug allergy: Patients who have experienced drug hypersensitivity in the past may have an increased tendency to develop sensitivity to new drugs and one should be more cautious in medicating such patients.

Multiple Drug Allergy Syndrome[9]: The term has been used to describe persons who had experienced well-documented immunologic drug reactions to two or more chemically unrelated medications.

Atopy: Contrary to popular belief, presence of atopic diseases is not a risk factor for drug hypersensitivity. But, once an atopic individual develops drug hypersensitivity he is at risk of developing more severe reactions.

Concurrent medical illnesss: Certain infections appear to be associated with the increased likelihood of drug hypersensitivity, eg., ampicillin induced maculopapular rashes in patients with infectious mononucleosis (EBV infection).

Approach to drug allergy

In suspected drug allergy the history is a very useful tool. Firstly we have to establish whether it is really a drug allergy or not and secondly if it is drug allergy to establish what is the nature of reaction and the severity of the reaction.

1. What were the signs and symptoms? In what order did they appear and resolve?

2. What was the time course of the reaction? Time interval from administration of drug and the onset of reaction, time to peak reaction and time to resolve after stopping the drug.

3. What was the illness at the time of drug administration? Sometimes an exanthematous rash following a viral infection will be considered as a drug allergy.

4. What other drugs or unusual food products (like mushroom or peanut) that have been taken at the same time?

5. Has the patient ever received the drug in the same or related class before? If so, how longs ago and what was the outcome? Look at the previous prescriptions of the patient's drugs. The patient might have taken the same drug in a different brand name without any reaction.

6. Has the patient ever had a history of any other drug reactions in the past?

Limitations of the clinical history: History alone is not sufficient for diagnosing current drug allergy. Studies performed on large series of patients with positive history of drug allergy have shown that only less than 20 percent actually react to the offending drug on direct challenge.[10]

Diagnostic tests

Diagnostic testing may be appropriate for some allergic reactions. Skin testing for type I reaction is extensively used but it is not standardized for most drugs except penicillin. Majority of in vitro test for drug allergy are investigational.

Prick (puncture) and intradermal tests used for IgE-mediated drug reactions. A positive skin test suggests that the patient may be at risk for IgE-mediated reactions. Skin test with high negative predictive value rules out the possibility of allergic hypersensitivity. Skin tests are not valid for 2-4 weeks after an episode of acute anaphylaxis (refractory period). For safety, prick tests must be negative before proceeding with intradermal tests.

Patch test: Used to identify the culprit drug in contact dermatitis, a type IV reaction.

Invitro immunoassays (e.g., RAST, Immunocap): are available, although most are not adequately standardized.

Graded challenge (Incremental provocative test dosing): Graded challenge or test dosing involves administering a medication to a patient in a graduated manner under close observation. Graded challenge is done only for patients who have a low risk for severe reaction. Unlike desensitization, graded challenges usually involve fewer doses, are of shorter duration, and not intended to induce tolerance. Graded challenge remains the only absolute method to establish or exclude an etiologic relationship between most suspected drugs and the clinical manifestations produced.

Treatment of allergic drug reactions

General principles

Withdrawal of the suspected drug is the most helpful diagnostic maneouver. At the same time, it is also the treatment of choice. Frequently, no additional treatment is necessary and the clinical manifestations often subside with

this. Severe reactions like anaphylaxis and exfoliative dermatitis (Steven Johnson syndrome, TEN) will need specific management.

Available options for continuing treatment

Administration of an unrelated medication: In case of penicillin allergy, a non beta-lactam antibiotic can be administered. But issues relating to cost effectiveness, drug toxicity and drug resistance need to be considered. In severe non anaphylactic reactions like Stevens Johnson Syndrome, administration of alternative medication remains the only option.

Administration of a related medication: Cephalosporins can be administered in patients with penicillin sensitivity. Since both the drugs got similar structure, there is a risk of cross sensitization. The patient would require skin testing and / or graded challenge before administering the new drug.

Desensitization: involves the conversion from a highly sensitive state to a state in which drug is tolerated. This produces a temporary non responsive state lasting as long as therapy is uninterrupted. If therapy is interrupted, anaphylactic sensitivity may return within 48 hours of stopping the drug. Acute desensitization with agents involves the administration of gradually increasing doses of the drug over several hours or days after starting with doses as low as 1/1,000,000 to 1/100,000 of the therapeutic dose. Both oral and parenteral routes have been used for desensitization.

Desensitization is classically used for type I IgE mediated allergy and it may be attempted with variable success to other types of drug reactions (Fig.2).

Specific drug allergies

Beta- lactam antibiotics

Penicillin: Preferable management of patients with true penicillin allergy is to administer an equally effective, non-cross reacting antibiotic. Approximately 10 percent of patients report penicillin allergy. However up to 90 percent of these individuals are able to tolerate penicillin and wrongly designated as having penicillin allergy.[11]

Penicillin is a low molecular weight compound and it is immunologically inert. It requires conjugation with tissue proteins to elicit immune response. About 90 percent is conjugated with lysine residues to form benzylpenicilloyl poly-L-lysine (PPL), termed as 'major antigenic determinant.' Rest of the penicillin conjugates, i.e., benzylpenicillin, benzylpenicilloic acid and benzylpenicilloate are termed as 'minor antigenic determinants'. Penicillin skin test is reliable if it is done with the testing kit having both the major and minor antigenic determinants. Negative test effectively rules out penicillin allergy as the negative predictive value is 99 percent.

Currently penicillin testing kit is not commercially available in India. If only benzylpenicillin is used for skin testing, a negative test does not rule out penicillin allergy. Therefore evaluation of penicillin allergy is based on history of previous reaction. If the reaction was vague and the likelihood of allergy is low then one has to proceed with graded challenge. If the risk of reaction is high it is better to use alternative drug. If there is a definite need to administer penicillin in an allergic individual, tolerance can be induced by desensitization. Oral penicillin desensitization is safe and effective. After oral desensitization, penicillin can be administered even through the parenteral route.

Ampicillin and amoxicillin: Can cause two types of skin rash, an early onset allergic urticarial rash or a late onset non allergic maculopapular rash. Patients with the maculopapular ampicillin rash are often incorrectly labeled as allergic to ampicillin/penicillin. Ampicillin can be continued and administered again in the future in these patients. This maculopapular rash could be due to concurrent viral infections and the rash resolves spontaneously in a few days without sequelae.

Cephalosporins: Compared to penicillins the overall reaction rate is 10 times less. Only 2 percent of penicillin allergic patients develop reactions with cephalosporins.[1]

Carbapenems: Cross reactivity with penicillin has been documented but is very rare.

Monobactam: Aztreonam does not cross react with penicillin.

Non beta-lactam antibiotics

Vancomycin: IgE mediated reaction is rare with vancomycin. Red man syndrome is due to non IgE mediated histamine release pseudo allergic reaction. The reaction could be prevented by premedication with antihistaminic and administering the drug by slow infusion.

Sulphonamide: Usually cause non IgE mediated delayed maculopapular rash. The risk of reaction is higher in patients with HIV infection.

Other drugs

Aspirin exacerbated respiratory disease (AERD): Describes patients with asthma and chronic rhinosinusitis

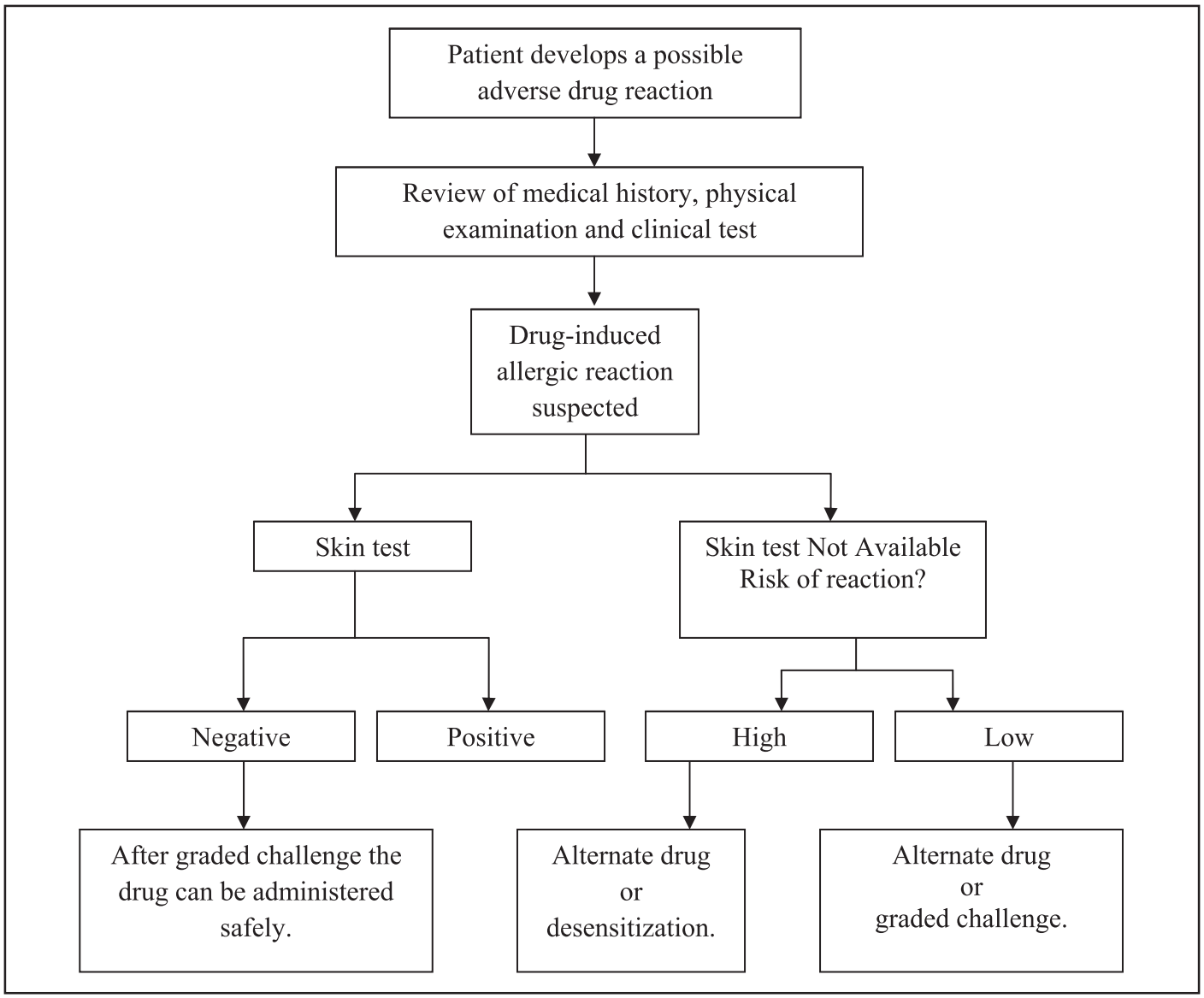

Fig.2. Approach to drug allergy

with nasal polyposis, who experience acute respiratory tract symptoms following the ingestion of aspirin or other NSAIDs. AERD affects 5 to 20 percent of all patients with asthma. It is a pseudo allergic reaction as it is not an IgE mediated reaction and is due to COX-1 inhibition. AERD can be successfully treated by aspirin desensitization.

Local anaesthetic agent: Reactions are usually non allergenic. In case of suspected allergy, skin testing is performed and then if negative the drug is administered safely after graded challenge.

Radio contrasts: Can cause anaphylactoid reactions by direct histamine release which could be prevented by premedication with antihistamines. The risk of reaction is lower with low molecular weight radio contrast material.

Conclusion

True drug allergy is not common and majority of patients labelled as allergic can tolerate medications after evaluation. Withdrawal of the offending agent and treatment with safe alternative medication is the mainstay of the management of drug allergy. In case of IgE mediated drug reaction, desensitization is done if there is no safe and effective alternative drug.

Points to Remember

- ***Drug allergies are over reported by patients.***
- ***Diagnosis of suspected drug allergy should be always confirmed after thorough evaluation.***
- ***Wrong diagnosis can lead to escalation of treatment***

costs, exposure to potentially more toxic drugs and there is also risk of developing drug resistance.

- ***Withdrawal of offending drug is the simplest and the most effective first step in the management of drug allergy.***
- ***Graded challenge and desensitization procedures are contraindicated after serious non anaphylactic reactions like Steven Johnson Syndrome.***

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CLIPPINGS

Cochrane review

Prebiotics in infants for prevention of allergic disease and food allergy

Prebiotics (commonly oligosaccharides) added to infant feeds have the potential to prevent sensitisation of infants to dietary allergens.

Objective of the analysis was to determine the effect of prebiotic given to infants for the prevention of allergy.

Further research is needed before routine use of prebiotics can be recommended for prevention of allergy in formula fed infants. There is some evidence that a prebiotic supplement added to infant feeds may prevent eczema. It is unclear whether the use of prebiotic should be restricted to infants at high risk of allergy or may have an effect in low risk populations; or whether it may have an effect on other allergic diseases including asthma.

Osborn DA, Sinn JKH. Prebiotics in infants for prevention of allergy. Cochrane Database of Systematic Reviews 2013, Issue 3. Art. No.: CD006474. DOI: 10.1002/14651858.CD006474.pub3. Published Online: March 28, 2013.

ALLERGIC DISORDERS

ALLERGIC RHINITIS

***Gowrishankar NC**

Abstract: *Allergic rhinitis (AR) is a common problem in children frequently underdiagnosed and undertreated. The classical symptoms are nasal obstruction, sneeze, rhinorrhea and nasal itch. AR affects quality of life by mainly affecting sleep and causing day time somnolence which in turn interferes with scholastic performance in school.AR is generally managed by allergen avoidance, which in reality is rarely feasible, drug treatment, which is mainly based on antihistamines and topical corticosteroids and allergen-specific immunotherapy.*

Keywords: *Allergic rhinitis, Clinical features, Management.*

Rhinitis is defined as inflammation of the membranes lining the nose. It is characterized by nasal congestion, rhinorrhea, sneezing, itching of the nose and/or post-nasal drainage. An important risk factor for rhinitis is atopy and allergic rhinitis (AR) is the most common form.[1] It is, the most common chronic disorder in the pediatric population and is IGE dependent. AR may also be one of the steps of the allergic march, which starts with atopic dermatitis and food allergy and includes atopic asthma. AR and asthma are frequently associated. Like in most countries in India, AR still does not receive the attention it deserves by both patients as well as clinicians.[2] AR is frequently under-diagnosed and undertreated. Though AR is not life threatening, it has a deleterious effect on the quality of life and school performance. The International Study of Asthma and Allergies in Childhood (ISAAC) phase one data from India revealed that nasal symptoms alone were present in 12.5% children in the 6-7 years age group and 18.6 % in the 13-14 years age group.[3]

Initially patients with perennial rhinitis were divided into two groups mainly based on their predominant symptoms. "Sneezers" were those whose predominant symptoms were sneezing and watery discharge while "Blockers" were those with nasal block and thick mucus secretion as their main symptoms.[4] "Blockers" are troubled by severe nasal blockage and thick nasal mucus which often leads to post nasal drip and breathlessness. The symptoms are constant day and night but may worsen during the night.

The next improvement in the classification was "seasonal allergic rhinitis (SAR)" and "perennial allergic rhinitis (PAR)", based on the time of occurrence of symptoms during the year. Seasonal allergic rhinitis ''hay fever'' is seen commonly in spring and early summer and is usually triggered by pollens. In "perennial allergic rhinitis", symptoms occur year round and is triggered by house dust mite, pollens and pet animals. In 2002, the World Health Organization (WHO) Allergic Rhinitis and its Impact on Asthma Workshop (ARIA) formulated the clinically relevant grading of rhinitis symptoms. The ARIA workshop report proposed that the disease be categorized as "intermittent" and "persistent" while severity was classified as "mild" and "moderate-severe". This new classification is based on number of days per week and number of weeks per year during which the patient is symptomatic. The updated ARIA document reiterates that AR should be sub divided into "intermittent" or "persistent" and severity be classified as "mild" or "moderate/severe"(Table I)[5]

Pathophysiology

In AR the symptoms occur due to early and late phase reactions. The early phase reaction will occurs within minutes of allergen exposure in sensitized subjects. Following the initial sensitization, the allergic response occurs upon subsequent exposure to the allergen. When allergen binds to the primed mast cell it causes the IgE molecules on the mast cell surface to crosslink. This opens up the calcium channels thus activating the mast cell. The mast cell not only releases the preformed mediators – histamine and proteases but also synthesise and release new mediators including leukotrienes,prostaglandin and platelet activating factor etc. the late phase reaction can take anywhere from 2-12 hours after exposure to allergen wherein nasal congestion is the the predominant symptom. The reaction occurs due to recruitment of eosinophils predominantly among other inflammatory cells which infiltrate the nasal mucosa. Mediators released from eosinophils maintain the inflammation and thus the symptoms.

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Table I. Classification of allergic rhinitis.[6]

1. Duration -	Intermittent	- Symptoms present < 4 days/week or < 4 weeks
	Persistent	- Symptoms present > 4 days/week or > 4 weeks
2. Intensity	Mild	- none of the following are present:
	Sleep disorder	
	Impairment of activities of daily living, leisure or sports	
	Impairment of activities at school or work	
	Unbearable symptoms	
	Moderate-to-severe	- one or more of the following are present
	Sleep disorder	
	Impairment of activities of daily living, leisure or sports	
	Impairment of activities at school or work	
	Unbearable symptoms	

Exposure to allergen in sensitised individuals can lead to release of inflammatory mediators through Immunoglobulin E (IgE)- dependent mechanism. Also if allergen exposure continues it can induce nasal airway hyperresponsiveness (NAHR), a hallmark of AR. NAHR is a pathophysiological state whereby the response of the nasal airway to both allergen and mediators (such as histamine and bradykinin) is increased compared with normal.

The ''united airways'' concept suggests that upper and lower airways inflammatory processes such as asthma and rhinitis are of a similar type. Rhinitis may influence asthma through various mechanisms, including: 1) the release of mediators into the airways or peripheral circulation; 2) neural reflexes; 3) increased production of bone marrow progenitors of inflammatory cells; 4) increased lower airway exposure to airborne contaminants from mouth breathing; and 5) increased need for conditioning the inspired air.[7]

AR and its effect

Nasal congestion is one of the most common and bothersome symptom of rhinitis. It can be a cause for impairment of sleep and sleep-disordered breathing. AR also can affect learning as a consequence of the frequent sleep disturbances and resulting daytime sleepiness. When sleep is affected it leads onto daytime sleepiness, fatigue and significant impairment in learning and cognition. All these leads onto school absenteeism, ''presenteeism'' (inattention, distraction, lack of concentration), irritability and restlessness, mood disturbances and even social and family problems that can further contribute to worsening school performance. AR also has a financial impact, as it is a possible causal factor of comorbidities such as asthma, sinusitis, otitis media, allergic conjunctivitis, eczema , sleep disordered breathing.[8,9,10]

Symptoms

Watery rhinorrhea, sneezing especially paroxysmal, nasal obstruction, nasal itching, itching of the eyes are the cardinal symptoms. If two or more of the above symptoms are present for more than one hour it is suggestive of allergic rhinitis. If the child has mouth breathing it can imply nasal obstruction. The presentation can be non-specific, with features such as ''fuzzy'' head, tiredness and daytime sleepiness, constant ''colds'', sniffing, blinking and eye rubbing, speech problems, snoring and dark circles under the eyes. The dark circle around the eyes 'Allergic shiners' is the result of venous congestion due to pressure on the draining veins by edematous allergic mucous membranes of nasal and paranasal sinuses.

'Dennie Morgan folds' are creases in lower eyelid due to Mueller's muscle spasm. A horizontal crease over the bridge of the nose indicates that the child constantly tries to keep off the watery secretions from coming out of the nose by rubbing the palm of the hand over the nostril. This produces the 'horizontal crease (allergic salute)' if this rubbing continues for prolonged period of time. Examination of the nose with nasal speculum can reveal enlarged turbinates with pale-bluish mucosa due to edema, clear nasal discharge but sometimes purulent and rarely nasal polyps. 'Cobble stone appearance' of the pharynx implies that the child has constant post nasal drip. Discoloration of frontal incisors, high arched palate and malocclusion associated with chronic mouth breathing may be seen in untreated AR

children. Also the child's voice will have a nasal quality and the tympanic membrane will be retracted in many children with allergic rhinitis. The eyes can have marked erythema of palpebral conjunctivae and papillary hypertrophy of tarsal conjunctivae. Chemosis of the conjunctivae, usually with a watery discharge can be seen in severe allergic rhinoconjunctivitis. Examination of the ears can reveal chronic infection or middle ear effusion or retracted tympanic membrane.

Rhinitis symptoms are characteristically nasal obstruction and rhinorrhea, with AR also featuring sneezing, itchy nose, eyes and throat.

Diagnosis of allergic rhinitis is clinical. But investigations are done when history is not typical. It includes nasal smear, complete blood count with differential, serum IgE. If the eosinophils are 20% or more in differential count with an elevated IgE value it is suggestive of the diagnosis. Alkaline nasal pH with more than 5 eosinophils per high power field in nasal mucosal scraping it also adds to the diagnosis. In the allergen-specific IgE testing [(radioallergosorbent test RAST)]: Can be helpful if a specific allergen is suspected skin prick testing: Highly sensitive and specific for aeroallergens. imaging studies are usually not needed in pediatric allergic rhinitis.

The diagnosis is made if 2 or more of the following symptoms for more than one hour on most days- Watery rhinorrhea, sneezing paroxysmal, nasal obstruction, nasal pruritis with or without conjunctivitis. Once the diagnosis is made then it has to be classified according to the severity as given in Table II.

Table II. Classification of allergic rhinitis

a) mild intermittent AR
b) mild persistent AR
c) moderate to severe intermittent AR
d) moderate to severe persistent AR

Treatment

Management of allergic rhinitis includes a) avoidance of allergens or environmental controls b) medications c) allergen-specific immunotherapy.[11]

Avoidance of allergens: The most important aspect of managing allergic rhinitis is allergen avoidance. The results of cutaneous or in vitro testing can be used to direct specific avoidance measures .This measure can substantially reduce symptoms and reliance on medication. Most often children with AR are often sensitive to more than one allergen. Air conditioning can dramatically relieve symptoms in those who are allergic to outdoor pollen. Air conditioning also significantly reduces mold spore and dust mite allergen levels by reducing indoor humidity.[13] Dust mites which are microscopic and rely on the indoor heat and humidity for survival and proliferation is a major source of allergens in house dust. Reducing indoor relative humidity, removing carpets, covering pillows and mattresses in impermeable covers and washing the bed linen weekly in hot water are some of the measures to reduce the dust mite exposure.[12]

For those who are allergic to dogs and cats dander the only available option is to remove them from home.But it will not bring in immediate benefit clinically as the allergens can persist for several months.[13] When it is not possible to remove pets from the home, second-best measures include excluding the pet from the allergic person's bedroom, using high-efficiency particulate air (HEPA) cleaners or electrostatic air cleaners, and removing carpets and other upholstered items that can serve as a reservoir for allergens. Although allergen reduction may be transient and the potential for clinical benefit has not been clearly established, bathing the pet (cat or dog) also might help.

Pharmacotherapy: Most often it may not be possible to avoid allergens in day to day life. Hence, medications will be needed in most if not all children with allergic rhinitis. The drugs used in AR includes oral or inhaled H1 antihistamines, intranasal corticosteroids and leukotriene receptor antagonists.

Antihistamines antagonize the action of histamine by blocking receptor sites on target cells. First-generation antihistamines are efficacious,but associated with drowsiness. Second-generation antihistamines which are lipophobic and hence have less CNS penetration are generally preferred. Second-generation antihistamines include fexofenadine, levocetirizine, loratidine, desloratidine, cetirizine and intranasal azelastine and olapatidine. To relieve nasal congestion topical decongestants are very effective but rebound congestion can occur as vasoconstrictive action of these agents decreases. With continued usage the decongestive action decreases and the nasal obstruction increases. This is believed to be due to down-regulation of α-adrenergic receptors. Topical decongestants usually should generally be used for about three days and stopped.

The most important and effective medication for treatment of AR is intranasal corticosteroids. Intranasal corticosteroids cause vasoconstriction and reduction of mucosal edema, inhibition of mediator release, suppression of cytokine production and inhibition of inflammatory cell infiltration and hence very effective in reducing nasal

congestion, rhinorrhea, sneezing and also ocular symptoms with minimal side effects. The therapeutic benefit of intranasal corticosteroids is statistically superior.[14]

INCS has to be delivered in to the nostrils in the proper way for getting optimal control. Before using INCS the nostrils are cleared off the secretions. The nozzle of the INCS spray is kept just inside the nose and the spray is directed towards the mucosa of the inferior turbinate on both sides.[15] The systemic bioavailability of the INCS is minimal. Intranasal steroids not only relieve nasal symptoms and ocular itch in allergic rhinitis but also the itchy ear and palate which are also common and bothersome symptoms.[16]

Oral leukotriene receptor antagonists (LTRA) also form part of the therapeutic armamentarium in allergic rhinitis. The efficacy of LTRA equals that of oral antihistamines but LTRA are not associated with wheal-and-flare suppression. But as many with allergic rhinitis also have concomitant asthma LTRA can be used to treat both. Treatment with intranasal corticosteroids has been shown to significantly reduce nasal congestion in AR patients and in those with congestion, they should be considered the drug of choice. Montelukast may be a second-line therapy in those intolerant to intranasal corticosteroids. In turn, sedating antihistamines should be avoided, as they may amplify the sedation and decrease productivity in those already compromised. The dosage of monteleukast sodium is 4 mg for 6 months to 5 years, 5 mg for 6 years to 14 years and 10 mg for those beyond 15 years.

Based on the severity of allergic rhinitis medications are chosen as given in Table III.

It is always necessary to review the child 2- 4 weeks after starting medications. If the symptoms decrease and the child is better, medication is continued for one more month and stopped. But if on the contrary there is no improvement, the treatment needs to be stepped up. In moderate to severe persistent AR if there is no improvement, first the compliance to the medication is checked. If the compliance is good then the dose of intranasal corticosteroid is increased. If there is nasal itch, H1 antihistamine is added. If nasal blockage is present, a short course of decongestant is added. If there is a failure, the diagnosis of AR has to be reconsidered. Table IV shows the commonly used intranasal steroids, dosage and the age from which it can be used.

Allergen-specific immunotherapy

Only immunotherapy with the right allergens has the potential to alter the natural history of the allergic march, by preventing the development of new allergen sensitizations and reducing the risk for the subsequent development of asthma. At present allergen immunotherapy is considered in patients with severe AR, insufficiently controlled by pharmacotherapy and who demonstrate specific IgE antibodies to relevant allergens. This modality of treatment has been proposed to have many advantages the foremost being that it can cure allergy symptoms. The prerequisite before this form of therapy is to find out the allergens by skin prick test. Then the child is exposed to small amounts of allergen gradually over a period of time so that tolerance to that particular antigen is induced. The treatment process usually is 4-5 years. It needs to be noted that it takes atleast 6 months to appreciate clinical improvement. Sublingual immunotherapy is a new addition in this form of therapy wherein small amounts of allergen are placed under the tongue on a daily basis. The main advantages are that treatment can be given at home and no injections are necessary. Sublingual immunotherapy is well tolerated.[17]

Table III. Treatment of Allergic rhinitis

Type	Drugs
Mild intermittent	# Oral or intranasal H1 antihistamines +/- oral decongestents / LTRA
Moderate – severe intermittent	# Oral or intranasal H1 antihistamines +/- oral decongestents / LTRA/ Intranasal corticosteroid
Mild persistent	# Oral or intranasal H1 antihistamines +/- oral decongestents / LTRA/ Intranasal corticosteroid
Moderate to severe persistent	* Intranasal corticosteroid Oral antihistamines / LTRA

Not in preferred order

* In preferred order

Table IV. Commonly used intranasal steroids and dosages

Drugs	Dose	Indications	Age
Mometasone furoate Each spray (50µg)	2 to 11 years : 1 spray / nostril OD > 12yrs : 2 sprays / nostril OD	Allergic rhinitis, Nasal Polyps and Acute Rhinosinusitis	> 2 yrs
Fluticasone proprionate Each spray (50µg)	4 to 12 years : 1 spray / nostril OD > 12 years : 2 sprays / nostril OD	Allergic rhinitis	> 4 yrs
Fluticasone furoate Each spray (27.5µg)	2 to 12 years : 1 spray / nostril OD ≥12 years : 2 sprays / nostril OD	Allergic rhinitis	> 2 yrs

To conclude epidemiologic data shows a high and increasing prevalence of allergic rhinitis throughout the world and AR is frequently seen in children. Though the first step in AR management is allergen avoidance most often it is rarely feasible. Hence, medications form the mainstay of treatment with allergen specific immunotherapy offering a glimmer of hope with its capacity to modify the natural course of the allergic disease.

Points to Remember

- ***Allergic rhinitis is commonly underdiagnosed and under treated.***
- ***Quality of life is affected in AR***
- ***AR is one cause for decreased scholastic performance, poor sleep quality***
- ***Drug therapy gives good control of symptoms though allergen avoidance is ideal***
- ***Allergen specific immunotherapy needs standardization.***

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CLIPPINGS

Vitamin C for preventing and treating pneumonia

Pneumonia is one of the most common, serious infections, causing two million deaths annually among young children in low-income countries. In high-income countries pneumonia is most significantly a problem of the elderly.

The objective was to assess the prophylactic and therapeutic effects of vitamin C on pneumonia.

The prophylactic use of vitamin C to prevent pneumonia should be further investigated in populations who have high incidence of pneumonia, especially if dietary vitamin C intake is low. Similarly, the therapeutic effects of vitamin C should be studied, especially in patients with low plasma vitamin C levels. The current evidence is too weak to advocate widespread prophylactic use of vitamin C to prevent pneumonia in the general population. However, therapeutic vitamin C supplementation may be reasonable for pneumonia patients who have low vitamin C plasma levels because its cost and risks are low.

Hemilä H, Louhiala P. Vitamin C for preventing and treating pneumonia. Cochrane Database of Systematic Reviews 2007, Issue 1. Art. No.: CD005532. DOI: 10.1002/14651858.CD005532.pub2. Published Online: July 6, 2011

Zinc for the common cold

The common cold is one of the most widespread illnesses and is a leading cause of visits to the doctor and absenteeism from school and work. Trials conducted in high-income countries since 1984 investigating the role of zinc for the common cold symptoms have had mixed results. Inadequate treatment masking and reduced bioavailability of zinc from some formulations have been cited as influencing results.

To assess whether zinc (irrespective of the zinc salt or formulation used) is efficacious in reducing the incidence, severity and duration of common cold symptoms. In addition, we aimed to identify potential sources of heterogeneity in results obtained and to assess their clinical significance.

Zinc administered within 24 hours of onset of symptoms reduces the duration of common cold symptoms in healthy people but some caution is needed due to the heterogeneity of the data. As the zinc lozenges formulation has been widely studied and there is a significant reduction in the duration of cold at a dose of e" 75 mg/day, for those considering using zinc it would be best to use it at this dose throughout the cold. Regarding prophylactic zinc supplementation, currently no firm recommendation can be made because of insufficient data. When using zinc lozenges (not as syrup or tablets) the likely benefit has to be balanced against side effects, notably a bad taste and nausea.

Singh M, Das RR. Zinc for the common cold. Cochrane Database of Systematic Reviews 2013, Issue 6. Art. No.: CD001364. DOI: 10.1002/14651858.CD001364.pub4. Published Online: June 18, 2013.

ALLERGIC DISORDERS

ALLERGY SCREENING TESTS: ROLE IN THE ASSESSMENT OF CHILDHOOD ALLERGY

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Abstract: *In the recent decades, there has been an increase in the prevalence and incidence of allergic diseases; both in the developed and developing nations. This trend has been particularly true of the pediatric age group. The increase has correlation with; change in the life style, emigration and urbanization of the population. In India, all these changes have been evident in the past 3 decades.*

Since allergic disorders form a significant portion of the pediatric practice, a pediatrician should be conversant with the screening techniques for allergic disorders. Needless to say this will have impact on both diagnosis and management of allergic disorders.

Keywords: *Allergy, Atopy, Sensitization, IgE, Food allergy*

Glossary of terms

PST= Prick skin test

RAST=Radio Allergo Sorbent Test

KUa/L=Kilo units of antibody/liter

ISAC=Immune Solid Phase Allergen Strip

Allergic diseases are common in the pediatric age group [1]. The prevalence of such disorders is also increasing worldwide due to several reasons.[2] India is no exception. Allergy is almost considered as a 'life style' disorder, along with hypertension, diabetes, cardiac disorders. Since there is significant change in the socioeconomic conditions of the developing world, the life styles of the population as well as migration have changed. There is a huge degree of urbanization of the rural areas and due to this dramatic change in the social fabric of the country, the disease patterns are also changing. Allergies and asthma are among the diseases that have increased in incidence and prevalence in the past 2-3 decades. Nearly 25% of the outpatient pediatric practice comprises of allergic children and several of them have asthma. Childhood allergies manifest as atopic dermatitis, food allergies and inhalant allergic disorders like allergic rhinitis, allergic conjunctivitis and asthma. These diseases have a significant morbidity and affect the quality of life of not only the affected child, but also the whole family. Hence, it is very important, that the pediatrician is well equipped to make a reliable diagnosis of atopic sensitization and clinical allergy, in such a patient population.

Allergic diseases can be suspected by good history and physical examination alone. To confirm the diagnosis or to document the sensitization, simple tests both in vivo and in vitro are made available. The tests are excellent for identifying a sensitized state in which allergen-specific IgE is present and may identify triggers to be eliminated and help guide immunotherapy treatment. It is important to differentiate between the terms 'Sensitization' and 'Allergy'. Sensitization is an 'immunological' term and signifies the presence of Specific IgE antibodies; either fixed to the mast cell and can be demonstrated by allergy skin tests, or present in patient's serum and can be demonstrated by RAST test. Sensitization does not mean that patient has clinical allergy. Many subjects in the general population may demonstrate sensitization to a wide variety of allergens but may never have had allergic symptoms. Subjects with sensitization however, have a higher risk of developing clinical allergy in their life time. Long-term follow-up of normal subjects who have had sensitization to house dust mites may have a life time risk of 50% for developing clinical allergy. Such data is not available for sensitization to other allergens. Sensitization could thus be taken as a precursor for developing clinical allergy, though many subjects will not develop clinical allergy, even though they have been

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sensitized. 'Allergy' is a clinical term and presents with various symptoms such as; sneezing, itching, rashes, wheezing, etc. It is very important for the pediatrician to appreciate that the interpretation of test results related to allergy is useful not only for diagnosis and treatment, but also for the education of the patient and family. It is important to emphasize at this juncture that 'we need to treat the patient and not the skin or blood tests'.

Allergic diseases (allergic rhinitis [hay fever], asthma, atopic dermatitis and allergic or anaphylactic reactions to foods, drugs, insect venom or other allergens) often warrant identification of specific allergic triggers for treatment. Most allergic responses are mediated by immuno-globulin E (IgE) antibodies specific for the trigger allergen, which can be detected with in vitro tests or skin testing.

Tests available for detecting specific IgE

1. Radioallergosorbent test (RAST): Radioallergo-sorbent Test (RAST) using radio labeled techniques has been the primary test 'in vitro' to measure specific IgE[3]. Since the inception of RAST, the measurement of specific IgE has undergone several changes using enzymatic assays. Automated tests used today report specific IgE in different readouts (classes, counts, units). All these tests are quite reliable, but unfortunately not comparable. Quantification of the specific IgE expressed as KUa/L (Kilo units of antibody /liter) is getting more common.[4] In spite of these advances there are confounding issues plaguing comparison of these techniques due to use of extracts with different allergen compositions as well as an important issue of non specific binding of patients IgE.

In the recent years multiple allergen assays has gained ground especially for screening in pediatric age group.[5] The current system offered by Phadia is a multi-array assay (ISAC, immune-solid phase allergen chip) that can be performed with 20 micro liters of serum and gives semi-quantitative results for specific IgE to multiple native or recombinant allergen components.[6] This has excellent clinical correlation and is used for screening for allergies by clinicians. Advantages of in vitro testing include lack of interference of medications as well as availability. Disadvantages include cost, delay, need of technician expertise, efforts in standardizing the lab methods, equipment maintenance and drawing of blood. The major advantage would be when testing in patients with anaphylaxis, for example to insect bites, wherein there is a remote possibility for a skin prick test (SPT) to trigger an anaphylactic reaction and there is no need to withhold any drugs prior to testing.

2. Allergy skin testing

Allergy skin prick test (SPT) is commonly employed by allergy specialists to detect specific IgE 'in vivo'.[7] This is based upon the principle of allergen sensitization, where the specific IgE are bound to the receptors on the surface of the mast cell in the tissues in an appropriate configuration. It does not measure the activity of the free IgE in the serum. SPT is performed using different devices (lancets, HS lancetter, small pox needle) causing minimal discomfort to the patient. The results are read in 15 minutes and are expressed as measurements in millimeters of wheal and erythema. Wheal is more important than erythema and in subjects with dark skin as in many of the population from the sub-continent, only wheal can be reliably measured. Saline and histamine phosphate are the most commonly used negative and positive controls. Positive SPT is interpreted as 3mm wheal or more compared to the saline control. Advantages of SPT are safety, low cost, immediate result and good clinical correlation. There is no need for a positive SPT to a large number of allergens to make a diagnosis of allergic sensitization. A positive SPT to a single allergen is enough to conclude that the child has allergic sensitization. Our experience in reviewing thousands of charts (unpublished data) at our center has revealed that SPT for 8 major antigens could pick up 80% of the sensitization. Disadvantages of SPT include withholding of antihistamines for several days prior to the testing.

3. Test selection

This is a crucial question to be considered in each individual patient, especially in the pediatric age group. It is a common notion among the public as well as physicians that 'more number of tests, better the results'. This is not true at all. It is the proper selection of antigens for testing based upon patient's history, available data in the literature and the clinical correlation. Generally Indoor antigens like house dust mites, cockroach, Alternaria and Aspergillus (an indoor and outdoor mold) are clinically more relevant in the causation of asthma, than the outdoor pollens. This is an important issue in pediatric allergy affecting the respiratory tract. A child sensitized to the indoor antigens is at a 'higher risk' of developing asthma.[8] Hence chronic rhinitis in childhood cannot be ignored; on the other hand needs to be evaluated for atopic sensitization. In a study in Mysore, India, evaluating the temporal relationship between the onset of rhinitis and the development of asthma in children, it was observed that the majority of the subjects had rhinitis before developing asthma. Eighty percent of the subjects with rhinitis developed asthma within 2 years after developing allergic rhinitis. Sensitization to house dust

mites increased the risk of developing asthma in children with allergic rhinitis, by more than 14 times and sensitization to tree pollens increased the risk by more than 2 times.[9] Another study also from Mysore, India has demonstrated that the sensitization patterns are similar in different settings with different socio-economic and environmental surroundings as in urban, semi-urban and rural areas except for a higher sensitization to cockroach in urban areas and for fungi in rural areas.[10] The sensitization prevalence however is higher in urban areas than rural areas.[11] There is a major need in India for collaborative work between the aero-biologists and clinical practitioners to identify the common local aeroallergens. Some of these pollens may not be entrapped in slides used for routine aerobiological studies, but could be important sensitizing agents. Recently, Dolichandrone platycalyx was demonstrated to be the fourth most common sensitizing pollen in Mysore.[12]

Antigens for testing from different commercial companies in India are not comparable. There are no standardized antigens available in India yet. This is a matter of major concern and can definitely compromise the results. The other in-vivo test that is sometimes followed is the intra-dermal testing for allergens. Skin prick testing is preferred over intra-dermal testing for routine screening for clinical allergy and the comparison of these two tests are given in Table I.

4. What does positive prick test mean?

A positive SPT means that the child is 'sensitized'. It does not mean that the child is 'allergic'. Sensitization is an immunologic phenomenon and indicates the binding of the specific IgE to the surface of the mast cell, which undergoes de-granulation releasing mediators such as histamine; when the coupling reaction takes place on exposure to the specific antigen. Allergy is a clinical term indicating the symptoms, signs of tissue involvement in specific clinical scenarios (allergic rhinitis, allergic conjunctivitis, asthma). The clinician has to be aware of these concepts, to ensure that his communication with the patient and their family is appropriate. It is important to treat the patient and not the skin tests or blood tests. These tests will only complement a well taken history. Hence it is important to reiterate the importance of a detailed history. Skin or blood tests will never replace a well taken history. In fact ordering such tests without spending time to take a detailed history should be condemned and could result in unjustifiable expenses, without tangible benefits.

5. Can a new born infant have allergy?

Yes, new born can have allergic manifestations. The rationale behind this is that, the fetus can produce its own IgE at 6 weeks of gestation. Maternal IgE does not cross the placenta. Food antigens can cross the placenta and cause sensitization, depending on the genetic susceptibility of the fetus. In newborns, the commonest allergy manifestation is with skin rashes.

6. What are the common allergies in childhood?

Food antigens play a major role in sensitization and allergy in the first 2 years of life.[13] The most common foods that are involved include: Eggs, milk, groundnut, soy, wheat.[13] As the child grows, the allergies to foods gradually resolve spontaneously for foods like milk, wheat, eggs and

Table I. Comparison between two in-vivo tests as screening tests for the diagnosis of allergy (Skin prick test versus intra-dermal test)

Characteristic	Skin prick test	Intra-dermal test
Performance of the test	Very easy to perform	Difficult to perform. Needs expertise
Safety	Very high	Vaso-vagal symptoms common Rarely anaphylaxis
Stability of the extract	More stable (glycerinated)	Less stable (Dilute)
Sensitivity and specificity of results	More specific (Less False+ ve)	Too sensitive (More False +ve)
Discomfort to the subject	Low	High
Suitability for children	Most suitable for any age	Unsuitable for children
Clinical relevance of the results	Excellent (82%)	Poor (< 50%)

gradually inhalant sensitization sets in. Some of the food allergies such as for ground nut and tree nuts usually persist for life. Inhalant antigens include dust mites, cockroach, alternaria and pollens such as weeds, grass and trees depending on the local aerobiology.

7. What are the tests that do not add much as screening tests for allergy?

A. Eosinophil percentage and absolute eosinophil counts: It is important for the clinician to realize that in allergic disease, although eosinophil has been identified as one of the key cells involved in the pathogenesis, it is the tissue eosinophilia that is important and not the eosinophilia in peripheral blood. There is also the fallacy of other causes of elevated absolute eosinophil counts in the peripheral blood, other than allergy, such as various eosinophilic lung diseases.[14] Sputum eosinophilia on the other hand is a good marker for allergic diseases.

B. Total IgE: Similarly, practitioners assessing total IgE are able to pick up only 60% of the cases of allergy, but miss out the other 40%. (unpublished observation).Due to low sensitivity of total IgE, low levels cannot exclude an atopic status with sufficient accuracy; whereas, high serum IgE levels have a better chance of confirming an atopic status[15]. Again, the fallacy remains that total IgE can be elevated in other conditions and also to agents which are not typical allergens such as staph. antigens, tubercular antigens, parasites, etc. It is the elevation of specific IgE that is relevant, and yet, the total IgE could be within the normal range.

C. Specific IgG: Many laboratories are offering specific IgG for various allergens, specifically foods. There is no basis for these tests in the diagnosis of clinical allergy and so their use is strongly discouraged.

Involvement of different organ systems

1. Respiratory allergies

The most common conditions are allergic rhinitis, allergic rhino conjuctivitis, allergic asthma. These disorders are very common and the prevalence and incidence are increasing. Allergic rhinitis affects nearly 15% of the pediatric population and allergic asthma affects around 8% of the children.[16] Allergies play a major role in the progression of the disease process (allergic march). It has been shown that the severity and persistence of asthma is closely related to atopic sensitization, especially to indoor allergens like cockroach, house dust mite. It is imperative that all patients with asthma needs to be evaluated for atopic sensitization (either by SPT or RAST) to assess the risk of progression. This additional information will also guide the pediatrician to advise on environmental control, pharmacotherapy as well as institution of specific allergen immunotherapy (AIT). In the recent decades, there has been excellent peer reviewed literature to support the use of AIT in treatment of asthma in addition to pharmacotherapy.[17] AIT is the only mode of therapy which causes immune modulation to modify patient's immune response from allergic (Th2) to non allergic (Th1). No other modality of treatment at present has the ability to cause this immunological change.

2. Food allergies

Food allergies (FA) are common in early childhood (6-8% < 2years of age); as the child grows the prevalence of FA decreases, although the sensitization may be persistent without clinical manifestations[18]. Hence it is not advisable to screen for foods, since it may not be clinically significant. The positive predictive value (PPV) of food SPT is around 50%, whereas the negative predictive value (NPV) is 95%. This means, negative SPT to foods is much more relevant to rule out clinical sensitivity, than a positive PST. False negative SPT for foods are not uncommon even in the presence of strong clinical history; in such cases, 'prick on prick' test using fresh fruits, vegetables, food items; using reliable control subjects may be done. At times supervised food challenges may give the final answer. Certain laboratories may report IgG RAST for multiple foods; such tests have no clinical relevance. As mentioned earlier, good correlation of the test results with history is essential for successful management.

3. Drug allergies

There are very few drugs that can be reliably tested by SPT or RAST.[19] One such group is Penicillin and its derivatives, for which there is reliable testing material available, mostly in developed nations. Unfortunately Prepen (Penicilloyl) the major determinant and PEN G (Penicilloate) the minor determinant are not commercially available in India. Hence in vitro test (RAST) may need to be done to evaluate. There is no reliable SPT for sulpha, local anesthetics, Tetracyclines etc. SPT for succinyl choline; a muscle relaxant is reliable since its adverse effects has been shown to be IgE mediated. Routine testing for drug allergy is not recommended.

4. Insects

Hymenoptera venom testing and immunotherapy are highly reliable.[20] Venom testing should be performed both by prick and intradermal techniques in all cases of anaphylaxis to insect stings. In children below the age of

16 years, routine SPT for venoms is not advisable for urticarial reactions after insect stings; this is in contrast to adults, where it is an indication for testing and specific immunotherapy. Serum IgE tests can be performed for venoms and may be useful when the SPT is negative with a suggestive history.

5. Vaccines and latex

SPT and intradermal skin tests can be performed using proper dilutions when allergic reactions are suspected. Care should be taken to prevent irritant reactions being over interpreted. There is no reliable SPT for latex sensitivity, although serum IgE test is available.[21]

Points to Remember

- ***Allergies are common in childhood***
- ***Food allergies affect 6% of the children in USA***
- ***Food allergies affect 33% ofchildren with Atopic dermatitis.***
- ***Screening for the common food and inhalants will help the pediatrician to manage better.***
- ***For children suspected of atopic sensitization, a panel of the most common indoor and outdoor allergens as well as a few common foods could be included.***
- ***The selection of antigens and the number of antigens tested is based upon the clinical presentation.***
- ***Skin prick testing and RAST/Phadia are all excellent screens for atopy.***
- ***It is important for the pediatrician to appreciate the difference between sensitization and allergy.***
- ***While tests are valuable aids to diagnose allergy, it is very important NOT to treat the skin test or the blood test; but to TREAT the whole patient.***

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CLIPPINGS

Cranberries for preventing urinary tract infections

Cranberries have been used widely for several decades for the prevention and treatment of urinary tract infections (UTIs). This is the third update of our review first published in 1998 and updated in 2004 and 2008.

The objective was to assess the effectiveness of cranberry products in preventing UTIs in susceptible populations.

Prior to the current update it appeared there was some evidence that cranberry juice may decrease the number of symptomatic UTIs over a 12 month period, particularly for women with recurrent UTIs. The addition of 14 further studies suggests that cranberry juice is less effective than previously indicated. Although some of small studies demonstrated a small benefit for women with recurrent UTIs, there were no statistically significant differences when the results of a much larger study were included. Cranberry products were not significantly different to antibiotics for preventing UTIs in three small studies. Given the large number of dropouts/withdrawals from studies (mainly attributed to the acceptability of consuming cranberry products particularly juice, over long periods), and the evidence that the benefit for preventing UTI is small, cranberry juice cannot currently be recommended for the prevention of UTIs. Other preparations (such as powders) need to be quantified using standardised methods to ensure the potency, and contain enough of the 'active' ingredient, before being evaluated in clinical studies or recommended for use.

Jepson RG, Williams G, Craig JC. Cranberries for preventing urinary tract infections. Cochrane Database of Systematic Reviews 2012, Issue 10. Art. No.: CD001321. DOI: 10.1002/14651858.CD001321.pub5. Published Online: April 30, 2013.

CRP versus evythrocyte sedimentation rate, white blood cell count and alkaline phosphatase in diagnosing bacteraemia in bone and joint infecdtions.

Bacteraemia is common in childhood acute bone and joint infections and demands urgent treatment.

Blood Creactive protein (CRP),erythrocyte sedimentation rate and white blood cell count (WBC) are well known and established markers in these infections. Instead, no information is available on serum alkaline phosphatase whose concentration is known to increase in septic conditions.

In a large prospective treatment trial comprising of 265 children with acute culture-positive bone or joint infection, all these laboratory indices were monitored on admission to hospital. The predictive value to detect bacteraemia was assessed for each of these four indices.

None of the markers could reliably diagnose bacteraemia. CRP alone was significantly higher among bacteraemic patients.

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ALLERGIC DISORDERS

ALLERGEN SPECIFIC IMMUNOTHERAPY

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Abstract: *Allergen immunotherapy is a disease modifying therapy and prevents the progression of allergic diseases especially in those patients who demonstrate specific IgE antibodies to relevant allergens. Immunotherapy involves giving gradually increasing doses of the allergen, to which the person is allergic. This in turn causes the immune system to become less sensitive to the substance, which reduces the symptoms of allergy when the same allergen is encountered in future. This article elaborates the various components involved in immunotherapy.*

Keywords: *Immunotherapy, Dust mites, SLIT, Allergic reactions.*

The dramatic changes in health-care delivery in the past decade have brought a renewed focus on the value and indications for many therapies. Allergen specific immunotherapy is one such treatment modality available to medical profession for IgE mediated allergic disorders. "Allergen specific immunotherapy (SIT)" refers to a gradual immunizing process in which increasing doses of antigens responsible for causing allergic symptoms are administered to a patient to induce increased tolerance to the allergen when natural exposure occurs. It is also known as hypo sensitization or desensitization. The benefit of specific immunotherapy is dependent on both the dose and the route of administration. Although the mechanism by which this benefit occurs is not fully understood, it is proposed that it works by inducing "allergen-specific T regulatory cells" that reduce the late-phase response to the allergen.

History

Noon introduced the technique of desensitization as early as 1911 by inoculating pollen extracts in cases of hay fever. Literature reveals that different methods have been applied from time to time viz. inhalation method in asthma sensitive to house dust mite and Rinkle method in pollen hay fever. Later Ohman and Bousquet, et al used the allergen immunotherapy in asthma and allergic diseases. In India, an array of workers reported hypo sensitization in respiratory allergies and asthma.

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Role of immunotherapy

Immunotherapy is effective in allergic rhinitis, allergic asthma, insect stinging and insect sensitivity, Recently FDA has approved this modality of therapy for atopic dermatitis.

Immunotherapy is not effective in eczema, food allergy, latex allergy and urticaria. Indications and contraindications for immunotherapy are mentioned in Table I and II respectively.

Table.I Indications for immunotherapy

Indications for Immunotherapy
• Insufficient response to pharmacotherapy.
• Insufficient response to environmental control.
• Significant side-effects to medical therapy.
• Patients who have perennial disease.
• Poor compliance to medical regime.
• Possible prevention of asthma from allergic rhinitis.
• Mild to moderate asthma.
• Moderate to severe allergic rhinitis.

Table.II Contraindications for immunotherapy

Absolute contraindications
Severe asthma – FEV1 < 70% with active treatment.
Relative contraindications
• Contraindications for epinephrine.
• Immuno deficiency / auto immune diseases.
• Pregnancy.*
• Malignancy.
• Psychological disorders.
• Mentally impaired patients.
• Short expected life span < 5 years.
• Non compliant patient.

*Although Pregnancy is not a contraindication, it cannot be started because in case of reactions it may affect the baby. During pregnancy maintenance therapy can be continued

Schedule of immunotherapy

Schedules of allergen administration are selected based on the sensitivity of the patient to the allergens in the extract. Dose ranges from 4-12µg administered subcutaneously.

Subcutaneous route of allergen administration is most widely used and well documented in the literature. Despite the established efficacy of subcutaneous injections of causal allergens, the therapy did not gain popularity due to risk of systemic reactions. FDA has approved injection Immunotherapy from 5 years and above, however sublingual immunotherapy can be used from 3 years in some cases.

Primary immunotherapy: To start with, low doses are administered which can be stepped up gradually in dosage and frequency until maintenance dose is reached. It has to be given for 3 – 5 months. Twice weekly regime from 1in 1,00,000 dilutions is started and increased slowly to reach 1 in 10 dilutions depending upon the severity of skin test reaction to particular allergen.

Maintenance immunotherapy: After attaining adequate control with twice weekly regime with 1 in 10 dilutions, change over to maintenance immunotherapy is made. Initially it is done with twice monthly until adequate control and later changed over to monthly once. To get adequate response one year of treatment is compulsory. If there is no response it can be discontinued. Progressive improvement occurs by 2-3 years. Maintenance immunotherapy is given for a period of 3- 5 years. Prediction of response is difficult.

Allergens used in immunotherapy

Allergen extracts are heterogeneous mixture of proteins and they lose potency on storage. The loss of potency affects the efficacy of immunotherapy. Concentrated aqueous extracts in 50% glycerin are stable for about 3 years, if stored in a refrigerator at 4^0C, but without glycerin, they lose their potency within 6 months. Immunotherapy is effective for pollens, fungi, animal dander, house dust mite,cockroach and hymenoptera venom. Allergen formulation requires proper standardization, efficacy and safety and depends upon multiple or single allergen mixture in single vial. For mixed allergen vaccine the following factors must be considered; 1) the cross reactivity of the allergens, 2) the optimal dose of each constituent and 3) enzymatic degradation of allergens. Allergen extracts are to be stored at 2-8°C in the refrigerator for optimal efficacy.

Safety and efficacy of immunotherapy

When properly administered to an appropriate candidate, it is a safe, effective form of therapy capable not only of reducing or preventing symptoms, but also potentially altering the natural history of the disease by minimizing disease duration and prevention of disease progression. The use of standardized extracts will give optimal results. Success of immunotherapy depends on optimal means of allergy testing, quality of allergen extract, correct initial dose of immunotherapy and follow-up with maintenance dose. Failure of immunotherapy is mainly due to inadequate environmental control. missed diagnosis (non-allergic rhinitis), failure to include allergen in SIT, exposure to unknown allergen, inadequate dose of allergen injection, non-compliance of schedule, development of new allergic sensitivities, unrealistic patient expectations for cure and inherent failure in some patients with inadequate response to immunotherapy itself.

Adverse reactions

Systemic reactions to immunotherapy occur within one hour of administration of the allergen which is usually scattered hives and rarely severe anaphylaxis, whereas local reactions can occur up to 24 hours. Incidences of fatal anaphylaxis will range from 1 per 2 million injections. Common local reactions are wheals, indurations or both mainly due to poor injection technique. Patient should be under observation for 30 minutes to monitor allergic reactions. Patient education is essential especially for delayed reactions. At the first step to the reaction a tourniquet may be applied above the injection site and epinephrine may be administered at an appropriate dose preferably by the intramuscular route. Equipment necessary for resuscitation including bag and mask, oxygen, etc should be available at the office while administering immunotherapy.

Alternative routes

Nasal immunotherapy is administered as spray allergen solution into the nose in a phased manner but lack of significant immunologic response led to discontinuation of this route

Sublingual swallow immunotherapy (SLIT) is administered as drops of high dose allergen solution underneath the tongue which is then swallowed. It may be started as the full maintenance dose, without the gradual increase in dose (Primary Immunotherapy). The common side effect of sublingual immunotherapy is local irritation in the mouth and under the tongue (47% to 52%) but it is

usually transient and does not progress to anaphylaxis. This side effect presumably reflects local allergic reactions to the allergen extract. SLIT has the added advantage of ease of administration, home based therapy and avoidance of painful injections. Though SLIT is effective it has its own disadvantages especially in our country, where it is not known some times whether parents are properly administering the drops (correct dosage and frequency), if they are adjusting the dose during acute illnesses such as diarrhea and vomiting, if they are carrying the SLIT antigens when on holidays (cold chain) and last but not the least any disruption in treatment due to financial constraints.

Intra bronchial administration is avoided due to untoward side effects.

Future strategies include "alum depot preparations" which act as adjuvants, allergoids which are chemically modified allergens, peptide immunotherapy which uses allergen derived T-cell peptide epitope, recombinant allergens and anti IgE antibodies (Fig.I).

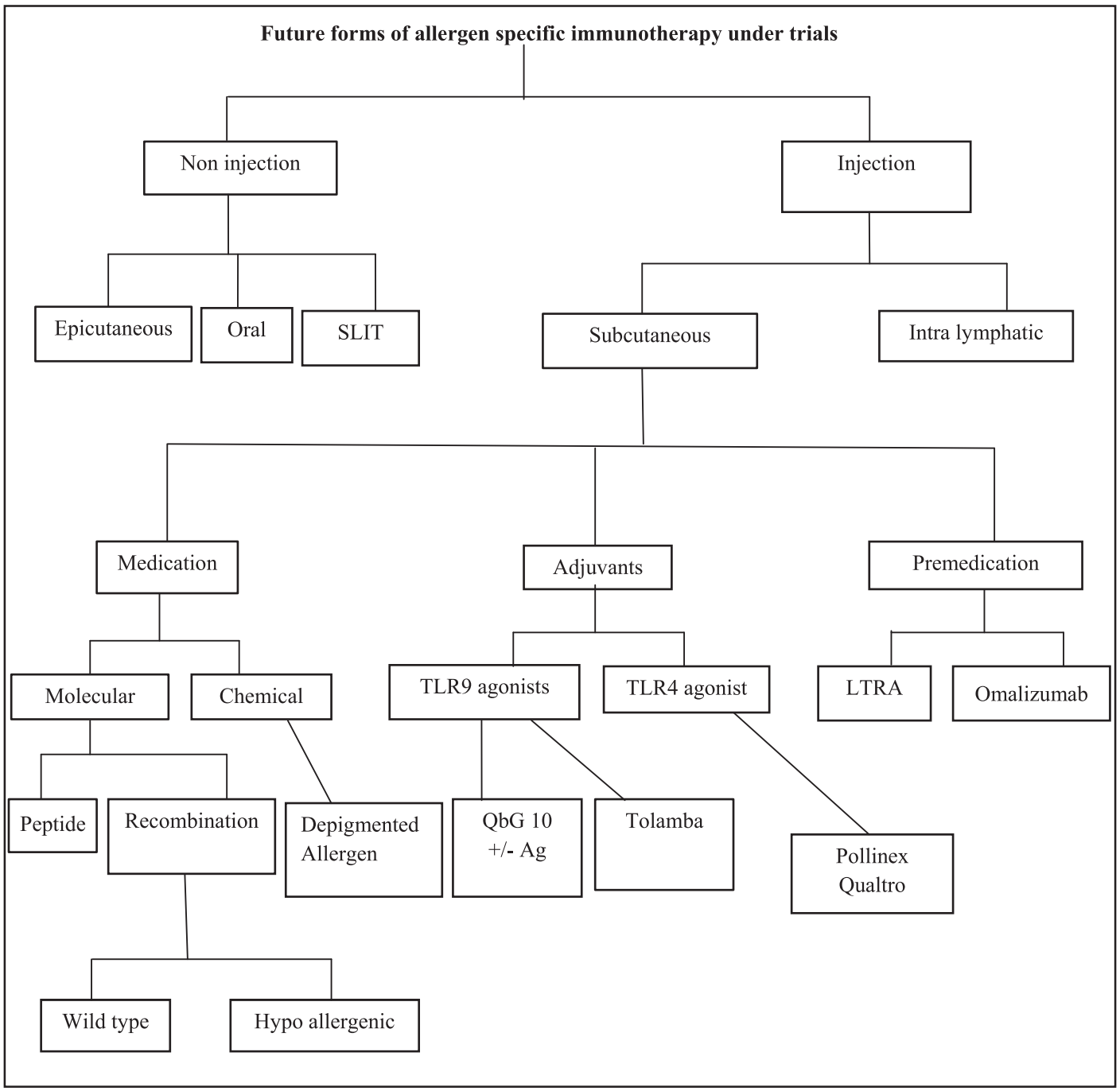

Fig.1. Future allegen specific immunotherapy

Oral desensitization for food allergies are under phase II and III trials in several parts of the world. Several studies done on cow's milk protein allergy and few studies for peanut and egg allergies are under trial. Recent results are encouraging.

Intra lymphatic immunotherapy (ILIT)

The long treatment duration and systemic reactions associated with conventional subcutaneous immunotherapy likely impedes broad acceptance. These problems will be overcome by intra lymphatic immunotherapy. Allergen doses could be reduced 100 times when administered directly in to the lymph nodes as compared with the subcutaneous route.

Recent clinical trials reveal that intra lymphatic immunotherapy allows high therapeutic efficacy with considerable reduced treatment dose and duration. Combined with its good safety profile, ILIT is therefore likely to increase treatment compliance and socioeconomic costs especially in our country.

Epicutaneous immunotherapy

Epicutaneous immunotherapy is a needle free and potentially self administered treatment modality recently preferred by several allergists. Blamoutier and colleagues applied the allergen drops onto heavily scarified skin and demonstrated amelioration of symptoms after 4 weeks therapy and treatment success rate was around 80%. Based on this principle, tape stripping method was developed with improved efficacy.

Rush immunotherapy

The process of inducing adequate immunological response in an accelerated pace, where in all the doses could be given with in a period of few days is termed as rush immunotherapy. Here the doses are spaced out in 2-6 hourly intervals so that maintenance dose is reached within few days. As the risk of systemic allergic reactions being high, this method is not recommended. It can be undertaken where facilities for intensive care and monitoring are available. Patients should be pretreated with anti histamines and corticosteroids.

What's on the horizon?

Researchers are into allergen immunotherapy to seek safer and more convenient allergy "vaccines". Approaches include humanised monoclonal anti-IgE antibodies**,** which have been shown to be effective in treating asthma and food allergies. Anti-cytokine therapy investigations are also underway. Anti-interleukin-5 therapy reduces the bad effects of reactivity, but doesn't improve bronchial hyper-responsiveness. Early trials of tumour necrosis factor alpha (TNF) blocking have shown some success, but further work is needed on specific blockers in allergic pathways. CpG-based immunotherapy significantly reversed both acute and chronic markers of inflammation as well as airway hyper responsiveness. CpG DNA may provide the basis for a novel form of immunotherapy of allergic asthma. Future options for treating allergic disease will focus on allergen specific routes, including further development of immunotherapy targeting specific mediators, an area with a great deal of promise, especially in people with refractory disease.

Points to Remember

- ***Immunotherapy is the only modality available now to modify the pattern of allergic diseases.***
- ***Subcutaneous immunotherapy is highly effective if instituted early by a trained person in carefully selected patients.***
- ***Subcutaneous immunotherapy may also prevent onset of new sensitizations and progression of rhinitis to asthma in children.***
- ***Sublingual immunotherapy has emerged as a promising alternative.***

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CLIPPINGS

Vitamin C for preventing and treating the common cold

Vitamin C (ascorbic acid) for preventing and treating the common cold has been a subject of controversy for 70 years.

The objective was to find out whether vitamin C reduces the incidence, the duration or severity of the common cold when used either as a continuous regular supplementation every day or as a therapy at the onset of cold symptoms.

The failure of vitamin C supplementation to reduce the incidence of colds in the general population indicates that routine vitamin C supplementation is not justified, yet vitamin C may be useful for people exposed to brief periods of severe physical exercise. Regular supplementation trials have shown that vitamin C reduces the duration of colds, but this was not replicated in the few therapeutic trials that have been carried out. Nevertheless, given the consistent effect of vitamin C on the duration and severity of colds in the regular supplementation studies, and the low cost and safety, it may be worthwhile for common cold patients to test on an individual basis whether therapeutic vitamin C is beneficial for them. Further therapeutic RCTs are warranted.

Hemilä H, Chalker E. Vitamin C for preventing and treating the common cold. Cochrane Database of Systematic Reviews 2013, Issue 1. Art. No.: CD000980. DOI: 10.1002/14651858.CD000980.pub4. Published Online: May 31, 2013.

Continuous support for women during childbirth

Historically, women have been attended and supported by other women during labour. However, in hospitals worldwide, continuous support during labour has become the exception rather than the routine.

Primary: to assess the effects of continuous, one-to-one intrapartum support compared with usual care. Secondary: to determine whether the effects of continuous support are influenced by: (1) routine practices and policies; (2) the provider's relationship to the hospital and to the woman; and (3) timing of onset.

Continuous support during labour has clinically meaningful benefits for women and infants and no known harm. All women should have support throughout labour and birth.

Hodnett ED, Gates S, Hofmeyr G, Sakala C. Continuous support for women during childbirth. Cochrane Database of Systematic Reviews 2013, Issue 7. Art. No.: CD003766. DOI: 10.1002/14651858.CD003766.pub5. Published Online: July 15, 2013.

ALLERGIC DISORDERS

ALLERGY PREVENTION STRATEGIES

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Abstract: *In the backdrop of rising allergic diathesis globally, strategies need to be planned for allergy prevention, especially for high risk infants. There has been a paradigm shift in the concept of allergy prevention from allergen avoidance to development of tolerance. Avoidance of smoking during pregnancy, healthy balanced diet during pregnancy and lactation, exclusive breastfeeding for first six months of life and timely introduction of complementary feed at about six months of age are the unequivocal recommendation for prevention of allergic manifestations in early as well as later life. Extensively hydrolyzed formula for top-fed infants; prenatal and postnatal dietary supplementation of n-3 long chain polyunsaturated fatty acid (LCPUFA), Vitamin D and anti-oxidants; pro/prebiotic during pregnancy are some other areas of allergy prevention which are under research and need more evidence before any public health guidelines can be formulated.*

Keywords: *Allergy prevention*

Allergic diatheses are increasing at an alarming rate in today's world. Around 20% of the global population suffer from IgE mediated allergic diseases. According to World Health Organization, an estimated 300 million people have asthma worldwide.[1] The disability and burden on health care resources are considerable. In such a scenario efforts towards prevention of allergic diseases are crucial for a healthier and more productive generation.

The strategies for prevention of allergic disorders are multifaceted and not very structured. Questions arise as to who should be the target of such intervention, how early should we start thinking of prevention and what should be the approaches. Allergen avoidance may appear the most logical way to proceed, but this may not be feasible always and there is not enough evidence to support this strategy. Of late the tolerogenic properties of allergens and immunomodulatory agents in diet and environment have been intriguing the researchers and clinicians.

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Who should we focus on?

In the background of increasing allergy and asthma it is prudent that general measures should be taken by everybody, but our focus of attention for prevention efforts should be the so called 'high risk individuals', i.e when there is a family history of allergic diseases. Family history of atopy confers a 50-80% risk of allergic conditions as compared to baseline risk of 20%.[2] Efforts for prevention needs to be started during early life itself and should be directed towards pregnant women and young children including neonates and infants.

When and how can we prevent allergies?

Allergic conditions seem to have a multifactorial etiology with complex gene environment interaction. Definite genes in the causation of allergy are yet to be identified though there are a number of potential candidate genes. The rising trend of allergies worldwide indicates a detrimental shift in the gene - environment interaction which has predisposed us to allergies. It could be the allergen overexposure or underexposure in the form of environmental pollution, dietary deficiencies, changing pattern of microbial infections which has made genetically susceptible individuals more prone to allergic diathesis. The possible modes of primary prevention of allergic disorders can be:

1. Avoidance of allergen/pollutant exposure - both ingested and inhaled
   a. During pregnancy
   b. During lactation
   c. During infancy and childhood
2. Breastfeeding
3. Hypoallergenic infant formula feed
4. Timely introduction of complementary feeding
5. Dietary modification of pregnant women and infants
6. Role of Pro/prebiotics

We will discuss the evidence available for and against each of these modalities of primary prevention.

Allergen exposure avoidance during pregnancy and lactation

The role of avoidance of specific or multiple food allergens in the antenatal period in preventing the subsequent development of food allergy and atopy in infants and children is not well established. A recent Cochrane review including four randomized controlled trials suggests that avoidance of food allergens during pregnancy did not have any protective effect on the incidence of atopic dermatitis during first eighteen months of life; all these RCTs included high-risk families. No conclusion could be drawn regarding conjunctivitis or allergic rhinitis or urticaria as data were limited.[3]

The same Cochrane review also suggested that maternal allergen avoidance during lactation did not have a protective effect on the incidence of atopic dermatitis or food allergy in infants or later up to seven years of age.[3]

Rigorous dietary restriction might adversely affect both the mother and fetus/infant. Hence currently most of the guidelines do not recommend ingested allergen avoidance during pregnancy or lactation. Contact with multiple dietary allergens could in general benefit the fetus by development of tolerance.[4]

Maternal exposure to traffic exhaust particles polycyclic aromatic hydrocarbons, is known to trigger epigenetic modification in the fetal nucleic acid and lead to early onset wheezing.[5] It is advisable to limit exposure of pregnant women to outdoor air pollutants as far as possible. Smoking on the part of mother in the antenatal period and both parents later is associated with increased risk of wheezing during early years.[6] Avoidance of smoking during pregnancy is an unambiguous recommendation in all guidelines.[7]

Some studies on birth cohorts have depicted that stringent environmental control measures with reduction in exposure to house dust mites in early life may lead to less frequent respiratory symptoms in first year of life, but long term effect on sensitization and prevention of atopic diseases are debatable.[8, 9]

Breast feeding

Besides the numerous health benefits of breastfeeding, prevention of asthma and atopy also seems to be one of the potential benefits, though evidences are inconsistent. Strong evidence in favour of this notion is hard to collect as randomization is never ethically possible. In a meta-analysis including 21 studies across various populations, exclusive breastfeeding for at least three months was associated with a decreased risk of atopic dermatitis (OR 0.70; 95% CI 0.50-0.99) compared to conventional formula feeding.[10] A prospective study on Swedish birth cohort of 4089 children showed that exclusive breast feeding for four months reduced the incidence of atopic dermatitis and halted the allergic march till four years of age.[11] The same birth cohort also showed that exclusive breast feeding for four months reduced the risk of asthma during first four years of life.[12] German Infant Nutritional Intervention Study Group which compared exclusively breastfed infants with partially or exclusively formula fed ones concluded that exclusive breast feeding for four months reduced the risk of atopic dermatitis in first year of life in high risk infants.[13]

On the other hand, a Japanese birth cohort of 763 infants was followed and it was found that neither exclusive nor partial breastfeeding for six months had a strong impact on the risk of atopic eczema.[14] A recent systematic analysis from Cochrane database did not find any long term protective effect of six months exclusive breastfeeding on atopic eczema, asthma, or other atopic outcomes as compared to shorter duration of 3- 4 months of exclusive breastfeeding; this aspect could be evaluated in 3 studies from developed countries.[15]

In spite of some contrary evidence, all guidelines recommend exclusive breast feeding for 4-6 months for the holistic health benefits and protective influence on asthma and atopy.

Infant formula feed

When exclusive breast feeding is not feasible, a hypo-allergenic formula feed should be chosen as replacement in infants at high-risk of developing allergies. Evidence suggests that partially hydrolyzed formula containing reduced oligo-peptides of molecular weight less than 5000 D and extensively hydrolyzed formula containing peptides of molecular weight of less than 3000 D fit this bill to some extent. The German Infant Nutritional Intervention Study Group found that in 945 infants who were formula fed, extensively hydrolyzed casein based formula significantly reduced allergic manifestations at 12 months of age compared to cow milk formula (OR, 0.42; 95% CI, 0.22-0.79).[16]

A meta-analysis found a significant reduction in infant allergy (seven studies, 2514 infants), but not in the incidence of childhood allergy (two studies, 950 infants) when hydrolyzed formula was used as compared to cow's milk formula.[17]

An updated meta-analysis including three studies concluded that soy formula did not have a role in prevention of allergy in high risk infants.[18]

Thus, extensively hydrolyzed formula may be used for prevention of allergy in infants at risk, but more evidence is needed to determine the long term effect and justify the cost effectiveness of this intervention. Extensively or partially hydrolyzed formula should never replace breast milk for this purpose.

Complementary feed

Zutavern, et al studied a birth cohort of 2612 infants and concluded that delaying introduction of solid food up to four months but not beyond six months of age decreased the odds of symptomatic atopic disease.[19] Zutavern et al also commented that food sensitization was more frequent when solid food was introduced later than six months.[20] A recent large birth cohort from Taiwan, when followed till 18 months of age, did not reveal any evidence to support the delayed introduction of solid food including food considered to be allergenic like egg, fish and peanuts.[21] As of now, most guidelines suggest the window period of 4-6 months as the ideal time for introduction of complementary feed.[7, 22]

Dietary intervention-Prenatal and postnatal

Diet deficient in antioxidants, n-3 long chain polyunsaturated fatty acid and other good nutrients is the peril of modern lifestyle and may have a causal relationship with rising allergic diseases. Efforts are ongoing to collect evidence whether supplementation of certain dietary factors during pregnancy and infancy may have a protective influence against allergy. In a recent randomized controlled study, dietary n-3 long chain polyunsaturated fatty acid (LCPUFA) supplementation of pregnant women led to a lower incidence of atopic dermatitis in first year of life.[23] Supplementation of LCPUFA during early life does not seem to have the same effect.

Deficiency of vitamin D and antioxidants like vitamin C, E, selenium have been implicated in the development of allergic disorders by many epidemiological studies.[24] Supplementation of these nutrients in perinatal period may be an effective strategy of allergy prevention which is yet to be supported by clinical trials.

Probiotics/prebiotics

Microbial infections and colonization plays an important part in the early development and polarization of the immune system. Intestinal microflora has an interesting relationship with allergic diseases. It has been noted that reduced diversity of gut microflora as well as decreased colonization by Lactobacillus and Bifidobacterium have been associated with allergic manifestations in later life.[25] Consequently, probiotics have been considered as one of the strategies in allergy prevention. Probiotics may help by shifting the immune response towards Th1 arm with reduced Th2 cytokines and allergen specific IgE. Early studies by Kalliomäki, et al showed an almost fifty percent reduction in incidence of atopic dermatitis in the first year of life when Lactobacillus GG was administered prenatally as well 6 months postnatally to high risk infants.[26] This has been followed by multiple studies showing heterogeneous results probably due to differences in methodology, timing of administration (prenatal vs. postnatal) and species and strains of micro-organism used. As of now, there is evidence to support that there is significant risk reduction for atopic eczema in children aged 2-7 years when lactobacilli is administered during pregnancy.[27] Maternal consumption of probiotics in the antenatal period is an important component, as postnatal administration of probiotics alone have failed to show any beneficial effect on allergy prevention.[28] Also, effects of probiotics have been pronounced only in respect to eczema and no other allergic manifestations.

Prebiotics, which are a mixture of non-digestible, fermentable oligosaccharides, tend to stabilize the gut microflora by promoting growth of beneficial commensals. Some evidence is emerging that adding of prebiotics in formula-fed infants may aid in reducing incidence of allergic conditions. Early dietary intervention with a mixture of neutral short-chain galacto-oligosaccharides (sc GOS) and long-chain fructo-oligosaccharides (lc FOS) in first six months of life has shown a reduced cumulative incidence of atopic dermatitis, urticaria and wheezing not only while the intervention lasted but also during the two years follow-up.[29] More recently, a German study also concluded that the cumulative incidence of atomic dermatitis in first year of life was lowered when formula feed was supplemented with oligosaccharides as compared to placebo.[30]

More research is required before any definitive guideline can be formulated regarding the use of pre or probiotics in prevention of allergy.

Points to Remember

- ***Definitive guidelines for prevention of allergy include avoidance of smoking during pregnancy, use of healthy balanced diet during pregnancy and lactation.***
- ***Exclusive breastfeeding for first six months of life and timely introduction of complementary feed at about six months of age.***

- ***Newer strategies still need the support of more extensive and conclusive research. Additional studies from the developing world are also desirable.***

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CLIPPINGS

Oral morphine for cancer pain

This is the second updated version of a Cochrane review first published in Issue 4, 2003 of The Cochrane Library and first updated in 2007. Morphine has been used for many years to relieve pain. Oral morphine in either immediate release or modified release form remains the analgesic of choice for moderate or severe cancer pain.

To determine the efficacy of oral morphine in relieving cancer pain, and assess the incidence and severity of adverse effects.

The effectiveness of oral morphine has stood the test of time, but the randomised trial literature for morphine is small given the importance of this medicine. Most trials recruited fewer than 100 participants and did not provide appropriate data for meta-analysis. Only a few reported how many people had good pain relief, but where it was reported, over 90% had no worse than mild pain within a reasonably short time period. The review demonstrates the wide dose range of morphine used in studies, and that a small percentage of participants are unable to tolerate oral morphine. The review also shows the wide range of study designs, and inconsistency in cross-over designs. Trial design was frequently based on titration of morphine or comparator to achieve adequate analgesia, then crossing participants over in cross-over design studies. It was not clear if these trials are sufficiently powered to detect any clinical differences between formulations or comparator drugs. New studies added to the review reinforce the view that it is possible to use modified release morphine to titrate to analgesic effect. There is qualitative evidence that oral morphine has much the same efficacy as other available opioids.

Wiffen PJ, Wee B, Moore R. Oral morphine for cancer pain. Cochrane Database of Systematic Reviews 2013, Issue 7. Art. No.: CD003868. DOI: 10.1002/14651858.CD003868.pub3. Published Online: July 23, 2013.

Clinical and EEG risk factors for subsequent epilepsy in patients with complex febrile seizures.

The study aims to identify the risk factors for subsequent epilepsy in patients with complex febrile seizures from a single–center retrospective cohort. The presence of epileptiform discharges is a significant risk factor for subsequent epilepsy in patients with complex febrile seizures. Electroencephalography should be considered in all patients with complex febrile seizures especially those who had multiple or prolonged seizures.

Kim H, Byun SH, Kim JS, Lim BC, Chae JH, Choi J, et al. Epilepsy Res Mar.2013

GENERAL ARTICLES

"INTERMITTENT AND LONG TERM PROPHYLAXIS IN FEBRILE SEIZURES"

*Verma A

Abstract: *Febrile seizure is a condition where seizure occurs in response to fever. The typical simple febrile seizures are generalized tonic clonic usually lasting less than 15 minutes. This is a common occurrence in children in the age group 6 to 60 months. The common queries, arising in mind of a treating physician are recurrence of febrile seizures, increased risk of epilepsy, decline in IQ and death after or during an episode of febrile seizure. This article aims to answer these queries and also to give comprehensive guidelines regarding intermittent and continuous prophylaxis in febrile seizures. Long-term prophylaxis in febrile seizures is not recommended. The prognosis is generally good.*

Keywords: *Febrile seizure, Epilepsy, Prophylaxis.*

What is febrile seizure?

Febrile seizures are the most common among seizure disorder in childhood, affecting 2% to 5% of children between the ages of 6 and 60 months. Simple febrile seizures are defined as brief (less than 15-minutes) generalized seizures that occur once during a 24-hour period in a febrile child who does not have an intracranial infection, metabolic disturbance, or history of afebrile seizures.

Complex febrile seizures are prolonged (15 minutes), are focal, or occur more than once in 24 hours. Late onset febrile seizures, persistent febrile seizures, generalized epilepsy and febrile seizure plus (GEFS+) and febrile status epilepticus (FSE) are part of the spectrum of febrile seizures.[1] The guidelines on long-term treatment of child with simple febrile seizures address the risks and benefits of both continuous and intermittent anticonvulsant therapy as well as the use of antipyretics in children with simple febrile seizures.[2]

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What is the theoretical risk of simple febrile seizures?

A child with simple febrile seizures can have the following possible out comes which can be of concern to a treating physician. 1. Decline in IQ 2. Increased risk of epilepsy 3. Risks of recurrent febrile seizures and 4. Death.[3]

It was inferred by many studies that neither a decline in academic performance or neurocognitive inattention nor behavioral abnormalities have been shown to be a consequence of recurrent febrile seizures.[4,5,6]

It has also been shown in many studies that children with simple febrile seizure have approximately the same risk of developing epilepsy by the age of 7 years as does the general population i.e. 1 %.[7] However if the age of the child is less than 1 year with family history of recurrent febrile seizure there is a higher chance of having afebrile seizures at 25 years of age which is 2.4%[8], hence it is clear that simple febrile seizures never cause structural brain damage nor do they cause epilepsy in future.

The third concern for a treating physician is the recurrence of febrile seizures in future after having a first simple febrile seizures. Children younger than one year at the time of presentation will have 50% probability of having recurrences in future, and children older than one year at the time of presentation will have 30 % probability of having a second febrile seizure. There is again 50% chance of developing future febrile seizures after a second attack of simple febrile seizures.[9]

The other concern is death after an attack of simple febrile seizure. It has never been reported in literature that death has occurred after simple febrile seizures. So, simple febrile seizures have no long-term adverse effect except for the recurrences.

Risk and benefit of intermittent antipyretic therapy

Antipyretic therapy is needed to make the patient comfortable from the effect of high grade temperature. It is clear from many studies that prophylactic administration of antipyretic does not prevent recurrence of febrile

seizures[10] and even a high dose of acetaminophen (20mg/kg) is not capable of reducing the recurrence of febrile seizures. It was also noted that administering prophylactic acetaminophen during febrile episodes was ineffective in preventing febrile-seizure recurrence.[11] Uhari, et al in a randomized double-blind placebo-controlled trial, reported that acetaminophen along with low dose oral diazepam did not show reduction of recurrence as compared to control group.[12] It is not only acetaminophen, but ibuprofen also was shown to be ineffective in preventing recurrence of febrile seizures.[13,14,15]

Acetaminophen and ibuprofen are safe antipyretics, used in controlling pyrexia in children but are not effective for controlling the recurrences of febrile seizures. Toxicity is reported with acetaminophen in the form of hepatotoxicity and with ibuprofen in the form of respiratory failure, metabolic acidosis, renal failure and coma in high doses.[16,17]

Risk and benefit of intermittent anticonvulsant therapy

The use of intermittent diazepam has been found to reduce the risk of recurrent febrile seizures. The side effects of diazepam seen are lethargy, irritability and ataxia, which can be minimized by adjusting the dose.[18]

Literature demonstrates the feasibility and safety of abolishing the seizure lasting more than 5 minutes with rectal diazepam, intranasal and buccal midazolam, but the long term out come is questionable.[19,20]

A twelve year follow up study by Knudsen et al, found no difference in occurrence of epilepsy, motor development and cognitive development in those who were given rectal diazepam for preventing seizure (at the onset of fever) or treating seizures (at the onset of seizures).[21]

There are studies to suggest the efficacy of clobazam in prevention of recurrence of febrile seizures, with advantage of oral administration, rapid pharmacological action and minor, infrequent transient side effects.[22,23] Oral clobazam in a dose of 0.75mg/kg for 2-3 days in 2 divided doses during fever is useful to prevent recurrences.[24]

The disadvantage of intermittent medication is that a seizure could occur before fever is noticed. It was noted that the recurrence of seizure was not due to the agent selection but the failure of method of administration. Also the sedation caused by benzodiazepine may mask the evolving signs of central nervous system infection.[3]

Continuous antiepileptic drugs

Valproic acid and phenobarbitone are equally effective in controlling the recurrence of febrile seizure.[25,25,27] The side effect of valproic acid includes the fatal hepatotoxicity in children under age of two years and though rare, thrombocytopenia, weight loss and gain, GIT disturbance and pancreatitis.[28] The side effect of phenobarbitone includes hyperactivity, irritability, and lethargy. The behavioral side effects may occur in up to 20-40% of patients and may be the cause of discontinuation of therapy.[29] The risk and potential side effects of valproic acid and phenobarbitone outweigh their benefit. There is no available data to suggest that the prevention of recurrent febrile seizures reduces the risk of developing epilepsy. Phenytoin and carbamazepine are not useful for continuous prophylaxis in febrile seizures.[24]

Points to Remember

- ***Simple febrile seizure is a benign and common event, seen between 6 to 60 months of age.***
- ***The prognosis of simple febrile seizures is excellent.***
- ***Acetaminophen and ibuprofen are good antipyretic drugs, but they do not reduce the incidence of febrile seizures.***
- ***Long-term prophylaxis with anticonvulsant therapy is not indicated in simple febrile seizures.***
- ***Intermittent anticonvulsant prophylaxis with clobazam can be used to prevent the recurrences in simple febrile seizures or when the parental anxiety is too much, but it will not prevent the future epilepsy.***
- ***Reassurance and adequate counseling to the family regarding the benign nature of the illness is important.***

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NEWS AND NOTES

East Zone Pedicon, Tezpur
Date: 15th to 17th November, 2013

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GENERAL ARTICLES

FEEDING ISSUES IN PRETERM BABIES

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Abstract: *The goal of feeding preterm infants is to maintain intrauterine growth rate until full term to support catch up growth thereafter. Feeding of preterm babies is challenging because of various physiological and pathological complications. The guidelines on feeding preterm babies are evidence based and have shown that a simple intervention such as early initiation of breastfeeding not only improves the survival in resource poor setting but also has great influence on long term neuro development outcome. The manuscript addresses the practical issues in feeding preterm babies which the health care providers face in day to day clinical practice.*

Keywords: *Preterm, Feeding issues, Evidence based practical guidelines*

Feeding issues in preterm babies

Preterm babies are the babies born before term gestation i.e. before 37 weeks of gestation. Proper nutrition of both preterm and term babies is essential for normal growth, resistance to infection and optimal neurological and cognitive development.[1] Term babies with normal birth weight require minimal assistance for feeding in immediate postnatal period as they are able to feed directly from the mother's breast. But feeding preterm babies is challenging because of several problems which include immaturity of bowel function, inability to suck and swallow, high risk of destructive inflammation of the gastrointestinal tract called necrotizing enterocolitis (NEC), etc. Following are some of the practical issues involved in the feeding of preterm babies, which will be addressed one by one

When to feed preterm babies?

What to feed preterm babies?

How to feed preterm babies?

How much to feed preterm babies?

When to suspect feeding intolerance?

How to supplement breast milk in preterm babies?

How to assess adequacy of feeding in preterm babies?

When to feed preterm babies?

Like term babies feeding should be initiated in preterm babies soon after birth except in the following situations

1. Preterm babies with gestation less than 28 weeks do not have proper sucking efforts and propulsive motility in the gut. So these babies cannot be started on feeds soon after birth.
2. Sick preterm babies with severe respiratory distress, shock, convulsions or severe birth asphyxia have a significant risk of developing feeding intolerance and NEC.

These babies should be started on intravenous fluids and enteral feeds should be started as soon as they are hemodynamically stable.

What to feed preterm babies?

Breast milk is the best choice for feeding preterm babies as there are potential short term and long term benefits from human milk. Data suggests that tolerance is better[2] and the incidence of NEC is lower[3] with human milk than low birth weight (LBW) / preterm baby formula. However, human milk contains insufficient quantities of nutrients to meet the needs of preterm babies less than 32 weeks gestation or birth weight less than 1500g.

Breast milk can be given to even those babies who are fed by paladai or gastric tube by giving expressed breast milk. Breast milk expression should be started soon after birth so that baby gets benefits of feeding with colostrum. Thereafter it should be done every 2 to 3 hours to ensure that the preterm baby is exclusively breastfed and the lactation is maintained.

In rare situations where mother is very sick or breast feeding is not advisable (eg. HIV positive mother), the other options available are:-

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1. LBW formula milk for preterm infants less than 2000g.
2. Animal milk eg. undiluted cow's milk.

How to feed preterm babies?

The method of feeding preterm babies depends on their gestation and oral feeding skills which mature with increasing gestation (Table I). It is important to understand that all babies born at a particular gestation do not have the same feeding skills. So, for an individual preterm baby, one should assess if the feeding skills expected for his/her gestation are present and then decide the initial feeding method. As the feeding skills mature, gradually shift to next feeding method. All preterm babies should ultimately be able to feed directly from the breast.

1. Nasal versus oral route for placing feeding tubes in preterm babies

When preterm babies are too immature or unwell to suck feeds, they can receive their milk through a feeding tube passed via either the nose or mouth. Only two small trials have compared nasal versus oral route for placing tube feeding and there is not enough evidence regarding the superiority of either route of feeding.[5] There is a concern that nasal tubes may partially obstruct breathing in infants below 2000 g, so oral route may be preferred over nasal route.

2. Continuous milk feeding vs intermittent bolus feeding for preterm babies

Milk feedings can be given via nasogastric tube intermittently, over 10 to 20 minutes every two to three hours, or continuously, using an infusion pump. Although theoretical benefits and risks of each method have been proposed, effects on clinically important outcomes remain uncertain. There is no difference in time to achieve full feedings in premature babies fed through a tube into the stomach either on a continuous basis or over 10 to 20 minutes every two to three hours.[6] Reports of the incidence of NEC are similar with the two methods.[6] But a major disadvantage of continuous feeding is that lipids in the milk tend to separate and stick to the syringe and tubes, so intermittent bolus feeding may be preferred.

3. Non-nutritive sucking (NNS)

All stable preterm babies, irrespective of the initial feeding method should be put on the mother's breast for non-nutritive sucking. For preterm babies on gavage feeding, non-nutritive sucking may encourage the development of sucking behavior and improve digestion of the feeding. Non-nutritive sucking may also have a calming effect on babies. With non-nutritive sucking, the transition to full enteral feeds is easier and there are no negative outcomes of non-nutritive sucking.[7] NNS helps in initiation and maintenance of successful breast feeding during hospital stay and after discharge.

How much to feed preterm babies?

It is essential to calculate the fluid requirements and feed volumes for babies on paladai or gastric tube feeding. The daily fluid requirement is determined by insensible water loss, urine output and other losses. Lesser the gestation more is the fluid requirement because of the high insensible water loss. Fluids are usually started at 80 and 60 mL/kg/day for babies with birth weight of less than 1500g

Table.I Maturation of oral feeding skills and the choice of initial feeding method in preterm babies[4]

Gestational age	Maturation of feeding skills	Initial feeding method
<28 weeks	No proper sucking efforts No propulsive motility in the gut	Intravenous fluids
28-31 weeks	Sucking bursts develop but no coordination between suck/swallow and breathing	Oro-gastric (or naso-gastric) tube feeding with occasional spoon/ padalai feeding
32-34 weeks	Slightly mature sucking pattern Coordination between breathing and swallowing begins	Feeding by spoon/paladai/cup
>34 weeks	Mature sucking pattern More coordination between breathing and swallowing	Breastfeeding

and 1500-2500g respectively on day1. Further requirements are calculated by daily estimation of weight loss/gain and urine output. The usual daily increment would be about 15-20 ml/kg day so that by the end of first week 150-170 ml/kg/day is reached.[8]

After calculating the fluid requirement, the individual feed volume to be given by gastric tube or paladai (2 to 3 hourly) should be calculated.

Minimal enteral nutrition or trophic feeding

The introduction of enteral feeds of sick preterm babies is often delayed due to concern that early introduction of feeds may not be tolerated and may increase the risk of NEC. However, early trophic feeding i.e. giving babies' very small volume of milk during the first week after birth, may promote intestinal maturation, enhance feeding tolerance and decrease time to reach full enteral feeding. Analysis of eight trials suggests that this practice of trophic feeding does not increase the risk of NEC.[9]

As soon as the sick preterm baby is hemodynamically stable, small amount of expressed breast milk (8-12 ml/kg/day) divided into 4-8 feedings should be given by gavage feeding. As the baby gains clinical stability, increase the feed volume by 20 ml/kg/day to achieve full enteral feeds. Discontinue intravenous fluids, when baby gets two-third fluid requirements via feeds. Also gradually shift the baby from gavage feeding to paladai/spoon feeding and subsequently to breast feeding.

When to suspect feeding intolerance?

Feeding intolerance is common among very small preterm babies, and most such babies will have episodes that require either temporary discontinuation of feedings or a delay in advancing feeds. Although most such episodes resolve spontaneously, any signs of feeding intolerance should be regarded as potentially serious because of increased risk of NEC among these babies. Feeding intolerance should be suspected if (1) baby is vomiting (altered milk/bile/blood stained), (2) abdominal girth increases by 2cm from baseline, (3) prefeed gastric aspirate is more than 25% of last feed.

The common causes of feeding intolerance are immature intestinal motility, immaturity of digestive enzymes, medical conditions e.g. sepsis, NEC etc. If there are signs of feeding intolerance, suspend oral feeds till abdominal distension improves. Evaluate the preterm baby for any medical illness and manage accordingly. For gastrointestinal immaturity, conservative management is the only option.

How to supplement breast milk in preterm babies?

Preterm infants are born with low skeletal stores of calcium and phosphorus. Preterm breast milk has insufficient amount of protein, calories, calcium, phosphorus, iron, zinc and vitamins to meet the growth requirements of preterm babies. Multinutrient supplementation of human milk may be done by one of the following methods:

1. Supplementation of breast milk with vitamins and minerals

Preterm infants who are exclusively breastfed should receive supplements of vitamin D, calcium, phosphorus and iron.

- Calcium and Phosphorus (140-160mg/kg/day and 70-80mg/kg/day respectively) should be started once the preterm baby is on full oral feeds and continue till one year of age.. Study from Safdarjung hospital shows that incidence of osteopenia of prematurity even in babies with birth weight 1500-2000g is as high as 28.2% at 3 months and 30.6% at 6 months of age. We in our neonatal unit supplement all preterm babies with birth weight less than 2 kg with calcium and phosphorus.
- Vitamin D (400 IU/day) should also be started once the baby is on full oral feeds and continued till one year of age.
- Iron should be given in dose of 2mg/kg/day (max.15mg/day), starting at 4-6 weeks of life and continue till one year of age. In babies less than 1500g, iron may be started as early as 2 weeks of age (if baby is on full oral feeds) to prevent apnea of prematurity.

2. Supplementation of breast milk with human milk fortifier (HMF)

Commercially produced multicomponent fortifiers provide additional nutrients to supplement human milk (in the form of protein, calcium, phosphorus, carbohydrates as well as vitamins and trace minerals). Use of HMF is associated with short term improvements in weight gain, linear growth and head growth without an increase in adverse effects such as NEC.[10] There is no evidence of long term benefits of HMF.

HMF is indicated to preterm babies less than 1500g birth weight who are not gaining weight despite receiving full calories through preterm expressed breast milk and in whom underlying cause for poor weight gain (anemia or

underlying sepsis) have been ruled out. HMF is started once the baby reaches 150ml/kg/day of enteral feeds. HMF is given in dose recommended by the manufacturer (usually a sachet of 2g is added to 50 ml of expressed breast milk). Preterm babies on expressed breast milk fortified with HMF do not require any other supplementation except for iron. Continue fortification of expressed breast milk with HMF till baby reaches 40 weeks of PMA or attains weight of 2 kg whichever is later.

How to assess adequacy of feeding in preterm babies?

The best method to assess adequacy of feeding in preterm babies is their regular growth monitoring. All preterm babies should be weighed daily till the time of discharge from the hospital and then every week till the baby attains weight of 2 kg. Length and head circumference measurements should be done weekly during nursery stay.

Preterm babies lose 1-2% weight daily during first 7-10 days with cumulative loss of 12-15%. Subsequently, birth weight is regained by 14 days of age. Thereafter, weight gain should be at least 15-20 g/kg/day till the weight of 2 kg is reached. After this, a gain of 20-30 g/day is adequate. Once the preterm baby reaches 40 weeks of post menstrual age, WHO growth charts should be used for growth monitoring.

Inadequate weight gain is usually due to inadequate milk intake and sometimes, due to medical conditions such as cold stress, anemia, sepsis, gastroesophageal reflux, etc. The commonest cause of inadequate weight gain in preterm babies is inadequate milk intake. If preterm baby is on breast feeding and is not gaining adequate weight, then mother needs to be counseled about proper positioning and attachment. Any breast problems such as sore nipples or inverted nipples should be well addressed. Mother should be advised to feed frequently, for a longer period and also during the night. Giving expressed breast milk by spoon or paladai after breast feeding helps those preterm babies who tire out while sucking from the breast.

Points to Remember

- ***Breast milk is the best choice for feeding preterm babies.***
- ***Well preterm babies should be started on feeds soon after birth. Sick preterm babies should be started on minimal enteral nutrition as soon as hemodynamically stable.***
- ***Preterm infants with good suck should be directly breastfed.***
- ***Preterm infants who are exclusively breastfed should receive supplements of vitamin D, calcium, phosphorus and iron.***
- ***Adequacy of feeding preterm babies should be assessed by regular growth monitoring.***

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DRUG PROFILE

ANTIHISTAMINES IN PEDIATRICS

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Abstract: *Antihistamines are very frequently prescribed by pediatricians. The 3 generations of antihistamines are available today as 40 different preparations. An attempt is made to review its use in pediatrics.*

Keywords: *Antihistamines, 1st generation antihistamines, 2nd generation antihistamines, 3rd generation antihistamines, children.*

Though many antihistamines are available for use, only 20 have been detailed in the IAP Drug Formulary.[1] They are used for a large number of indications in pediatrics. The evidence based recommendations for their use in these various conditions need to be reviewed as newer molecules are now available.

Mechanism of action

Antihistamines competitively inhibit the action of histamine by blocking its attachment to histamine receptors, inhibiting the enzymatic activity of histidine decarboxylase or catalyzing the transformation of histidine into histamine. They thereby suppress the histamine-induced wheal and flare response by blocking the binding of histamine to its receptors on nerves, vascular smooth muscle, glandular cells, endothelium, and mast cells. Itching and sneezing are suppressed by antihistamine blocking of H1-receptors on nasal sensory nerves.[2]

Uses

Evidence exists for the use of antihistamines in children and adolescents for treating allergic rhinitis,[3] conjunctivitis, atopic eczema[4], urticaria[5], insect bites or stings[6] and mild or moderate allergic reactions that are caused by drugs and food allergies. They have also been used for treating motion sickness (limited data)[7], gastric ulcers (limited high quality evidence)[8], vomiting (limited data of effectiveness)[9] and psychiatric illnesses [a poor substitute to newer drugs but probably included in the WHO Essential medicine list for children because of its low cost and therefore its cost-effectiveness in low and middle income countries].[10,11] In short, evidence based pediatric use of antihistamines is restricted to control of allergic symptomatology and these antihistamines will be detailed in this article. Antihistamines are mainly used to provide symptomatic relief. They do not cure illnesses as they do not affect the underlying cause.

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The classification of antihistamines

Antihistamines are classified[12] as

a) First generation [sedating antihistamines including chlorpheniramine, diphenhydramine, promethazine, hydroxyzine]

b) The newer antihistamines which include the second generation (relatively nonsedating, including terfenadine, astemizole, loratadine, cetirizine and ketotifen; topical azelastine and olapatadine – of these, the first 2 were were discovered first and use of both were discontinued due to toxicity) and

c) Third generation (including fexofenadine, desloratidine, levocetirizine). Third-generation antihistamines are active metabolites of second-generation drugs, developed with the goal of improving clinical efficacy and minimizing side effects.

Pharmacokinetics

Oral solid and liquid formulations of antihistamines are well absorbed and achieve maximum plasma concentration within 1-4 hours. The drug metabolization and clearance processes are accelerated in children in the case of certain antihistamines. As a result, ideal dosing in such cases is once every 12 hours instead of once every 24 hours (eg. levocetirizine).[13,14,15] Both 1st and 2nd generation antihistamines are metabolized in the liver by the P450 cytochrome enzyme system. However, cetirizine, levocetirizine and fexofenadine are largely eliminated without metabolic transformation (first 2 drugs in the urine and fexofenadine in bile). First-generation antihistamines are highly lipophilic and therefore readily cross the blood-brain barrier, contributing to adverse central nervous system effects including sedation, drowsiness and decreased cognitive processing. First-generation drugs also have relatively short half-lives, necessitating multiple daily doses.[16] Second-generation antihistamines have a higher

specificity for binding to H1 receptors, lower affinity for non-histamine receptors and are lipo-phobic (thus have poor penetration of the blood brain barrier). These drugs are thereby less likely to be sedating than first generation drugs. They also have longer half-lives, permitting once- or twice-daily dosing.[16]

Cautions and contra-indications

Antihistamines should be used with caution in children with epilepsy. First-generation H1-antagonists are known to occasionally provoke convulsions in healthy children as well as epileptic patients. And reports of similar effect of 2nd generation antihistamines is emerging.[17] Most antihistamines should be avoided in acute porphyria. But alimemazine, chlorpheniramine, desloratadine, fexofenadine, ketotifen, loratadine, and promethazine are thought to be safe in this condition.[18] Sedating antihistamines inhibit the effects of histamine not only peripherally but also in the brain and additionally have potent antimuscarinic, anti-**a**-adrenergic and antiserotonin effects leading to symptoms such as visual disturbances (mydriasis, photophobia and diplopia), dry mouth, tachycardia, constipation, urinary retention, agitation and confusion.[19] They should not be used in neonates and should be used with caution in children with urinary retention, glaucoma or pyloroduodenal obstruction.[18] Sedating antihistamines, such as alimemazine and promethazine, should not be given to children under 2 years, except on specialist advice, because the safety of such use has not been established. Sedating antihistamines have detrimental effects on learning and examination performance in children[20] and are better avoided in children with learning disorders.

Dosages[1]

Name of the drug, route and dosages of individual drugs are shown in Table I, II and III.

Table.I 1st Generation antihistamines : Drugs, route and dosage

Name of the drug	Route	Dosage
Chlorpheniramine:	Oral	<2yr 1 mg 2 times (max. 2mg) 2-5yr 1-2mg 3 times (max 6mg) 6-12yr 2-4 mg 3-4 times (max 12mg) 12-18yr 4mg 4-6 times daily (max 2 4 mg)
	IM/IV/SC	<1yr 250mg/kg; 1-5yr 2.5-5mg, 6-12yr 5-10mg, 12-18yr 10-20mg once. Repeated upto 4 times daily. (max 49 mg in adults)
Diphenhydramine:	Oral	2-12 yr 10-25 mg 12-18 yr 25-50 mg once at bedtime.
Promethazine:		
Symptomatic relief of allergy	Oral	< 1yr 2.5-5mg, 1-6 yr 5-10mg, 6-12 yr 10-15mg and 12-18yr 10-20mg 2-3 times daily.
Vomiting and nausea	Oral	1mg/kg/24hr in 4 divided doses.
Sedation	Oral	1-2mg/kg as single dose.
Sedation in ICU - Start with lower dose and increase gradually depending on response. May use along with chloral hydrate.	Slow IV/ Oral/deep IM	<12 yr 2-4mg/kg/day and > 12 yr 100-200mg in 4 divided doses.
Hydroxyzine:		
Pruritis	Oral	6month -6 yr 5-15 mg ; 7-12 yr 10-15 mg and 12-18 yr 25mg at bedtime. Increase if required to max dose of 50mg/day in 6 month-6 yr., 50-100 mg /day in 7-12 yr and 100 mg/day in 12-18 yr in 3-4 divided doses.
Anxiety	Oral	12-18 yr 50-100 mg/dose 4 times daily. In renal impairment dose needs to be reduced by half.

Table.II 2nd Generation antihistamines : Drugs, route and dosage

Name of the drug	Route	Dosage
Loratadine	Oral	<6yr 5mg, >6 yr 10mg once daily.
Cetrizine	Oral	2-6 yr 5mg and 6-18 yr 10mg as single or 2 divided doses. In renal impairment give 50% of above dose.
Ketotifen		Adolescents: 1-2mg once daily with food. Initial treatment is 0.5 -1mg at night. Children: Over 2yrs: 1mg once daily with food. Not recommended for children below 2 years.
Olapatadine Allergic conjunctivitis, including ocular pruritus:	Ocular administration	Children < 3 years: Safety and efficacy have not been established. Adolescents, and Children > 3 years: 1 drop in each affected eye two times per day at an interval of 6-8 hours. (this is the maximum dosage allowed) No dosage adjustment is necessary for ocular administration in patients with renal or hepatic impairment.

Table.III 3rd Generation antihistamines : Drugs, route and dosage

Name of the drug	Route	Dosage
Fexofenadine		
Seasonal allergic rhinitis	Oral	2-11yr 30mg, 12-18yr 60mg 2 times daily/120mg daily once.
Chronic idiopathic urticaria	Oral	6 mths-2yr 15 mg twice daily 2-11yr 30mg twice daily 12- 18yr - 180mg once daily. With decreased renal function 6 mos-2 yrs: 15 mg once daily 2 to 11 yrs : 30 mg once daily
Desloratidine	Oral	2-5 yr 1.25mg; 6-11 yr 2.5mg; 12-18 yr 5mg once daily.
Levocetrizine	Orally to be given in the evening -	6-11yrs 2.5mg (max dose); >12yrs 5mg (max dose; 2.5mg may be sufficient)

Toxicity

1st generation, sedating antihistamines reduce rapid eye movement (REM) sleep, impair learning and reduce work efficiency. They are implicated in civil aviation, motor vehicle and boating accidents, deaths as a result of accidental or intentional overdosing in infants and young children and suicide in teenagers and adults.[21] Some exhibit cardiotoxicity in overdose. As mentioned earlier they inhibit the effects of histamine not only peripherally but also in the brain and additionally have potent antimuscarinic, anti-α-adrenergic and antiserotonin effects leading to symptoms such as visual disturbances (mydriasis, photophobia, and diplopia), dry mouth, tachycardia, constipation, urinary retention, agitation and confusion.[19] Cetirizine does sedate some patients and therefore although the risk of sedation with this drug is low, fexofenadine and loratidine may be appropriate when doing anything that requires concentration and where safety of self and others are at stake.[22] In patients with a perceived history of sedation with cetirizine, most were able to tolerate levocetirizine.[23] But this study also suggested that these very patients might tolerate cetirizine if given the drug without

their knowledge. Therefore, patients with a history of mild to moderate sedation with cetirizine are unlikely to experience a different sedation profile with levocetirizine.

Some second-generation antihistamines have highly lipophilic general structure, so that the active ingredient binds stronger with lean tissue and may account for some organic toxicity. For examples: loratadine and cetirizine. Ventricular arrhythmia (torsades de pointes) commonly reported with astemizole, then with terfenadine. Finally, European Commission and US FDA withdrew these medications (terfenadine 120 mg, all terfenadine-pseudoephedrine and astemizole). Based on cardio-safety, loratadine's results in animal trials and human data are conflicting. In human, loratadine has not shown any effect on QT prolongation. But in animal study, this effect still emerges. Cetirizine is the only second-generation antihistamine which is considered as "really safe" for the heart. Cetirizine never shows any prolongation of QT interval in any studies which have been conducted, even in the case reports of cetirizine accidental overdose. So does levocetirizine, newer generation of antihistamine that is derived from cetrizine's enantiomer.

Theoritically, fexofenadine is said to be the cardio-safe active metabolite of terfenadine. But from field experience, fexofenadine still causes QT interval lengthening and life-threatening arrhythmia in patients with mild hypertension or mild left-ventricular hypertrophy. Desloratadine is the cardio-safe-form of loratadine, while levocetirizine is an L-enantiomer of racemic cetirizine.

Drug interactions

There are no studies of the effects of possible drug interactions in pediatric age groups between antihistamines and P450 cytochrome inhibitors, or drugs which are metabolized via this pathway. The only exception is a study of children with chloroquine-resistant malaria, where the plasma concentrations of this drug were seen to be significantly greater and were reached sooner, when administered in combination with chlorpheniramine.[24] However, second-generation antihistamines could interact with several macrolides (erythromycin, clarithromycin, and azithromycin) and ketokonazole. This effect is due to CYP3A4 inhibitor effect. So it is better if macrolide antibiotics are not given concomitantly with second-generation antihistamines in patient with history of heart disease, liver disease, or electrolyte imbalance.

Conclusion

Antihistamines are widely used by pediatricians in India. There have been many clinical studies on its use in pediatrics over the last 2 decades which give us some confidence in suggesting recommendations for its use in children. Over the counter (OTC) dispensing of these drugs especially the first generation antihistamines for illnesses such as 'common cold', 'allergic rash', non-specific cough and vomiting and for sedation and analgesia is worrying as it adds to the potential for adverse effects.

Points to Remember

- ***Antihistamines are mainly used to provide symptomatic relief. They do not cure illnesses as they do not affect the underlying cause.***
- ***As far as possible, avoid sedating antihistamines in children less than 2 years age and school going children and adolescents.***
- ***Evidence exists for the use of antihistamines in children and adolescents for treating allergic rhinitis and conjunctivitis, atopic eczema, urticaria, insect bites or stings.***
- ***All other indications for its use including common cold, cough, motion sickness, gastric ulcers, vomiting and psychiatric illnesses require further validation.***
- ***2nd generation antihistamines are less sedating.***
- ***3rd generation antihistamines further decrease the possible cardiotoxicity of antihistamines.***

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CONTRIBUTORS TO CORPUS FUND OF IJPP

Rs.1500/-

Dr.G.Venkatesan, Tamil Nadu

Rs.2500/-

Dr.D.Murrugesan, Chennai

Dr.Vishal S. Dudihalli, Dharwad

Dr.V.Satyamurthi, Kanchipuram

Dr.Arun Walia, Ambala Cantt

Dr.Vijaylaxmi Vasdani , Navi Mumbai

Rs.2525/-

Dr.Mahendra B. Bhagat, Surat

DERMATOLOGY

POLYMORPHIC LIGHT ERUPTION

***Madhu R**

Abstract: *Photosenstivity is defined as an abnormal reaction of the skin to exposure of ultraviolet light or visible light. Polymorphic light eruption (PMLE) is the most common photodermatoses seen in children. PMLE is an immunologically mediated disorder which is postulated to occur due to the failure of UV induced immunosuppression and a delayed hypersensitivity reaction to an endogenous, cutaneous neoantigen produced after ultraviolet light exposure. It occurs in healthy children and is characterized by the presence of polymorphic skin lesions such as skin coloured or erythematous, pruritic papules, vesicles and plaques, hypopigmented and eczematous patches in the sun exposed sites, in different individuals. Lesions tend to be monomorphic in a single individual. Photoprotection plays a pivotal role in the management of PMLE. General measures include avoidance of sun exposure, use of protective clothing, wide-brimmed hat, umbrella, sun glasses and a broad spectrum sun screen. Topical steroids and anti-histamines are useful.*

Keywords: *Ultraviolet light, Photoprotection, Sunscreens.*

Solar spectrum is comprised of 56% infra red light (wave length 780-5000 nm), 39% visible light (400- 700 nm) and 5% ultra violet light (200 - 400 nm). Ultra violet (UV) radiation is composed of UVC (200-290 nm) which is entirely absorbed by the ozone layer, UVB (290-320 nm) and UVA (320 - 400 nm). While UVB causes sun burn, UVA elicits a tanning response and chronic exposure to UVA radiation results in photo aging and carcinogenesis. In the recent times, visible light has also been known to induce a tanning response which is more persistent than that induced by UVA light.[1] Action spectrum of photodermatoses lies in UVA and / or UVB (mostly 290 - 365 nm) and rarely visible light range.[2] Photosensitivity in a child is said to occur when there is an abnormal or adverse reaction of the skin to ultra violet and or visible radiation. In other words, it is an abnormal response to ordinary light exposure. Photosensitivity disorders or photodermatoses in children are much less common compared to adults. Photodermatoses in children are classified into 4 main categories namely immunologically mediated photodermatoses (formerly called idiopathic photodermatoses), drug or chemical induced photosensitivity, hereditary photodermatoses and photo aggravated dermatoses. Immunologically mediated photodermatoses include polymorphous light eruption, juvenile spring eruption, actinic prurigo, hydroa vacciniforme and solar urticaria.[1]

Polymorphous light eruption is the most common photodermatoses seen in children.[1,3] This condition was first described in 1817, by Robert Willan who used the term 'Eczema solare'.[4] In 1900, Carl Rasch coined the term, 'Polymorphous light eruption" and in the recent times, it came to be known as "Polymorphic light eruption".[5,6] Polymorphic light eruption (PMLE) is a common, intermittent sunlight or artificial UV induced eruption, which occurs particularly at temperate latitudes, resulting in itching in the sun exposed area within hours to rarely days after exposure and thereafter lasting for a week or two once the exposure ceases.[7] All ethnic groups are affected. There is a higher prevalence in temperate climates; due to the greater proportion of long wave (UVA) to shortwave ultraviolet light (UVB) with increasing distance from the equator.[8] Not much data is available regarding the prevalence of PMLE in children in India. A study of pediatric dermatoses done in a referral centre in Bangalore reports a prevalence of 2.5% of all photodermatoses.[9] While PMLE commonly presents in older school going children, inherited geno photodermatoses and metabolic disorders present with photosensitivity in the neonatal period or infancy.[10] However, age of onset of PMLE is found to range from childhood to late adult life.[1,11] PMLE occurs in 47% of individuals under the age of 20 years and in 20 % under the age of 10 years.[12] It has been reported to occur predominantly in females during the second and third decades of life with a ratio of 2:1.[1,5] This condition is more common in fair skinned individuals with Fitzpatrick's skin types I - IV. PMLE attacks are more common in spring (March) and early summer, with a reduction in severity

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and frequency during late summer due to the hardening phenomenon.[7] Hardening refers to the increased tolerance of the skin with continued sun exposure.[4] A study done by Sharma L ,et al at Varanasi reported a high incidence during March and September.[13] Even during winter, sunlight at high altitudes can produce PMLE. In addition, ultraviolet A (UVA) penetrating through window glass can also result in PMLE.[5]

Etiopathogenesis

PMLE is considered to occur as a result of delayed hypersensitivity to an endogenous cutaneous antigen induced by UV exposure. Specific nature of these antigens is not known. Exposure to UVB is said to create neo-antigens that have the potential to provoke auto immune reactivity. In normal individuals, this adverse reaction is prevented by the concurrent immunosuppression induced by UV radiation. In patients with PLE, persistence of Langerhans cells and failure of UV induced immunosuppression results in an enhanced immune response to the cutaneous neoantigens produced after UV light exposure. It is hypothesized that when compared to healthy individuals, there is a decrease in neutrophil infiltration into the skin of patients with PMLE on exposure to UVB radiation. This decrease is associated with a reduced expression of TNF alpha, IL-4 and IL-10, suppressed macrophage infiltration and Langerhans cell resistance, which results in a non-suppressive microenvironment in the skin.[14,15] There seems to be a genetic predisposition to PMLE. But, the disease manifestation in these susceptible individuals depends on the environmental factors.[7,16] Western literature reports family history in about a fifth of patients with PMLE.[16]Hereditary form of PMLE which is autosomal dominantly inherited, with an onset during childhood has been reported in native Americans of North and South America.[17]

Clinical features

PMLE attacks usually occur after initial exposure to sunlight during spring or early summer. Individual susceptibility differs and hence the duration of exposure to produce lesions may range from few minutes to hours and sometimes to a few days. Pruritus occurs within minutes to be followed by the skin lesions in the sun exposed sites within hours to days after sun exposure. Affected children usually present with itching, burning sensation and erythema after exposure to sunlight. Spontaneous resolution of lesions may occur in 1-2 weeks in the absence of further sun exposure. Lesions heal without scarring. If the sun exposure continues, lesions may last for weeks. As summer advances, there will be a gradual improvement due to 'hardening' effect. Hardening is a specific feature of PMLE, which is not present in other idiopathic photodermatoses except some cases of solar urticaria and actinic prurigo. Skin lesions of PMLE are polymorphic as the name implies, but in any given individual, lesions are always monomorphic that, even recurrent lesions tend to occur with the same morphology and consistent time of onset of lesions after sunlight exposure. Polymorphic light eruption ranges from pruritic, erythematous / skin colored grouped papules, vesicles, plaques to papulovesicles, nodules, hypopigmented and eczematous patches. Hyperpigmentation may be seen within the hypopigmented patch. A pin-point variant has been reported in individuals with dark colour, which is characterized by tiny papules resembling lichen nitidus. Papular form of PMLE is the most common type, followed by the plaque (Fig 1) and papulovesicular forms. Uncommon forms such as chronic plaque hemorrhagic PLE, PLE sine eruptione (pruritus without clinical signs), erythema multiforme like and urticarial lesions may occur. Lesions of PMLE tend to be symmetrical. In children, the face is more commonly affected than in the adults. Usually affected sites are the malar areas of the cheek, bridge of the nose, chin, sides, nape and 'V' area of the neck, extensor aspect of the forearms and arms, dorsa of the hands, upper back and at times, the dorsal aspect of the feet. As a corollary, in any photosensitivity disorder, the upper eyelids, retroauricular and submental areas, nasolabial folds, antecubital fossae and volar aspect of the wrist generally tend to be spared. Systemic symptoms such as headache, nausea, fever, chills are rare.[5,7,16-20]

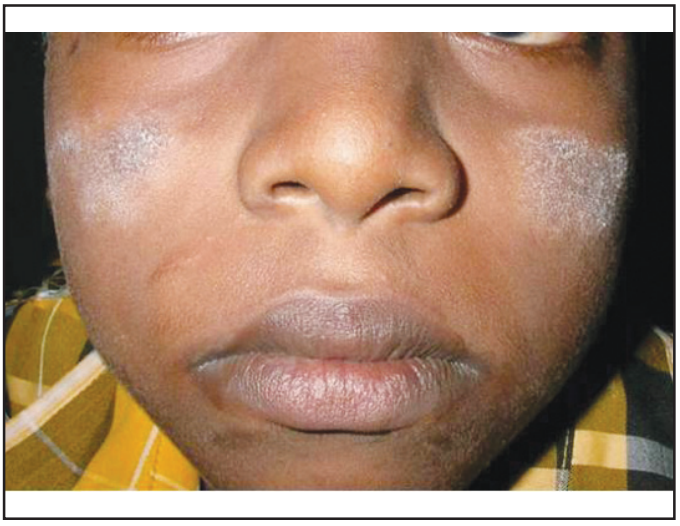

Fig.1. Scaly plaques seen over both malar (sun exposed) area.

Juvenile spring eruption

Juvenile spring eruption is a variant of PMLE, which occurs in epidemics during spring and early summer, mainly affecting young boys between the ages of 5 and 12 years. Relapses occur every year during spring. This condition is characterized by the presence of pruritic, erythematous papules that evolve into vesicles and crust over the helices of the ears. Lesions heal with minimal or no scarring.[1,21]

Investigations

Diagnosis of PMLE is mainly by history and clinical findings. When in doubt, a patient may be examined after exposure to sunlight or a provocative phototesting may be done. PMLE may be elicited by UVA, UVB, UVA & UVB and solar simulated light. Phototesting is done by irradiating the volar aspect of the forearm with 0.75 MED to four times the MED (Minimal erythema dose is the lowest dose that induces erythema) or suberythemogenic UV doses for 3 to 4 days. Patient is then examined after 24 to 48 hours for the typical PMLE lesions. Higher multiplications of MED may be required in the case of solar simulated light.[1,12] At times, if warranted, lupus serology and porphyrin screening may be done to exclude lupus erythematosus and porphyria.[14]

Differential diagnosis

The differential diagnosis of PMLE include photo aggrevated dermatoses such as lupus erythematosus, atopic dermatitis, porphyria, other immunologically mediated dermatoses such as solar urticaria, hydroa vacciniforme and photosensitive conditions induced by drugs and chemicals, etc. Solar urticaria is characterised by the presence of wheals that occur within 5 to 10 minutes after exposure to sunlight and resolve within 24 hours. Hydroa vacciniforme is a rare photodermatosis that occurs exclusively in children. In this condition, recurrent crops of blisters develop that heal with varioliform scars. It is worthwhile to remember that onset of photosensitivity occurs in the neonatal or infantile stage in geno-photo dermatoses, while in PMLE, it is seen in school going children. Hypopigmented patch of PMLE on the face has to be differentiated from Pityriasis alba which occurs as an asymptomatic ill defined patch and Pityriasis versicolor, a superficial fungal infection characterised by the presence of aymptomatic, well defined macules and patches with fine scales.[1,12]

Management

The first and foremost step in the treatment of PMLE is prophylactic photo protection by avoidance or limiting exposure to sunlight between 9.00 am to 4.00 pm (period of highest UVB intensity), use of protective clothing, broad - brimmed hat, umbrella and sunglasses and regular application of broad spectrum sunscreens that will protect against both UVA and UVB. Exposure to mid day sun is best avoided. A broad- brimmed hat is one which has at least 3-inch brim all around. Dark colored, thick, tightly woven fabric and older, washed clothes provide good UV protection. Loose- fitting clothing is preferable as the distance of the fabric from the skin is directly proportional to the degree of UV protection. It is advisable to use clothing that covers (eg. Long sleeve shirts and pants) and minimizes the area of skin exposed to skin. Wet clothes offer less UV protection. Stretching and bleaching also reduces the UV protection.[22-24]

Sunscreens are broadly classified into organic (Chemical) and inorganic (physical) sun screens. Organic sunscreens absorb high energy ultraviolet rays, while the latter reflect or scatter light. While the most commonly used organic UVB filter is Octinoxate, most common organic UVA filter is Oxybenzone (Benzophenone-3). Zinc oxide and Titanium dioxide are physical blockers that are effective against both UVB and UVA. Though, Sunscreen ideally should be applied in a dosage of 2 mg/cm^2, most of the times there is an inadequate application. Sunscreens are not recommended in infants below 6 months ofage. In children under 12 years, alcohol based gels, liquids or sprays are not to be used as they may cause irritation. Sun Protection Factor (SPF) is a measure of protection against erythema that is mainly caused by UVB and 15% to 20% by UVA. SPF mainly denotes UVB protection as UVB is 1000 times more erythemogenic than UVA. SPF is defined as the dose of UVB required to produce 1 minimal erythema dose (MED) on protected skin after application of 2 mg/cm^2 of product divided by the UVR to produce 1 MED on unprotected skin. For example, an SPF 15 product allows an individual to remain in the sun up to 15 times longer without sunburn in comparison to that allowed by his unprotected skin. With regard to the correlation of the SPF with the proportion of the filtered UVR, it has been observed that SPF 15 blocks 93.3% UVR, SPF 30 absorbs 96.7% UVR and SPF 50 blocks 98% of UVR. The FDA monograph 1999 states that photosensitive individuals will benefit from sunscreen with SPF above 30. As there is photosensitivity to both UVA and UVB in the affected individuals, a product with higher SPF (50-60) which will provide greater UVA II protection may be preferable. Sunscreen should be applied 30 minutes before going outdoors and has to be reapplied every 2 hours and after excessive sweating, swimming and vigorous exercise. Water-resistant, water proof and sweat- resistant

sunscreens are available. Children who go swimming or play water games could use these sunscreens. A Water-resistant sunscreen is one that maintains the label SPF value after two sequential 20 minutes of immersion (40 minutes). Very water resistant sunscreen maintains the label SPF value after 4 sequential immersions of 20 minutes each (80 minutes). Sweat- resistant sunscreen protects up to 30 minutes of continuous heavy perspiration. Sunscreens must be applied to all sun exposed areas in adequate quantities to ensure sufficient protection. Allergic contact dermatitis may be caused by sunscreens that contain PABA, cinnamates and oxybenzone. There is increasing concern about diminished levels of vitamin D while using sunscreens. However, in practice, it has been observed that, most of the times sunscreens are never applied in the correct dose or frequency to interfere with the levels of vitamin D. Moreover, even with regular use of sunscreens, patients received enough sunlight to maintain normal levels of vitamin D.[25-29]

Patients with mild PMLE respond well to the above mentioned measures of photo protection. Next line of treatment is application of low potent steroids (Hydrocortisone) for lesions on the face and mid potent steroids (Fluticasone, mometosone) for lesions elsewhere. Antihistamines are given to allay the pruritus. Systemic steroids are warranted only in the case of severe photosensitivity. Hydroxychloroquine in a dose of 5-7mg/kg /day for a short course may be effective in such children. Children with recurrent episodes may benefit from exposure to sunlight in the early morning after sun rise or before sunset or prophylactic narrowband UVB therapy, which will promote natural or artificial hardening respectively.[12]

Conclusion

Prophylactic photoprotection being the main anchor of treatment of polymorphic light eruption, education and counseling the children and the parents regarding avoidance or limiting exposure to sunlight, use of protective clothing and broad spectrum sunscreens is imperative. Sunscreens are to be applied in sufficient quantity and frequency to ensure effective protection against UV light. Children who undergo regular sports training should be encouraged to use sunscreens.

Points to Remember

- ***PMLE is the most common pediatric photodermatoses.***
- ***PMLE occurs in older school going healthy children in contrast to the hereditary photodermatoses that present during neonatal/ infantile period.***
- ***Face is more commonly affected in children.***
- ***Photoprotection plays a major role in the management of PMLE. General measures include avoidance of high intensity sunlight, use of protective clothing, wide-brimmed hat, umbrella and broad spectrum sunscreen.***
- ***Counseling the children and parents is very important. Sunscreens are to be applied in sufficient quantity regularly to ensure effective protection against UV light.***

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NEWS AND NOTES

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Pedicon – 2013, Khammam, AP, Date: 15th to 17th November, 2013

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RADIOLOGY

PROPTOSIS

*** Vijayalakshmi G**
****Malathy K**
*****Natarajan B**
*****Rajiah J**
*****Visalakshi K**

The orbit is a confined space where even small lesions can cause increased pressure resulting in proptosis. Orbital lesions are rare in children and early diagnosis requires careful examination as mild proptosis can be missed. Rhabdomyosarcomas(RMS) are the commonest childhood malignancy of the head and neck and orbital RMS is the commonest orbital malignancy. It is a rapidly growing tumor causing proptosis. The less common aggressive alveolar subtype has a predeliction for the inferior orbit, while the more common, less aggressive embryonal type frequently starts in the supero-medial quadrant. On CT, rhabdomyosarcomas are seen as well defined, extraconal masses isodense to muscle. There is invasion of the adjacent bone but lymphnode and intracranial invasion are relatively uncommon. The globe is displaced but rarely invaded. Spread into the eyelid can cause painful swelling. On MRI images the mass is isointense to muscle in T1W images and hyperintense to muscle in T2W images. There is enhancement following contrast. Neuroblastoma is the most common primary childhood malignancy to metastasise to the orbit. The bone involvement is more common in the superolateral quadrant. Imaging will help in treatment planning.

The optic nerve glioma is a slow growing tumour involving any portion of the visual pathway. In the orbit it is seen as a fusiform enlargement of the optic nerve. There may be widening of the optic canal. These tumours are hypo intense on T1 images and hyperintense on T2W images. Posterior extension can be studied. Optic nerve gliomas can be differentiated from meningiomas as meningiomas are hypointense on T2W images also and enhance brilliantly on contrast administration. About half of patients with optic nerve glioma have Neurofibromatoses type 1(NF1). NF1 patients can also present with plexiform neurofibroma involving sensory nerves in the orbit and eyelid. Dysplasia of the greater sphenoid wing gives rise to the bare orbit appearance where the innominate line or the greater wing of the sphenoid is not seen in the orbit.

Langerhans histiocytosis shows bony destruction and replacement of those areas with abnormal proliferation of Langerhans cells. Fig.1 A and B shows a well defined lytic lesion in the supero lateral wall of the orbit, which is a common site. There is soft tissue extension into the orbit which has caused a mild proptosis.

The benign lesions in the orbit are usually vascular. Capillary hemangiomas, as anywhere else, appear shortly after birth, increase in size for the next one year and then involute over the next five years. The orbital muscles and lacrimal glands can sometimes be involved. The cavernous

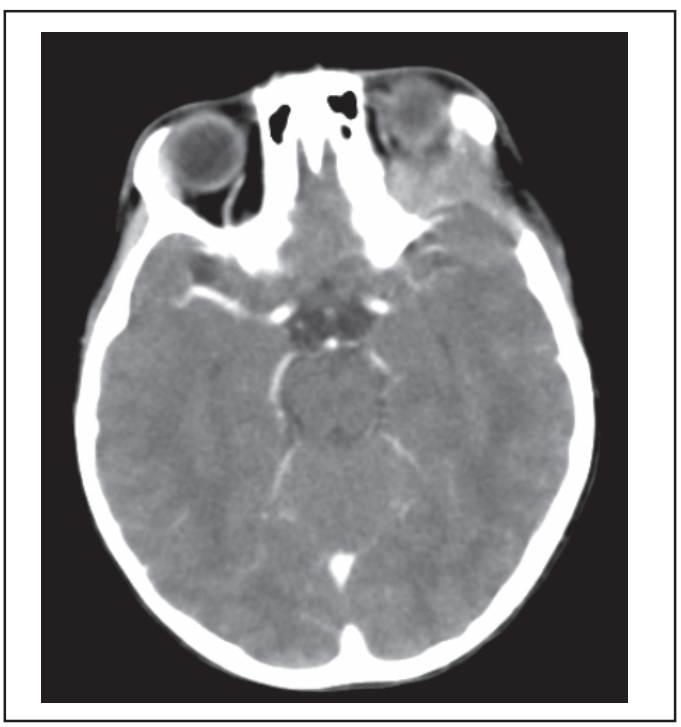

Fig.1A. LCH- erosion of the roof of orbit and squamous temporal bone on the left

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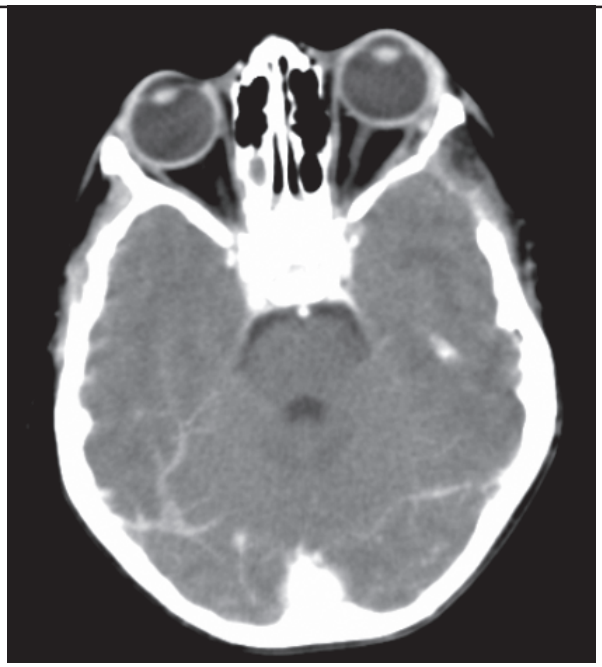

Fig.1B. LCH- proptosis on left

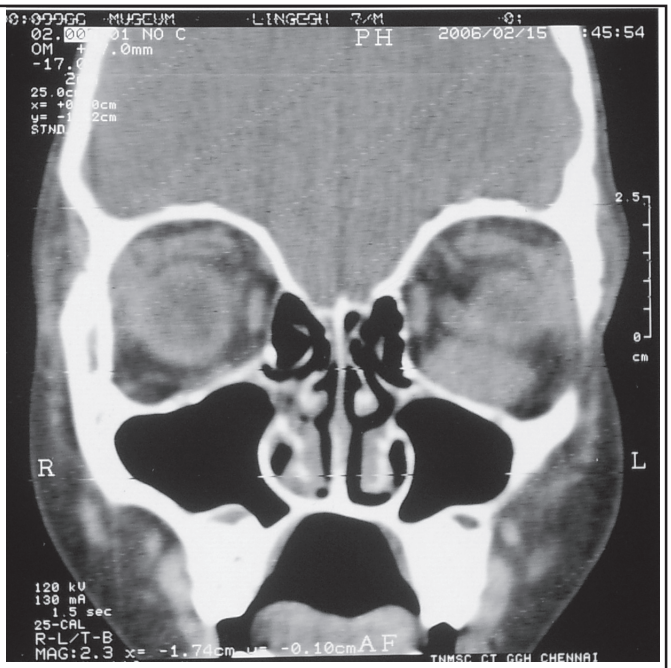

Fig.2. Cavernous hemangioma - Rounded lobular enhancing lesion in left orbit

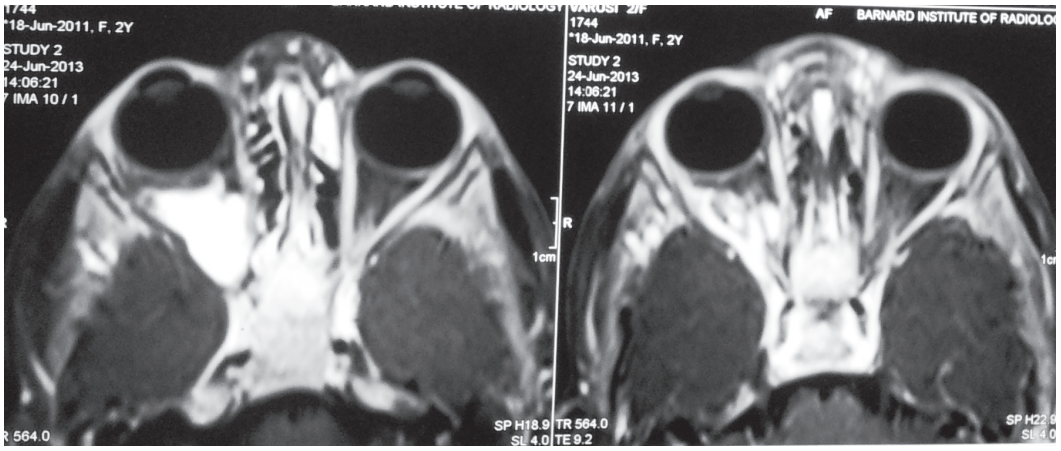

Fig.3. Orbital varices. Enhancing bright shadows on the right behind the globe

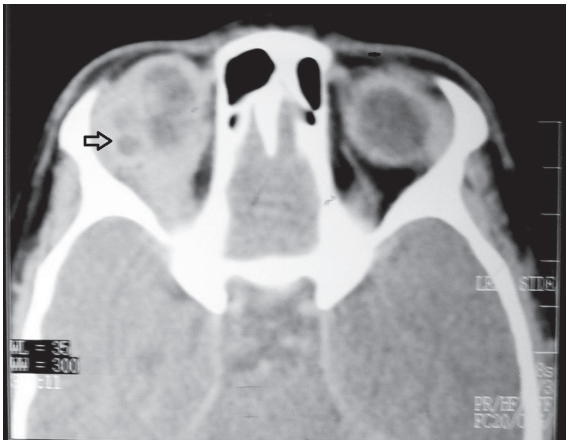

Fig.4. Abscess - right orbit

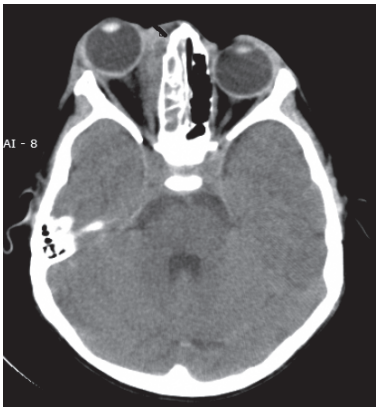

Fig.5. Infection from neighbouring ethmoid sinuses. Small subperiosteal collection in the medial wall of orbit.

hemangioma (Fig.2) is seen as a homogenously dense mass with smooth margins that enhance in the late venous phase with contrast. The globe is just pushed forward and not involved. The intra orbital muscles and optic nerve can be visualised separately. They do not increase in size on straining or changing to the prone position. The lymphangioma is slow growing but more likely to show hemorrhage into the lesion and worsening of symptoms. There is no enhancement. Fig.3 is a 3 year old girl with a history of increased proptosis on crying. This history is typical of orbital varices. Orbital varices are just varicose veins. They may not be evident if the child is not straining or crying. There are hyper intense enhancing lesions in the right retroorbital region extending to the apex of the orbit. The condition is painless unless there is thrombophlebitis.

Inflammatory conditions can also cause proptosis. Abscesses can occur in the orbit. They exhibit the classical enhancing rim that is pathognomonic of an abscess.(Fig.4) Infection can also spread into the orbit from sinuses. Fig.5 shows a small subperiosteal collection in the medial wall of the orbit causing proptosis. The adjacent ethmoid sinuses are opacified with thick intercellular bony septae due to chronic sinusitis. Sinus infection and infective foci in the middle third of the face can cause cavernous sinus thrombophlebitis and thrombosis which can also cause proptosis. The proptosis is due to inflammation of the orbital tissues, venous congestion and a dilated superior ophthalmic vein. The superior ophthalmic vein is the most consistent of the orbital veins and forms an important anastomotic channel between the extracranial and intracranial venous systems. The normal superior ophthalmic vein is only about 2mm. A dilated superior ophthalmic vein is shown in Fig.6 and is a clue for certain conditions. It is a feature of carotico-cavernous fistulae, cavernous sinus thrombosis or thrombophlebitis, orbital pseudotumor and parasellar meningioma. The MRI (Fig.7) film of the same child shows an enlarged cavernous sinus on the right . The outer border is convex compared to the other side. The internal carotid artery seen as a black shadow or flow void within the cavernous sinus appears smaller.

Proptosis is an alarming sign. While the globe can be viewed with an ophthalmoscope, the retroorbital area requires higher imaging like CT and MRI.

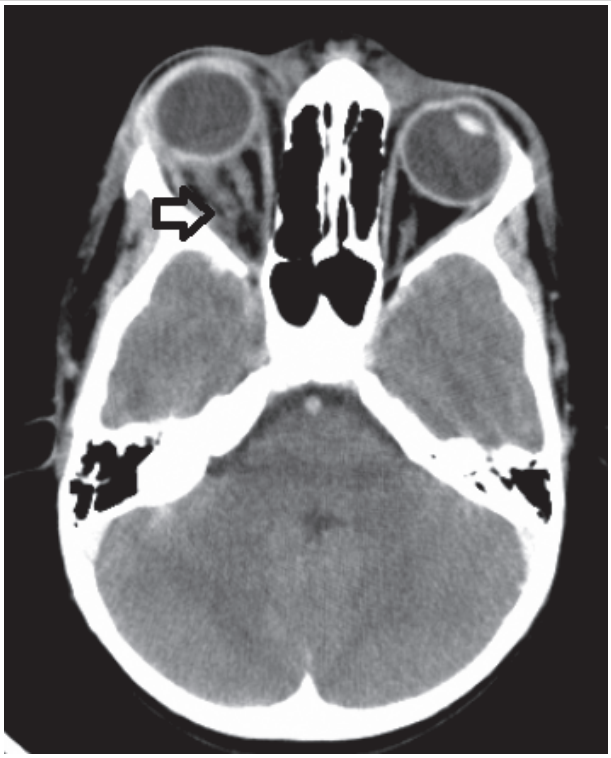

Fig.6. Superior orbital vein(arrow)

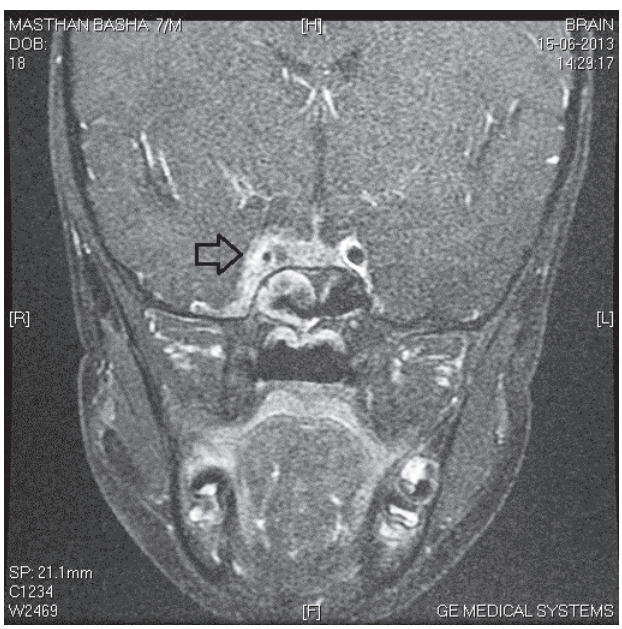

Fig.7. Cavernous sinus thrombophlebitis on right (arrow)

CASE STUDY

AN INTERESTING CASE OF ARTERIOVENOUS MALFORMATION

*Ramya R
***Sundari S
**Ravisekar CV
**Kumarasamy K
**Karamath SP

Abstract: *Arteriovenous malformation (AVM) is a rare condition seen in children that results from abnormalities in blood vessels which may be potentially fatal. AVM with high flow of the head and neck are characterised by massive bleeding and aesthetic defects.Here we report a case of high flow arteriovenous malformation in the right retro maxillary region in a ten year old female child who presented with massive pulsatile bleeding from the oral cavity.*

Keywords: *Arteriovenous malformations, Pulsatile bleeding, Retro maxillary region*

Case Report

Ten year old female child, apparently normal earlier presented with massive bleeding from the oral cavity of three days duration. There was history of swelling of right cheek for one week without bleeding manifestations or trauma. On examination child had massive bleeding requiring resuscitation with fluids and whole blood. Hematological work up was found to be normal. The child continued to have pulsatile bleed from oral cavity adjacent to upper 2nd molar tooth (Fig.1). Hence, CT-Paranasal sinus (PNS) was done.

CT- PNS showed lytic lesion with soft tissue density and bony expansion in right maxillary region (Fig. 2). As the bleeding was pulsatile, CT- angiogram was also planned.

CT angiogram showed high flow arteriovenous malformation of the right retromaxillary region with feeding from external carotid system (Fig.3,4) and hence planned for embolization of the feeding vessels of the AVM.

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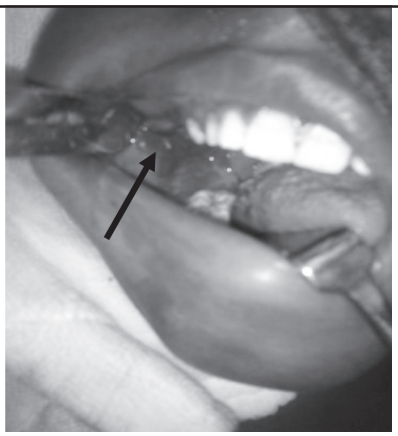

Fig.1. Pulsatile bleed near upper molar tooth

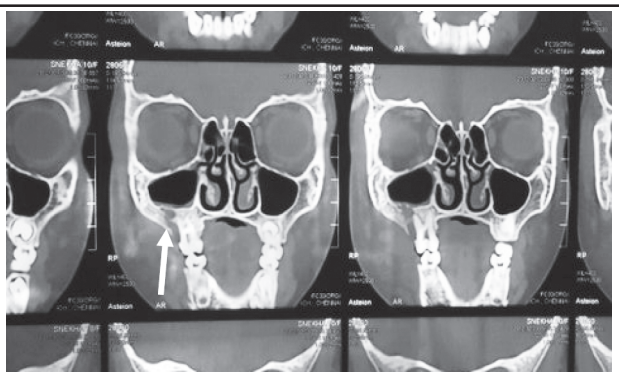

Fig.2. CT-PNS showing lytic lesion of right maxilla

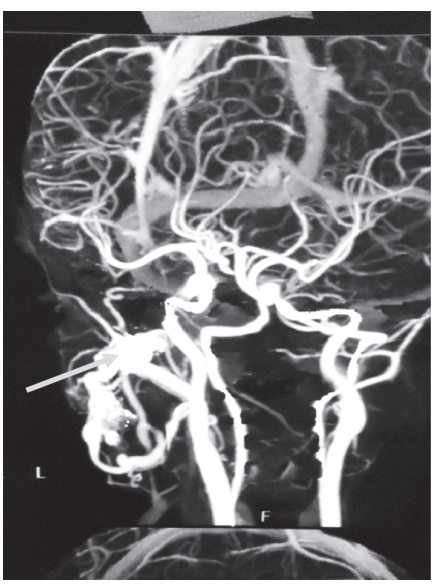

Fig.3. CT- angiogram showing AVM in right maxillary region

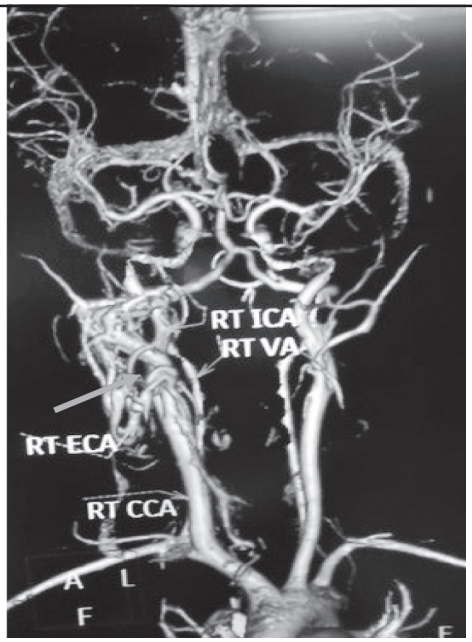

Fig.4. 3D reconstruction view of the same

Through right transfemoral approach, embolization of the right internal maxillary artery using gel foam was done by the interventional radiologist. Although intensity of bleed reduced, child continued to have ooze from the oral cavity which required packing. So definitive surgery to remove the AVM in toto was planned after discussion with vascular surgeon and oromaxillary facial surgeon (OMFS). Under general anaesthesia, ligation of the feeding vessels of the AVM was done by vascular surgery team (Fig.5). Removal of the AVM in toto along with the right maxilla was done by the OMFS team (Fig.6).

Fig.5. Ligation of the feeding vessels

Fig.6. Removed maxillary region

The child did not have further episodes of bleed and is on regular follow up in the pediatric OP department.

Discussion

AVMs are vascular defects caused by the absence of normal capillary beds, which lead to the development of abnormal blood channels that connect the arterial circulation to the venous circulation directly. These defects are usually benign, but in some cases they can be life-threatening because of their potential for intractable bleeding. Arteriovenous malformations are both congenital and acquired.[1] The detection rate of AVM in the general population is approximately 1.34 per 100,000 persons.[2]

AVMs can be classified into low flow (capillaries, venous, lymphatic or combined) and high flow (arteriovenous) types. The most common symptom of this condition is the presence of a slowly growing mass a followed by bleeding from the involved site. Intraosseous vascular malformations near the alveolar bone often presents with pericoronal bleeding, mobile teeth, and sometimes occlusal anomalies.[3]

Colour doppler ultrasound can provide information about the flow velocity. CT scan will show the extent of the lesion and bone erosion.[3] Angiography and MR imaging are the preferred imaging modalities.[4] MRI depicts the anatomic relation of the vascular lesion with adjacent organs. Angiography is currently the gold standard for the determination of location and flow characteristics of vascular lesions. Embolization, which consists of occluding the vessels contributing to the lesion, has been used to control bleeding.[5] Several materials, usually inserted by means of femoral catheterization,[3] have been used such as polyvinyl alcohol,[6] gelfoam[5] and metal coils.[7]

Embolization controls the acute hemorrhagic phase, but does not eliminate the risk of a recurrence, owing to the appearance of a collateral circulation. It, however, reduces the blood flow, allowing time for excision surgery to be performed.[5] Embolization, combined with surgical treatment, is the most preferred approach.[5,8] Surgical treatment includes complete excision of the lesion. Mortality rate is 10–15% of patients, who have significant hemorrhage and morbidity of various degrees occurs in approximately 50%.[9] Mortality and morbidity rates are significant because of the fact that AVMs located in the head and neck region are clinically silent until they are manually manipulated or subjected to some sort of trauma and hemorrhage.

In comparison to AVM case reported by Dalkilie et al, the present case of AVM studied also had similar presentation as recurrent bleeding from oral cavity and maxillary mass.[10] The case management was also similar as embolization followed by surgery, but in contrast to AVM case study by Dalkilie et al, the present case studied did not develop any new lesions elsewhere in follow up.

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CLIPPINGS

Vitamin C for preventing and treating pneumonia

Pneumonia is one of the most common, serious infections, causing two million deaths annually among young children in low-income countries. In high-income countries pneumonia is most significantly a problem of the elderly.

The objective was to assess the prophylactic and therapeutic effects of vitamin C on pneumonia.

The prophylactic use of vitamin C to prevent pneumonia should be further investigated in populations who have high incidence of pneumonia, especially if dietary vitamin C intake is low. Similarly, the therapeutic effects of vitamin C should be studied, especially in patients with low plasma vitamin C levels. The current evidence is too weak to advocate widespread prophylactic use of vitamin C to prevent pneumonia in the general population. However, therapeutic vitamin C supplementation may be reasonable for pneumonia patients who have low vitamin C plasma levels because its cost and risks are low.

Hemilä H, Louhiala P. Vitamin C for preventing and treating pneumonia. Cochrane Database of Systematic Reviews 2007, Issue 1. Art. No.: CD005532. DOI: 10.1002/14651858.CD005532.pub2. Published Online: July 6, 2011.

CASE STUDY

CAFFEY'S DISEASE WITH BILATERAL ULNAR INVOLVEMENT

*Nancy Jeniffer V
** Pushpalatha K
***Udayakumar S

Abstract: *"Caffey's disease" or "infantile cortical hyperostosis", a rare disorder in childhood, is a self limiting disease of unknown aetiology occurring in infants, characterised by fever, irritability, swelling of soft tissues and cortical bone thickening. Mandible, legs and forearm are the most common sites of osseous involvement. Among the long bones, tibia and ulna are the most common to be affected but symmetrical involvement is rare. We report an unusual case of symmetrical involvement of ulna.*

Keywords: *Caffey's disease, Bilateral ulnar hyperostosis, Symmetrical hyperostosis and self limiting hyperostosis.*

"Caffey's disease" or "infantile cortical hyperostosis", a rare disorder in childhood, is a self limiting disease of unknown aetiology occurring in infants. It is characterised by fever, irritability, swelling of soft tissues and cortical bone thickening. Thickening of mandible and forearm bones are the most common presentations but with the exception of the mandible, single bone involvement is suggestive of trauma rather than Caffey's disease.[1,2] Though ulna involvement is common among tubular bones, symmetrical involvement is rare. We report a case of bilateral ulnar bone involvement with Caffey's disease and emphasize the importance of considering Caffey's disease in infants presenting with swelling involving more than one site as a diagnosis of exclusion. Differential diagnosis include syphilis, bilateral osteomyelitis, scurvy, hypervitaminosis A, metastatic bone disease and child abuse / non accidental trauma.

* Post Graduate Student, Pediatrics

** Professor and Head, Department of Pediatrics

*** Associate Professor,
Department of Pediatrics,
ESIC MC and PGIMSR,
Bangalore.

Case Report

An eight month old boy presented to us with history of bilateral forearm swelling, fever and excessive cry of two week duration. On examination there was bilateral symmetrical forearm swelling with tenderness and pseudo-paralysis. Radiograph of both forearms showed fusiform swelling of soft tissues around radius and ulna besides irregular periosteal reaction in both ulna. Laboratory investigations revealed markedly elevated ESR and CRP with leucocytosis. Congenital syphilis was ruled out. Sickling test was negative. MRI scan of both forearms was suggestive of osteomyelitis. Total body MRI done to rule out any primary site of malignancy was negative. A diagnosis of sclerosing osteomyelitis of ulna was made and the child was treated empirically for bilateral osteomyelitis for six weeks. Blood cultures showed no growth. The swelling of the forearms showed a waxing and waning course over the following three months without suppuration prompting to revise the diagnosis.

Caffey's disease was suspected when the infant was readmitted with similar complaints without suppuration characteristic of long standing osteomyelitis, absence of lytic lesions in the bone, repeated negative blood cultures, presence of leucocytosis, increased ESR, elevated CRP, raised alkaline phosphatase, response to anti-inflammatory drugs and typical features of marked periosteal new bone formation surrounding diaphysis sparing the metaphysis and epiphysis (Fig.1). Histopathologial examination of the bone biopsy showed features suggestive of Caffey's disease (Fig.2). The next flare up was given a trial of NSAIDS followed by corticosteroids with which good clinical response was seen. Now the child is two years old and there is resolution of the disease symptomatically as well as radiologically (Fig.3) classical of Caffey's disease.

Discussion

Caffey's disease also known as infantile cortical hyperostosis/Caffey-Silverman syndrome/de-Toni Caffey's disease[1] is a rare condition characterised by irritability, pain, tenderness, hyperaesthesia, tissue swelling and redness involving one or several areas of body.[2]

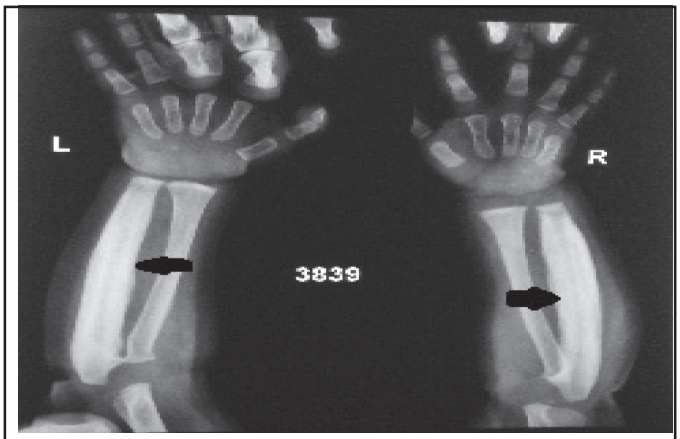

Fig.1. X-Ray both forearms. Severe periosteal reaction involving only the diaphysis.

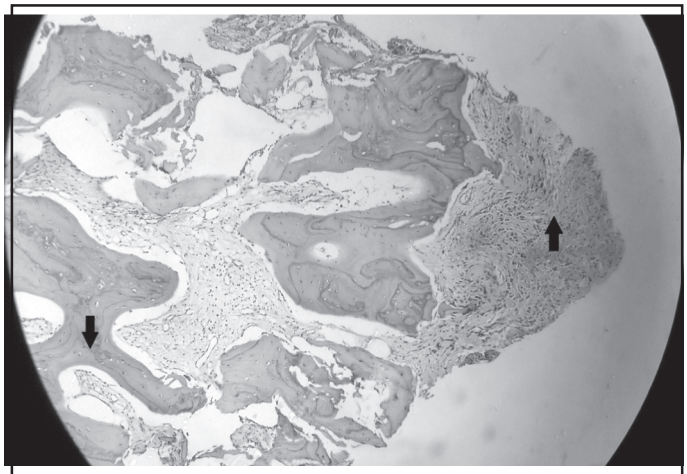

Fig.2. HPE of bone biopsy from right ulna. Shows hyperplasia of lamellar cortical bone lined by osteoblasts (down arrow) and the inter trabecular marrow shows vascular fibrous tissue (up arrow).

Disease affects skeleton and adjacent fascia, muscles and connective tissue. Mandible is the most common bone to be involved and is characteristic while in the extremities though ulna is commonly involved it is usually asymmetric involvement. Single bone involvement other than the mandible is suggestive of trauma rather than Caffey's disease.

The clinical course is variable but usually acute symptoms resolve over the course of few months and outcome is good with spontaneous resolution.[2] Radiological evaluation reveals periosteal new bone formation which leads to pronounced cortical thickening along with underlying areas of soft tissue swelling. The lesions in the long bones typically involve the diaphysis sparing the metaphysis and the epiphysis.[2]

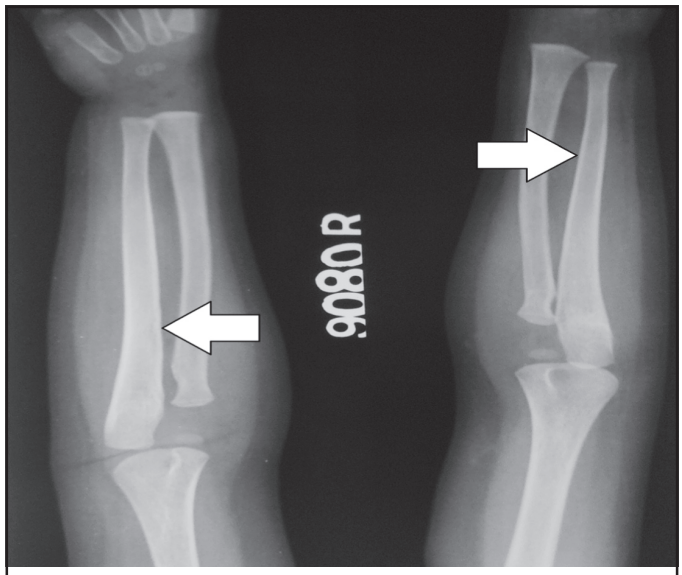

Fig.3. Radiograph of both forearms of the child taken one year later when the symptoms reduced, showing resolution of the hyperostosis of the ulna (white arrows) and clearing of marrow cavity with disappearance of soft tissue swelling.

Lytic lesions involving the skull have been reported but are rare.[3] Investigations reveal increased erythrocyte sedimentation rate, increased total count, high alkaline phosphatase levels and increased C- reactive protein levels. Biopsy and histopathological examination of the affected area shows fibrinoid degeneration in hyperostotic bone and hyperplastic collagen fibres. There is no specific treatment.[2] Complete recovery is the rule. Several months to years are required for resolution to be complete.[4] Late recurrences have been reported. Management trials with indomethacin and corticosteriods have been used to hasten bone remodelling.[5]

Multifocal involvement require differentiation from multifocal osteomyelitis, congenital syphilis, leukaemia, Vitamin A toxicity, long term treatment with PGE-1 for ductus dependent cyanotic CHD.[6,7] This child was diagnosed as a case of Caffey's disease after meticulous work up, ruling out other possible conditions.

Points to Remember

- ***Caffey's disease is a diagnosis of exclusion, to be considered when hyperostosis of bones is seen and an important differential diagnosis of sclerosing osteomyelitis.***
- ***It is a benign condition showing a waxing and waning course.***

- ***The disease shows remission by 4 to 5 years of age.***

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CLIPPINGS

Paakkonen M, Kallio MJ, Kallio PE, Peltola H. CRP versus evythrocyte sedimentation rate, white blood cell count and alkaline phosphatase indiagnosing bacteraemia in bone and joint infecdtions. Ja Paediatr Child Health. 2013, March.

Bacteraemia is common in childhood acute bone and joint infections and demands urgent treatment.

Blood Creactive protein (CRP),erythrocyte sedimentation rate and white blood cell count (WBC) are well known and established markers in these infections. Instead, no information is available on serum alkaline phosphatase whose concentration is known to increase in septic conditions.

In a large prospective treatment trial comprising of 265 children with acute culture-positive bone or joint infection, all these laboratory indices were monitored on admission to hospital. The predictive value to detect bacteraemia was assessed for each of these four indices.

None of the markers could reliably diagnose bacteraemia. CRP alone was significantly higher among bacteraemic patients.

Continuous support for women during childbirth

Historically, women have been attended and supported by other women during labour. However, in hospitals worldwide, continuous support during labour has become the exception rather than the routine.

Primary: to assess the effects of continuous, one-to-one intrapartum support compared with usual care. Secondary: to determine whether the effects of continuous support are influenced by: (1) routine practices and policies; (2) the provider's relationship to the hospital and to the woman; and (3) timing of onset.

Continuous support during labour has clinically meaningful benefits for women and infants and no known harm. All women should have support throughout labour and birth.

Hodnett ED, Gates S, Hofmeyr G, Sakala C. Continuous support for women during childbirth. Cochrane Database of Systematic Reviews 2013, Issue 7. Art. No.: CD003766. DOI: 10.1002/ 14651858.CD003766.pub5. Published Online: July 15, 2013.

ELECTION NOTICE

To Date: June 25, 2013

ALL FELLOW, LIFE & ORDINARY IAP MEMBERS IN DELHI STATE

Dear Fellow Academicians,

Greetings from Central IAP Office!

Through this circular letter we invite nomination for the post of Editor – in – Chief of Indian Pediatrics from the Central IAP members from Delhi State.

NOTICE

TO ALL ELIGIBLE FELLOW / LIFE / ORDINARY MEMBERS OF IAP FROM DELHI STATE

The term of office of the present Editor-in-Chief of the INDIAN PEDIATRICS expires on 31st December 2013. Biodata of not more than 400 words are invited from interested candidates. The Fellow, Life & Ordinary members of the Indian Academy of Pediatrics from Delhi State are eligible to apply for this post. The appointment will be made by the Executive Board at its forthcoming meeting in November 2013 for the term beginning from 1st January 2014 to 31st December 2016. The biodata should be submitted to the Secretary General, Indian Academy of Pediatrics, Kailas Darshan, Kennedy Bridge, Mumbai – 400007 not later than **15 September 2013.**

We would like to bring to your notice some additional points for submission of nomination & the IAP's constitutional provisions with regards to selection / election of the Editor – in - Chief:

(1) Nomination form is attached. Kindly fill-up the same and submit it along with your biodata.

(2) The last date for submission of nomination is 15 September 2013.

(3) The nomination should be accompanied by a bank draft of Rs.2,000/- towards nomination fee, in the name of "Indian Academy of Pediatrics" payable at Mumbai.

(4) The IAP's constitutional provisions related to selection / election of Editor – in – Chief are given overleaf.

(5) This notice will be printed in Indian Pediatrics and Indian Journal of Practical Pediatrics.

With warm regards and best wishes.

Yours sincerely,

Dr. C. P. Bansal
President

Dr.Sailesh Gupta
Hon. Secretary General

IAP's Constitutional provisions related to selection / election of Editor – in – Chief

11.2 The Society shall have the following Office Bearers:-

President - One

President – Elect – One

Vice-president - One

Immediate Past President - One

Secretary General – From Mumbai, Navi Mumbai, Thane One by all India election

Treasurer – From Mumbai, Navi Mumbai, Thane One by all India election

Editor – in – Chief of Indian Pediatrics

Editor – in – Chief of Indian Journal of Practical Pediatrics

Joint Secretary – From Delhi, Gurgaon, Bahadurgarh, Sonepat, Ghaziabad, Faridabad and Noida by all India election

11.3 The term of the President, President Elect, the Immediate Past President and the Vice-President shall be for one year, (not eligible for re-election subsequently), that of the Secretary General, Joint Secretary and the Treasurer, will be of 2 years (not eligible for re-election). The Editors-in-Chief will be of three years (eligible for re-appointment for one more term). In case of resignation, or otherwise the concerned Office Bearers or Executive Board member shall continue in office till a successor is elected or selected or appointed as the case may be.

11.8 All the terms of Office Bearers and Executive Board shall be from January 1 to December 31.

14.4 The Ordinary/Life member contesting for the post of President Elect should have been a member of the Society for 10 complete years consecutively as on 1st January to be eligible to contest for the ensuing election and should have served on the Executive Board or as Office Bearer or both for a period of 2 complete years before contesting for the post of President Elect. The Chief editors of Indian Pediatrics and Indian Journal of Practical Pediatrics, Honorary Secretary, Joint Secretary, Treasurer and Organizing Secretary of Pedicon will not seek election for any the post of President elect till the completion of their present term in the office. *These changes in the constitution will not affect the eligibility of candidates to re-contest for the future elections who contested before these changes.

14.9 The Secretary General and the Treasurer shall be residents of Mumbai or Navi Mumbai or Thane city, Joint Secretary shall be from Delhi, Gurgaon, Bahadurgarh, Sonepat, Ghaziabad, Faridabad and Noida and the Editor – in – Chief of Indian Pediatrics shall be the member of the society from Delhi State and the Editor – in – Chief of Indian Journal of Practical Pediatrics shall be a member from Chennai. The Organizing Secretary of the Annual Conference of the Society shall be a resident of the city / district / state of the respective city / district / state branch hosting the conference.

14.10 Nominations for the post of Editor-in-Chief of Indian Pediatrics shall be invited from amongst Life members of Society from Delhi State. This will be advertised in all the three publications of the Society i.e. Indian Pediatrics, Indian Journal of Practical Pediatrics, Academy Today at scheduled time. The nominations will be then scrutinized by the Executive Board, and the Editor-in-Chief will be appointed/elected by the Executive Board as necessary. The eligibility criteria for Editor - in Chief are that he / she must have served the journal for at least 6 years in combination or isolation as member of Editorial Board and Executive Editor and Managing Editor.

INDIAN ACADEMY OF PEDIATRICS

Kailas Darshan, Kennedy Bridge (Nana Chowk), Mumbai-400007

ELECTION TO THE POST OF EDITOR – IN – CHIEF OF INDIAN PEDIATRICS, 2014 - 16

NOMINATION FORM

(PLEASE FILL-UP THE FORM IN BLOCK LETTERS)

Name of the Office for which the Candidate is Nominated …….....

Name of the Candidate (in full) ……..…….....

(As registered with IAP)

Candidate's Address ……...

……STATE ..…….....

IAP Membership No. of the Candidate ……..since ……...

Telephones (STD CODE ……) (OFF) …….. (RESI) …….....

Mobile ……..Fax …….. Email:…….....

Offices held by the candidates in Central IAP & Year(s) …….....

Name of the Proposer ……..…….

(As registered with IAP)

Proposer's Address -……...

Membership No. of the Proposer.…….…….....

Telephones (STD CODE ……) (OFF) …….. (RESI) …….…….....

Mobile ……..Fax …….. Email:…….....

Proposer's Signature & Date …….....

Name of the Seconder ……..

(As registered with IAP)

Seconder's Address ……...

Membership No. of the Seconder …….…….....

Telephones (STD CODE ……) (OFF) …….. (RESI) …….....

Mobile ……..Fax …….. Email:…….....

Seconder's Signature & Date …….

DECLARATION BY THE CANDIDATE

"I hereby declare that I consent to this nomination and that the information given hereinabove is true and correct to the best of my knowledge and belief".

Place:

Date: .....

(Signature of the Candidate)

ELECTION NOTICE

To

Date: June 25, 2013

ALL FELLOW, LIFE & ORDINARY IAP MEMBERS IN CHENNAI

Dear Fellow Academicians,

Greetings from Central IAP Office!

Through this circular letter we invite nomination for the post of Editor – in – Chief of Indian Journal of Practical Pediatrics from the Central IAP members from Chennai.

NOTICE

TO ALL ELIGIBLE FELLOW / LIFE / ORDINARY MEMBERS OF IAP FROM CHENNAI

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President

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INDIAN ACADEMY OF PEDIATRICS

Kailas Darshan, Kennedy Bridge (Nana Chowk), Mumbai-400007

ELECTION TO THE POST OF EDITOR – IN – CHIEF OF

INDIAN JOURNAL OF PRACTICAL PEDIATRICS, 2014 - 16

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"I hereby declare that I consent to this nomination and that the information given hereinabove is true and correct to the best of my knowledge and belief".

Place:

Date: **……**

(Signature of the Candidate)

The Annual Refresher Course for Pediatric Intensive Care is back……..

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5th Refresher Course on Pediatric Critical Care& Emergencies

August 15th-17th 2013

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Organizing Committee : Dr Suchitra Ranjit & Dr Indira Jayakumar

Contact Phone Numbers: Dr Rajeshwari (Ph No: 9884058200)

Demand draft to be raised in favor of **- *"Pediatric ICU"***, payable at Indian Overseas Bank, Apollo Hospitals-Greams Lane Branch, Chennai.

Address: Dr Suchitra Ranjit, Department of Pediatric Intensive care Unit, 3rd Floor, Apollo Children's Hospital, No.15, Shafi Mohammed Road, Thousand lights, Chennai-600006.

FAMILY BENEFIT SCHEME
INDIAN ACADEMY OF PEDIATRICS

Enroll in the Scheme and provide financial security to your family and also to help your FBS - IAP colleague

Family Benefit Scheme of IAP

- Mutual Benefit Scheme.
- To Provide immediate substantial financial aid to the family members on death of the members who are in the scheme.
- Scheme is for the Life Members and Associate Life Members of IAP who have not completed the age of 65 years at the time of joining the Scheme
- "Founder Members", who have joined the Scheme on or before 31.03.2013 have to pay Fraternity Contribution for 20 years only.
- "Regular Members", who enroll in the Scheme on or after 01-04-2013 have to pay Fraternity Contribution for 25 years only.

JOINING FEE from 01.04.2013

For Age between 25+ to 30 Years - ₹ 5,000/-
For Age between 30+ to 35 Years - ₹ 7,500/-
For Age between 35+ to 40 Years - ₹ 10,000/-
For Age between 40+ to 45 Years - ₹ 12,500/-
For Age between 45+ to 55 Years - ₹ 15,000/-
For Age between 55+ to 60 Years - ₹ 30,000/-
For Age between 60+ to 65 Years - ₹ 45,000/-

Caution deposit - ₹ 1500, Annual Admin Fee - ₹ 400/

Total amount to pay is Joining fee (as per age slab) + Caution deposit + Annual Administration fee.

For Eg. A member age 34 years old has to pay
₹ 7,500 + ₹ 1,500 + ₹ 400 = Total - ₹ 9,400/-

How to apply for membership

Life members & Associate Life Members of IAP will have to apply in the prescribed Application form which can be obtained from FBS-IAP Office, Hyderabad or can be downloaded from **www.fbsiap.org.** The application form should be submitted to the Scheme office with relevant fee by Cheque / D.D in favor of " **Family Benefit Society**" payable at Hyderabad.

Electronic direct transfer can be made to **"Family Benefit Society" Account No. 62184506297 State Bank of Hyderabad, Gunfoundry, Hyderabad, mentioning IFSC CODE: SBHY0020066**

Proof of IAP Life membership or Associate Life membership, Proof of Age along with the Nominee details are to be submitted with the application form to the Hon. Secretary of the Scheme.

Fraternity Contribution

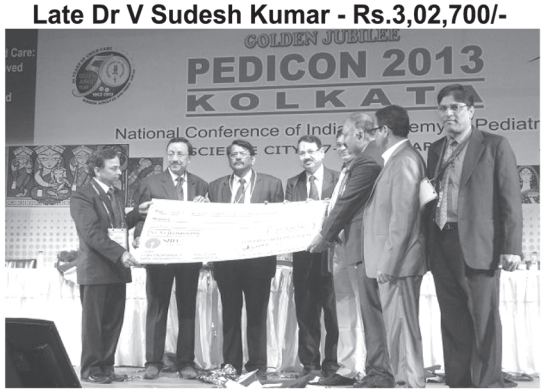
Fraternity Contribution Bill will be raised **once in a year on 30th September.**

Advance Fraternity of ₹ 10,000/- can also be paid for future adjustments. (Optional)

Every member of the Scheme shall pay Fraternity Contribution of ₹ **360/-** (Death Benefit Fund ₹ 300 + Future Liability Fund of ₹ 60 {i.e 20% of DBF}) per death of FBS-IAP members. The amount calculated accordingly to the number of Members who expired in one year. The amount thus collected from the members of the Scheme will be paid after verifying the claim to the Nominee of the members who have expired.

A member can voluntarily retire from Membership of the Scheme by giving a written request to the Hon. Secretary of the Scheme

First DBF paid to the nominees of Late Dr V Sudesh Kumar - Rs.3,02,700/-



Second DBF to the nominees of Late Dr V Jose Kuruvilla will be aprox - Rs.4,26,000/-

Dr C.P. Bansal
President IAP

Dr. George F. Moolayil
Chairman FBS IAP

Dr Sailesh Gupta
Hon. Secretary IAP

Dr Ajoy Kumar
Hon. Secretary FBS IAP
hysecfbs@gmail.com

Dr Praveen J Mehta
Hon. Treasurer IAP

Dr M Surendranath
Hon. Joint Secretary & Treasurer FBS IAP
hontrfbs@gmail.com

For any other details contact Hon. Secretary of FBS IAP

6-3-598/1, 1st Floor, Navata Castle, Venkatramana Colony,
Khairatabad, Hyderabad Andhra Pradesh – 500 004 Mobile : +91 9848034599 (Hon. Secretary)
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Venue: Hotel GRT Convention centre, T.Nagar, Chennai. India.

Date: 10-12, Jan 2014

We cordially invite you for the Myocon 2014, 2nd International conference on Neuromuscular diseases. This conference has lectures, workshop, Paper presentations, Oration, Clinical case discussions, Parents session etc.

Important topics at the conference .....

- Introduction to Neuromuscular Diseases, Genetic testing,
- Peripheral Neuropathies in India
- Charcot Marie Tooth Disease & other genetic neuropathies
- Use of novel proteomic technologies to investigate early events in the pathogenesis of DMD
- Treat NMD-Neuromuscular network & other international initiatives

Siddharth Memorial Oration

"Opportunities and challenges of therapeutic approaches for Duchenne Muscular Dystrophy"

- Physiotherapy in Neuromuscular Diseases, RASCH analysis & Outcome measures in Muscle Disease & Orthotics & Wheelchair modification
- Mitochondrial diseases : Clinical features, diagnostics & future perspectives
- Congenital Myasthenic syndromes, diagnosis & Therapy
- Future directions for antisense-mediated exon skipping for Duchenne muscular dystrophy
- Paper Presentations, Clinical case discussion,
- Parents session

Pre conference workshops on the 10th Jan 2014 – (pre registration compulsory)

1. Basics of neurophysiology in children – Dr.Vasudevan (For Doctors only)
2. Physiotherapy in children with neuromuscular disorders – Dr Michelle Eagle & Dr.Anna Mayhew

(For therapists only)

Dr.G.Kumaresan	**Dr V.Viswanathan**	**Dr. Satish Khadilkar**	**Dr. M.D. Nair**
Org. Chairman	Org. Secretary	Jt. Org. Secretary	Jt. Org. Secretary

Many International & National faculties have consented to participate as Faculty in this International conference. Details of the programme can be seen in www.mdindia.org

For Further Details Contact:

Muscular Dystrophy Association India, C/O: V.J. Clinic

New no: 6 (Old no:21) 4th cross road, Sastri nagar, Adyar, Chennai – 600020. Tamilnadu. India

Phone: 9444456056. Mail: myocon2014@gmail.com, Website : www.mdindia.org

This conference attracts CME credits from Tamil Nadu Dr. MGR Medical University

SOUTH PEDICON 2013

XXVII South Zone & XXXII Karnataka State Annual Conference of Indian Academy of Pediatrics.

Theme: Child survival—Meeting the unmet challenges

Hosted by :

- IAP, Belgaum district branch
- Dept of Pediatrics, KLE University's J N Medical College, Belgaum
- Dept of Pediatrics, Belgaum Institute of Medical Sciences, Belgaum.

Venue: J N Medical College, Belgaum. Karnataka

Dates: 18, 19, 20 October 2013.

Associate IAP Branches: IAP, Kerala State branch, IAP Tamil Nadu State branch

- southpedicon2013@gmail.com
- website:southpedicon2013.org

Dr Niranjana Mahantashetti
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Registration Tariff

Sl No.	Nature of Registration	Till 30/6/2013	1/7/2013-17/10/2013	Spot
1	Delegate	300/-	3500/-	4000/-
2	Accompanying Person	2000/-	2500/-	3000/-
3	Post Graduates**	2000/-	2500/-	2500/-
4	Workshops	500/-	500/-	No Spot Entry

**Note: Postgraduates Should attach certificate from Head of Dept.

RIPE 2013

Ramachandra Intensive Pediatric Postgraduate Exam review –RIPE 2013 is to be conducted on October 26th and 27th 2013 (Saturday and Sunday) at University Auditorium, Sri Ramachandra Medical Centre, Chennai.

This is a 2 day programme of extensive clinical case discussions by eminent and experienced teachers, with demonstration of important clinical signs, dedicated neonatology session, methodical video demonstration of normal development assessment, viva voce, X-rays discussion and OSCE.

Registration details : Registration fee : Rs. 3000/- Spot registration fee : Rs.3500/-

Payment to be made by Cheque/DD in favour of : "Sri RamachandraUniversity", payable at Chennai. Out station cheques Rs. 50/- in addition to registration fee.

Address : Dr. Julius Scott, Pediatric Hemato Oncologist, Department of Pediatrics, Sri Ramachandra Medical Centre, No.1, Ramachandra Nagar, Porur, Chennai – 116.

For details, contact Mr. Rajesh, social worker : 9952280823

Organizing chairpersons:

Prof. L.N. Padmasani

Prof. P.Ramachandran

Prof. P. Venkataraman

Organizing Secretary :

Dr.Julius Xavier Scott

HOPE 2013

Organized by Med Hope, a foundation by Medical Students for Hemato Oncology in Pediatrics, HOPE 2013, is an comprehensive undergraduate pediatric exam review with clinical case discussion by eminent professors, pediatric quiz, best case/poster presentations (with cash prizes and trophies for winners) and a panel discussion on career prospects.

Date : October 5th and 6th 2013 (Saturday and Sunday)

Venue : University Auditorium, Sri Ramachandra Medical Centre, Chennai.

Registration Fees: Rs. 600/- After 1st of October, Rs. 800/-

Payment to be made by DD/Cheques in favour of " Sri RamachandraUniversity" payable at Chennai.

Address for correspondence : Dr. Julius Scott, Pediatric Hemato Oncologist, Department of Pediatrics, Sri Ramachandra Medical Centre, 1, Ramachandra Nagar, Porur, Chennai – 116.

Organizing chairperson: Dr. S. Roshini

Staff Advisors: Prof. L.N. Padmasani

Dr. Julius Scott

Organizing Secretaries : Dr. A.K. Sanjay, Dr. R.R. Mahin.

For details regarding: Case presentations, contact : casereports@medhopefoundation.org

Registration, contact : registration@medhopefoundation.org

Any queries, contact : enquiry@medhopefoundation.org

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