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EDITOR'S DESK

We are pleased to bring out the issue on 'Laboratory Medicine', which will be of immense use to all our readers.

This issue was meticulously formulated by Dr. S. Thangavelu, Asst. Professor, Pediatric Intensive Care Unit (PICU), Institute of Child Health and Hospital for Children, Chennai. He has carefully chosen the topics which are relevant to all the practising pediatricians, academicians and postgraduates. We are thankful to him for his sincere effort in bringing out this interesting and informative issue.

The new strides in the day to day developments in laboratory medicine need periodic review by experts in the field.

The editorial by Dr. Elizabeth Mathai is very informative for all those engaged in clinical practice. She has given the guidelines for collection of specimens for microbiological investigations. We thank all the authors who have contributed articles to this special issue in their respective field of interest. They have shared their rich knowledge and vast experience in their articles for the benefit of our readers.

In the current scenario of increasing consumer awareness about the laboratory investigations, this issue will be of immense help to the practicing pediatricians while ordering investigations in the management of day to day problems in clinical practice.

We have also included an article on Severe Acute Respiratory Syndrome (SARS) for the benefit of our readers to highlight the salient features of the recent outbreak of this disease.

The third and fourth issue of IJPP for this year will be on "Infectious diseases" and "HIV infection" respectively.

We welcome the comments and suggestions from the members for further betterment of the journal. We also invite you to share the problems faced in clinical management by practising pediatricians. This will be discussed by experts in the journal.

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NEWS & NOTES

INFANT AND YOUNG CHILD NUTRITION CONFERENCE

Theme: "Men in Child nutrition and Care"

Organised by

IAP – Tamilnadu State Chapter, IAP-Chennai City Branch,
Breastfeeding Promotion Network of India & Nutrition Society of India

Date : 13th July, 2003

Venue : Hotel Vijay Park, 12 Jawahar Lal Nehru Salai, Inner Ring Road, Arumbakkam, Chennai – 600 106. Ph. No. 23791314
Near Hotel Radha Park Inn

Delegate Fee: Rs.300/- **PG Student:** Rs.250/-

Preconference Lactation Management Course : Date: 12th July, 2003

Venue: ICH & HC and M.H., Egmore, Chennai – 600 008.

Registration Fee: Rs.200/- (Limited to 40 delegates only)

Last Date for registration: 5th July, 2003

Cheque / DD should be drawn in favour of "CHEN NUTRICON 2003".

For outstation cheque please add Rs.50/-.

For registration contact

Dr.D.Gunasingh
Organising Secretary, Infant and Young Child Nutrition Conference
IAP Flat, 'F' block, Halls Tower, 56 (Old No33), Halls Road, Egmore, Chennai – 600 008.
Ph. No.044-28191524 Email: iaptnsc@vsnl.net

1ST NATIONAL CME ON INFECTIOUS DISEASES IN CHILDREN: FROM PROBLEMS TO SOLUTION

Organised by : IAP Infectious Diseases Chapter

Venue**: Asutosh Birth Centenary Hall: Indian Museum, Kolkata,**

Date**: 17th, 18th May 2003**

Registration Fee	Upto 28.02.2003	Upto 30.04.2003	Spot
Delegate	Rs.500/-	Rs.600/-	Rs.750/-
Postgraduate	Rs.400/-	Rs.500/-	Rs.600/-

DD or Cheque to be drawn in favour of 'IAP INFECTIOUS DISEASES CHAPTER' payable at Kolkata. Rs.50/- to be paid extra for outstation cheque. No cheque will be accepted after 15.04.2003

Address for correspondance: Dr.Tapan Kr. Ghosh, Organising Chairperson, National CME on Infectious Diseases in Children, 13, Neogi Pukur Bye Lane, Kolkata 7000 014. Ph: 033-22445551/ 22164351, Mobile: 9831179718. Email: dr_tkghosh@rediffmail.com

EDITORIAL

GUIDELINES FOR COLLECTING SPECIMENS FOR MICROBIOLOGICAL INVESTIGATIONS

The most important factor that determines the accuracy of any report is the quality of the sample received for testing. A wrong sample can not only miss the pathogen but also lead to wrong therapy. For example, a badly collected sputum sample can lead to identification of members of commensal flora as pathogens resulting in wrong choice of antibiotics. Therefore, it is important that all individuals involved in patient care should understand the critical nature of maintaining specimen quality.

Diagnostic tests offered by microbiology laboratories include cultures to isolate the pathogen, immunological tests to detect antibody response or antigens and more recently, molecular techniques to detect nucleic acids of the suspected pathogen. In India, however, laboratories mostly offer bacterial and fungal cultures and serology only. Therefore some important guidelines for collecting specimens for these investigations are presented.

The sample received in the laboratory should ideally have the original numbers and proportions (or close to it) of bacteria as in the infected site, in a viable state. In order to achieve this, one has to choose the appropriate anatomical site for sampling, collect and transport the sample properly. It is helpful to remember the following general principles in this regard.

1. The sample has to be appropriate and representative. Collect samples from the site where the pathogen is most likely to be found (usually the infected site) and at a stage when organisms may be found in maximum numbers. (S.typhi is most likely isolated from blood during the first week of illness).

2. Care must be taken to send adequate quantity of specimen as adequate material is required for making smears and performing cultures on multiple media. If different types of cultures (e.g., fungal, anaerobic, mycobacterial) are required, additional material should be sent.

3. Collect samples taking care to avoid/minimize contamination with normal flora. In certain situations like, swabs from burn wounds, decubitus ulcer, etc it is impossible to avoid contamination with normal flora. In these cases, care should be exercised in interpreting culture reports. It is also advisable that items like Foley's catheter tips, which are likely to contain a variety of colonizing organisms, are not sent for culture.

4. Antibiotic therapy can make organisms nonviable or decrease the numbers. Therefore, collect samples for bacterial culture prior to initiating antibiotic therapy. In limited conditions, for example, infection with bacteria resistant to the antibiotic being used or when there is lack of penetration of antimicrobial to the site of infection, bacteria can still be isolated from infected sites. While interpreting culture results take this information into consideration.

5. For culture, always use sterile leak proof containers that can be closed tightly. Do not fill to the brim and always avoid soiling of the exterior with sample while collecting and transporting. Avoid soaking swabs in saline/ distilled water prior to specimen collection.

6. Label the container clearly with patient identification details and send the sample to the laboratory along with the request slip detailing the nature of infection, type of sample, time of collection and any other pertinent information. Adequate clinical information will help the microbiologist to assess the sample and modify processing for special needs.

7. All samples are to be considered potentially infective. It is therefore mandatory that appropriate precautions are taken like wearing of gloves and mask are taken while handling samples.

8. In general, transport without delay and without additives.

1. Urinary tract infection (UTI)

UTI is diagnosed by demonstrating infected urine in the bladder. The most reliable method of achieving this is by culture of a representative sample of urine.

To avoid contamination with perineal and urethral flora, 'midstream clean catch' urine is collected directly into a wide mouth sterile container. Since this is a specimen collected by the patient, clear instructions should be given regarding method of collection; children need to be supervised when samples are collected. In babies and children who cannot co-operate, urine may be collected by suprapubic aspiration. Urine may be collected by aspiration from long term indwelling catheters after cleaning the site of aspiration with disinfectant. Catheter tips are not good samples for diagnosing UTI and should be avoided.

Urine for culture should reach the lab within two hours. If this cannot be achieved, urine can be refrigerated up to a maximum of 4 to 6 hours.

Urine for dark field microscopy for lepto-spirosis should be collected before antimicrobial therapy and transported immediately to the laboratory, to visualise motile spirochaetes.

2. Pyogenic infections like wound and burns infection / ulcers / abscesses / cellulitis

The most appropriate specimen to diagnose a pyogenic infection is aspirated pus or biopsy of the infected tissue. Since this is not always practical, swabs of the infected site are used. Swabs however are not suitable for anaerobic culture and culture for fungus.

Prior to swabbing do not apply antiseptics. If there are crusts, these can be removed using sterile distilled water or sterile saline. Be absolutely sure that saline/distilled water is sterile. Using two swabs collect adequate pus or exudate by allowing sufficient contact by rolling the swab over the infected site. If exudate is absent, rub the floor and margins of the infected areas with the swab. Do not wet swabs with saline/distilled water.

If there is an abscess, aspirate the pus and transfer into a sterile plain (no additives) tube with tight fitting stopper. The 'column' of pus will also allow anaerobic conditions to be maintained for a period of time. Biopsies should be sent in sterile plain (no additives) container as early as possible to the laboratory. If the tissue is very small and liable to drying, transport in a small amount of sterile (make absolutely sure) saline.

Transport without delay. If delay is inevitable the sample can be refrigerated for a maximum period of 4 to 6 hours. Samples for anaerobic culture should not be refrigerated.

3. Fluids

Fluids from normally sterile areas like the CSF, ascitic fluid, pleural fluid, synovial fluid etc should be sent in sterile containers. If they are liable to clot, collect in containers with

anticoagulants such as 2.5% sodium citrate. Do not submit swabs dipped in fluid for culture.

Do not refrigerate these samples since some of the potential pathogens are temperature sensitive.

4. Upper respiratory infection.

Collect respiratory samples taking care to minimize contamination with normal flora.

Throat swab: Collect throat swab under proper vision. Depress the tongue and make the patient say a long 'ah'. Using two swabs rub well over tonsils, the tonsillar fossa on both sides and lastly the posterior pharyngeal wall. In addition, collect any obvious exudate. Withdraw the swabs without touching tongue and cheek. Place the swab in a sterile container without additives. Drying of the swab will not affect the recovery of beta haemolytic streptococci.

If 'membrane like' lesions are present, collect a bit and send for culture. It is extremely important in this situation, to give the laboratory the relevant clinical information.

Throat and nasopharyngeal swabs are not useful for identifying the aetiogical agents of sinusitis, or acute otitis media. Culture is not required on a routine basis for these infections. Treatment can be started empirically since most infections are caused by a few limited pathogens. For resistant sinusitis, sinus pus should be cultured. To identify the cause of otitis, collect fresh discharge (if present) under vision and after cleaning the crusts away using sterile saline/ distilled water. If there is no discharge, tympanocentesis may be required.

Nasal swabs are taken if a staphylococcal carrier state is suspected. Nasopharyngeal sampling requires special swabs and is indicated mostly in detecting carrier states (e.g. meningococci).

5. Acute lower respiratory infections (LRI)

The most frequently sent sample for the diagnosis of LRI is sputum. However, the value of sputum culture is limited by the inability to avoid contamination with oral flora.

Rinse the mouth prior to collection, with water, a few times. Encourage the patient to cough deeply and collect the coughed out material directly into a wide mouthed sterile bottle with screw cap. Do not add saliva into this. Early morning sample, collected during the first bout of cough after waking up, is best for isolating pathogens. For children, sputum collection should be done under the supervision of a trained person.

Send the sample without delay and without additives. Refrigeration can affect the recovery of pathogens like H.influenzae

In the laboratory, sputum is assessed for quality. A good quality specimen will have large number of pus cells with very few squamous epithelial cells.

Since the agents of bacterial pneumonia like S. pneumoniae and H .influenzae can be normal commensals in the upper respiratory tract, care has to be taken while interpreting results. It should also be remembered that bacterial respiratory pathogens like Mycoplasma pneumoniae, Chlamydiae pneumoniae and Legionella pneumophila will not grow in routine sputum culture and cannot be identified using Gram stain. These infections are currently diagnosed using non cultural methods like immuno-diagnosis and/ or PCR.

M.tuberculosis will also not grow in routine culture and cannot be seen in Gram stain. Therefore a special request should be made if pulmonary tuberculosis is suspected.

Nosocomial pathogens are 'survivors' and will grow on routinely used media.

Agents of pneumonia in an immuno-compromised patient may be different from those in a normal host. Therefore, this information should be given to the laboratory and tests for agents like P.carinii, requested separately if indicated.

Broncho-alveolar lavage (BAL) collected properly is a better sample than sputum. However contamination with normal flora can not be ruled out in this sample also.

6. Infections in the eye

Corneal ulcers require microbiological investigation. Corneal scraping is the best sample and it is advisable that this is done by an ophthalmologist. Since the sample is extremely small and organisms likely to be fastidious, the sample is best inoculated at the site of collection itself on to media for isolation - Blood agar and Chocolate agar for bacteria; Sabouraud's dextrose agar for fungi. If acanthamoeba keratitis is suspected, the medium for this culture also should be included. Extra-material may be used for microscopy. Sample both eyes separately.

7. Faeces

Culture is not required on a routine basis for the management of diarrhea/dysentery.

If culture is indicated, collect the sample directly into a sterile wide mouthed container with screw cap or snap on cap. Samples mixed with urine and water are not suitable.

Clean containers are sufficient for parasitological examination.

8. Blood

Blood for culture should be drawn under strict aseptic condition. Prepare the skin over the vein as for a surgical procedure. Clean with 70% alcohol and apply povidone iodine. Allow about a minute for the iodine to act. Do not touch this area again, without sterile gloves. Collect adequate quantity of blood using a sterile dry syringe and inoculate directly into blood culture media, using the same needle. Several commercial media are now available for blood culture. Additional media may be needed for fungal and mycobacterial culture. Blood to medium ratio can range from1:10 to 1:5.

Warm the media to room temperature prior to inoculation. Do not refrigerate after inoculation. Multiple blood cultures may be required for the diagnosis of endocarditis.

Bone marrow cultures may yield better results in situations like typhoid fever and brucellosis. These may be sent to the laboratory or directly inoculated into blood culture medium.

Specimens for Mycobacteria smear and culture

Collect specimens from the site of infection as for routine culture.

Sputum is the recommended sample for diagnosing pulmonary tuberculosis. Since the sensitivity of sputum examination is low, the test has to be repeated at least three times. An alternative to sputum is fasting gastric juice, aspirated early in the morning. The entire amount should be sent in a sterile container within 30 minutes. Delay can make the organisms non-viable.

Likelihood of a positive report from 'fluids' increase with the quantity sampled. Therefore send as much as possible in sterile containers, to enable the laboratory to concentrate the material.

For renal tuberculosis, send the entire early morning collection of urine.

Specimens for anaerobic culture

Anaerobes can become nonviable even within 30 minutes, when exposed to atmospheric

oxygen. Therefore samples collected without additives should reach the laboratory within this period.

Aspirated pus and biopsies are ideal for anaerobic culture. Blood for anaerobic culture should be inoculated directly into appropriate media. Specimens collected using swabs and sputum give unreliable results on anaerobic culture and should not be sent.

Specimens for fungal culture

Culture is most often done to diagnose subcutaneous, systemic and opportunistic fungal infections. Biopsy of the affected site is the most reliable specimen. Swabs are not suitable. Do not refrigerate the samples, as some fungi are temperature sensitive. If there are discharging sinuses, collect and send any granules seen on the gauze dressing.

CSF should be tested for diagnosing Cryptococcal meningitis. This should be sent in sterile containers, clearly mentioning the suspected diagnosis.

For suspected pulmonary fungal infections, BAL may be sent. However, results should be interpreted carefully. Candida spp grown from sputum and even BAL are most likely from oral or oesophageal candidiasis. Similarly, Aspergillus spp could be environmental contaminants. Therefore, always correlate culture report with clinical features; send another sample - which should also yield the same fungus, and request for a microscopy report of original sample. In true infections the organism will be seen almost always on microscopy of the sample.

To diagnose P.carinii infection, coughed out sputum is not suitable. Induced sputum after saline nebulisation can be used. Better still are BAL and lung biopsy.

Blood for Serology

Serum is most commonly used for antibody tests. Collect about 5ml blood (more if several tests are required) using a dry syringe and transfer into a clean dry test tube without anticoagulants. Remove the needle before expelling blood into the tube. If serum should be transported or stored for a few days, use sterile tubes. To prevent serum from being chylous, collect blood prior to food intake or only after 4 hours following food.

For most antibody detection tests, blood can be refrigerated for a day if delay is unavoidable. Blood collected for cold agglutination test should not be refrigerated prior to serum separation as antibodies can attach to erythrocytes in the cold.

After separation, serum can be refrigerated for a few days and frozen for a few months, without loss in antibodies.

For functional assays like complement assay, serum should be sent immediately to the laboratory (to be received within 30 minutes) as complement components are heat labile.

Antigen detection tests

Most of these are commercial tests. Manufacturer's instructions should be followed for specimen collection and transport. In general, collect the specimen from the site of infection. .

Elizabeth Mathai
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Christian Medical College, Vellore, Tamilnadu

Further reading

1. Guidelines for collection, transport, processing, analysis and reporting of cultures from specific specimen sources. In: Koneman EW, Allen SD, Janda WM, Schreckenberger PC, Winn WC (ed) Color atlas and text book of diagnostic microbiology, Lippincott, Philadelphia 1997; pp 121-170

2. Miller JM, Holms HJ. Specimen collection, transport and storage In: Murray PR, Baron EJ, Pfaller MA, Tenover FC, Yolken RH (ed) Manual of Clinical Microbiology 7th ed, American Soceity of Microbiology Press, Washington DC 1999; pp 33-63

3. Myer's and Koshi's manual of diagnostic procedures in medical microbiology and immunology/serology, compiled by faculty of microbiology, Christian Medical College, Vellore, 2001

NEWS AND NOTES

USE OF IAP LOGO

1. The individual primary member of the IAP can use the Logo on his/her academy/professional card and letterhead and cannot use the Logo on prescription pads and trade cards.
2. Every primary members has the privilege to use IAP Logo sticker on his personal vehicle, however he/she cannot use it on commercial vehicles owned by them.
3. Primary member of any branch can use Logo for propagating the objectives of the IAP in the Media / AIR/DD/Newsletter/Bulletin however local branch should be informed of this academic activity.
4. The local branch/state branch/chapter/group/cell/center/committees cannot sale the Logo or use it on the accessories for the purpose of the making funds for its activities. The propriety and the power of use of Logo for sale or use by the trade lies with the Central IAP without voiding the norms of the Academy.
5. It is local branch/state branch/chapter/group/cell/center/committees to print Logo on the Letterheads and all the official correspondence by the office bearers should be done on this letterhead.
6. The communication sent on IAP letterhead is presumed to be the voice of the IAP in unanimity expressed by the Office Bearers of that concerned local branch/state branch/chapter/group/cell/center/committees if any primary member wants to express his/her personal views may express on the personal letterhead and views are purely personal and individual.
7. Avoid individual criticism on IAP letterhead even as an officer bearer of the particular local branch/state branch/chapter/group/cell/center/committees, such members who are disregarding this norm would invite disciplinary action by the Executive Board.
8. The Executive Board of IAP has the privilege and authority to warn any such member whose writings are controversial, disrespecting and not conducive to the ideals of the IAP and direct him not to indulge in a manner which would undermine the prestige of the IAP.
9. In spite of memorandum of warning if the member is not conducting properly, the Executive Board has the right to temporarily suspend the member from the primary membership for a period of one year and may be re-instate into the academy after reviewing his/her conduct by the EBM. During the period of suspension such member cannot officially participate in the IAP meeting or contest any from of IAP Elections.
10. It is the responsibility bestowed on Executive Board to be vigilant and alert on such activities of the primary members, which are derogatory to the mission of the IAP.

LABORATORY MEDICINE

INTERPRETATION OF LABORATORY INVESTIGATIONS IN THE DIAGNOSIS OF INTRAUTERINE INFECTIONS

**** Indrashekar Rao***

Introduction

Maternal infection acquired shortly before conception or during gestation can adversely affect pregnancy outcome either by non specific effects of maternal illness or directly through microbial invasion of fetus or neonate.

The organisms causing intrauterine infections can be classified as :

Viral: Rubella, CMV, HSV, HIV, VZV, Parvovirus , hepatitis, coxsackie

Protozoal : Toxoplasma, malaria

Spirochaetal : Treponema

Bacterial : Listeria monocytogenes

The mode of infection can be haematogenous across placenta, ascending infection from infected cervix or due to contact between fetus and infected genitalia during parturition.

There is a possibility of intrauterine infection in an infant if there is a known exposure of mother to infectious agent or if the infant is small for gestational age or there is failure to thrive. The other manifestations are petechiae, hepatosplenomegaly, congenital malformations, thrombocytopenia and skin rash.

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The interpretation of various investigations will be dealt as follows

Viral Infections

1. Rubella: [German measles]

This human specific RNA virus is a member of togavirus family causing mild self-limiting infection in adults but has a devastating effect on fetus. Infection can occur at any time during pregnancy but early gestation infection is very destructive. Congenital rubella syndrome presents as cataract, IUGR, retinopathy, microcephaly, meningoencephalitis, congenital heart disease, splenomegaly, thrombocytopenic purpura. With maternal infection in first 12 weeks, the rate of foetal infection is 81%. As the gestational age advances the infection rate drops. Risk for congenital defects is low if foetal infection occurs beyond 20 weeks.

Prenatal diagnosis: It is mainly done by isolating virus from amniotic fluid and by identification of rubella specific IgM by percutaneous umbilical blood sampling. These tests are limited by sensitivity and specificity.

Postnatal diagnosis: Definitive diagnosis is by virus isolation in pharyngeal washings, CSF, conjunctiva and lens at autopsy. Rubella virus RNA can be detected by PCR in clinical specimens. Detection of rubella specific IgM in neonatal or cord blood is also confirmatory. In addition to the congenital defects, the persistent rubella specific IgG with no decline as expected from maternally acquired IgG points to the diagnosis of congenital rubella syndrome. The interpretation of ELISA for rubella specific antibodies is as given in Table 1.

Table 1. Interpretation of ELISA for rubella specific antibodies

Age of infant		Test result	Interpretation
0 - 3 Months		IgM +	Intrauterine infection
3 - 12 Months		IgM +	Probably intrauterine infection
		IgG +	although widespread early post-natal infection cannot be ruled out
[Rubella IgM/IgG	Negative	< 0.9 U/ ml	
	Equivocal	0.91 - 1.1 U/ml	
	Positive	> 1.1 U/ ml]	
Persistence of rubella specific haemagglutination inhibition titres beyond the period expected from that of passively transferred maternal antibodies			

2. Cytomegalovirus

Infection by members of herpes virus family is characterised by typical cytopathology of infected cells like cellular enlargement with intranuclear and cytoplasmic inclusions . The rate of intrauterine transmission from primary maternal infection is 30-40 %. Approximately 18% develop significant disease. In mothers with recurrent infection the fetus and newborn rarely show clinical symptoms. Risk of transmission in relation to gestational age is uncertain although infection during early gestation carries a higher risk of fetal disease.

Symptomatic CMV presents either as an acute fulminant infection with multisystem involvement like petechiae, purpura, hepato splenomegaly and jaundice. A second insidious presentation is with microcephaly, IUGR, chorioretinitis, periventricular calcifications, mental retardation, hearing deficits, motor abnormalities, visual disturbances etc.

Prenatal diagnosis

Amniocentesis and cordocentesis to detect CMV DNA by PCR.

Postnatal diagnosis

Infant presents with the characteristic symptoms.

Isolation of virus or demonstration of CMV DNA by PCR from urine or saliva at birth or within 1 - 2 weeks indicates definitive diagnosis. When detected after 2 weeks it might have been perinatally acquired. Shell viral cultures are used for better isolation.

The determination of CMV antibody titres has got limited use. (Table 2)

Table 2. Interpretation of CMV antibody titres

Antibody	Result	Interpretation
IgM	+ VE	unreliable for diagnosis; low sensitivity
IgG	+ VE	can be maternally acquired; on followup positive in infected infants
IgG	- VE	In both mother and fetus excludes congenital infection
CMV IgG/IgM antibodies Negative : < 0. 91 U / ml Equivocal : 0.91-1.1 U / ml Positive : >1.1 U / ml]		

3. Herpes simplex virus

There are 2 distinct types and type 2 is an important cause of neonatal disease. Intrapartum transmission is the most common mode of transmission and is associated with active shedding from cervix and vagina. Intra uterine infection is rare. Diagnosis is by high degree of clinical suspicion. An infant presents with the disease as vesicles on 6 th – 9 th day over skin, eye and mucocutaneous membranes. One third of affected children present with encephalitis and another one third with disseminated infection with seizures, shock and DIC / hepatitis.

- IgM serology is of little use as it may not reach diagnostic levels upto 3 weeks.
- Virus isolation from lesions of oro and nasopharynx.
- In encephalitis identification of viral DNA in CSF by PCR, increased CSF protein levels and pleocytosis.

4. Human immunodeficiency virus

HIV is a cytopathic RNA retro virus which enters the host CD 4 cell and destroys the host immune system. Inutero and intrapartum transmission from infected mother accounts for 90 % of paediatric cases. Transmission can occur throughout gestation and HIV has been isloated from cord blood and products of conception as early as 14 – 20 weeks of gestation.

Diagnosis: In the early neonatal period is difficult as HIV specific IgG antibody is passively transferred. The median age of clearance is 13 months.

- Positive IgG in a child less than 18 months indicates maternal infection but cannot diagnose fetal infection.
- Virus co-culture, p 24 antigen detection, HIV specific IgM / IgA all three have low sensitivity in 1st week of life.
- Early diagnosis of HIV DNA is by PCR assay, positive predictive value in neonates is 56% and older infants is 83%.

Interpretation of PCR assay

Age	Result	Interpretation
At birth	30 – 50 % + ve	Intrauterine infection
7 days	-ve at birth but + ve at 7 days	Intrapartum transmission

False positive PCR : contamination with maternal blood

- Child exposed to HIV should be tested at 1, 2, 4 months by viral culture and PCR. If negative at 4 months there is a > 95 % assurance that infant is not infected.
- Exposed infant is considered negative of there are
  - no physical finding of infection
  - virological tests are - ve
  - immunological tests - CD 4 counts are normal
  - > 12 months of age and two or more HIV antibody tests are negative.

5. Varicella zoster virus

It is a member of herpes virus family. Intrauterine transmission occurs but prior to peripartum period no obvious clinical impairment is seen. Congenital varicella syndrome following maternal infection in first trimester is 2 %

Prenatal diagnosis: By sonographic abnormalities like hypoplastic extremities,

clubfoot, flexed limbs, ventriculomegaly, porencephalic cyst, polyhydramnios, ascites, hydrops and calcification of lungs and myocardium .

- VZV specific IgM in fetal blood is nonspecific
- VZV DNA detection by PCR in amniotic fluid is specific

At birth: Virus isolation from vesicular fluid on culture. Demonstration of four fold rise in VZV antibody titre by fluorescent antibody to membrane antigen.

6. Parvo virus

These are small unenveloped viruses, most infectious strain is B19 whose overall rate of transmission from an infected mother to fetus is 33%. Risk of fetal loss is 10 % . It has been firmly linked to nonimmune fetal hydrops by affecting the haematopoietic cell lines. If acute or recent parvovirus B 19 infection is confirmed in pregnant woman by positive B19 specific IgM assay, serial ultrasonogram should be done for fetal hydrops or meconium peritonitis.

Prenatal diagnosis: Fetal blood and amniotic fluid for parvovirus IgM specific antibody .

- PCR to detect B 19 DNA . 100 % results when fetal blood is subjected to insitu hybridisation .

Postnatal diagnosis: Serum IgM rises in 3 days and falls by 2 –3 months. Serum IgG appears a few days after IgM disappears and lasts for years .

7. Hepatitis viruses

a. Hepatitis C

Single stranded RNA virus related to flavivirus family. There is high transmission rate in mothers with high viral loads. Coinfection with HIV increases transmission.

Diagnosis

Children born to HCV infected women screened at 6 –12 months by PCR assay of HCV RNA

Age	Test result [HCV/RNA by PCR]	Interpretation
0-6 mo	+ ve	can be due to maternal antibody
6 -12	+ve	Reliable of fetal infection

b. Hepatitis B

Intrauterine transmission is rare. Detection is by HBsAg specific IgG in serum

SPIROCHETAL INFECTIONS

Syphilis

Syphilis can be transmitted to the infant regardless of duration of maternal disease but more so in the first year of infection. Transmission occurs more commonly after fourth month of pregnancy. Liver is the primary site of infection followed by secondary spread to skin, mucous membranes and bones.

Prenatal diagnosis: Amniocentesis and fetal blood sampling to detect spirochaetes by:

- dark field microscopy
- indirect immunoflourescent staining
- inoculation in rabbit

Detection of DNA by PCR at 17 weeks of gestation is also diagnostic.

At birth: Dark field examination of mucocutaneous lesions.

- If RPR and VDRL titres are fourfold greater than maternal titres, fetal infection is very likely
- IgM fluorescent antibody is false positive in 35 % due to interference by fetal IgM directed against maternal IgG. This can be minimised by separating both fractions.
- Congenital neurosyphilis is difficult to diagnose. CSF mononuclear pleocytosis, increased protein, reactive CSF VDRL may indicate infection.

PROTOZOAL INFECTIONS

1. Toxoplasmosis

An intracellular protozoan with 30-40 % vertical transmission. Rate increases with gestational age at which acute infection occurs and appears to correlate well with increasing placental blood flow and is 90 % at term. The severity of fetal disease is inversely proportional to gestational age. Primary neurological disease presents with intracranial calcifications, chorioretinitis and convulsions. The generalised disease presents with hepatosplenomegaly, lymphadenopathy ,jaundice and anemia.

Prenatal diagnosis

- Serial USG to detect hydrops, ventricular dilatation, cerebral or hepatic calcification and ascites.
- Amniocentesis to isolate organisms by inoculation in mice or by tissue culture.
- PCR analysis-B1 gene amplification of amniotic fluid has 97 .4 % sensitivity

Postnatal diagnosis

- Isolation of toxoplasma in infant blood peaks in first week
- Detecting antigen / DNA by PCR in body fluids is diagnostic.
- Levels of maternally acquired IgG drops at the rate of 50% per month, if not so active fetal infection is suspected.
- In infants, less than 3 months of age transformation of lymphocytes on exposure to toxoplasma antigen is a sensitive test.

2. Malaria

It is an obligate intracellular protozoan of genus plasmodium. Neonatal infection has been recorded with all species. The placenta has been involved in most women who acquire malaria during pregnancy. It is not clear whether transmission to infant is transplacental or from direct contact with maternal blood during parturition.

Most infants have onset of symptoms by 8th week of life with fever, anemia and splenomegaly. About one third have jaundice.

Diagnosis

Maternal history of febrile illness can be elicited in most cases. The diagnosis of congenital malaria can be entertained in any infant who presents with fever, anemia, hepatosplenomegaly and born to mother who resided in an endemic area .The parasite can be identified in cord blood and peripheral blood by thick and thin smear.

BACTERIAL INFECTIONS

Listeria monocytogenes

It is a nonsporulating, β-haemolytic gram + ve organism. Transplacental transmission is believed to be the most significant mechanism for acquiring early onset disease although ingestion of aspirated amniotic fluid before delivery is possible. Infected neonates present with sepsis and pneumonia. They manifest with anorexia, lethargy, vomiting, respiratory distress, apnea, cyanosis and petechial rash.

Diagnosis

Diagnosis is prompted by maternal history of still birth and repeated abortions. Diagnosis is by culture of blood , urine and CSF. Gram staining shows gram variable organisms which look like diphtheroids.

Conclusion

To conclude, the specific IgM concentration in serum may be increased due to leakage of maternal blood. Under these circumstances a repeat IgM concentration shows a fall in case of maternal transfusion but increased in active infection . Due to recent advances direct serological and DNA analysis of fetoplacental unit is possible and it can be used to determine whether infection has occurred or not. In rubella it facilitates continuation of pregnancy, while in toxoplasmosis it guides the choice of antimicrobial, but has no role in evaluating HIV as the proceedure itself can inoculate the fetus.

NEWS AND NOTES

5TH NATIONAL CONGRESS ON PEDIATRIC CRITICAL CARE

Annual conference of Critical Care subchapter of IAP is hosted by IAP, Surat branch, on October 10th, 11th & 12th, 2003 at Hotel Holiday Inn , Surat. Theme of the conference: 'Demystification of Critical Care'.

CME: October 10th, 2003. Conference: October 11th & 12th, 2003 Pre-Conference workshop / course,

a) PALS - 8th & 9th October b) Basic Pediatric Critical Care Course - 8th & 9th October
c) Workshop A - Advanced Mechanical Ventilation + All about Equipments - 9th October
d) Workshop B - Peritoneal Dialysis + IV access + All about Equipments - 9th October

Registration Details:

A) Conference:	**Till 30.04.03**	**Till 30.06.03**	**Till 15.09.03**	**Spot**
1. IAP Member	2000	2400	2800	3400
2. P. G. Student *	1600	2000	2400	2800
3. Non IAP Member	2200	2600	3000	3600
4. Associate Delegate	1250	1250	1500	1500
B)Workshop /Course	**Till 30.04.03**	**Till 30.06.03**	**Till 15.09.03**	
1 PALS	1200	1200	1200	No Spot
2 Basic Pediatric Critical Care course	2000	2250	2500	No Spot
For PG Student *	1500	1750	2000	No Spot
3 Workshop A	500	650	800	No Spot
4 Workshop B	500	650	800	No Spot

Note:- 1. Conference registration includes CME & Banquet.
2. Except PALS, registration for the conference is a prerequisite for participating in the workshops / basic course.
3. Limited participants to be taken for all the 4 workshops on 1st come 1st serve basis.
4. P.G. Students are required to attach certificate from the Head of the Department.
5. Registration not required for children below 12 years.

For children between age 5 & 12 years, lunch / dinner coupons available at reasonable rate.

Organizing secretary, Dr.Kamlesh H. Parekh, Amruta Hospital, Raj Complex , Near Vaishno Devi Temple, Bhatar Road, Surat. 395001, Ph: 3240141, 3244979, 3237280; Fax: 0261-8313636, E-Mail:amrutahosp6@hotmail.com

LABORATORY MEDICINE

DIAGNOSTIC APPROACH TO THE CHILD WITH ARTHRITIS

*** Ramanan AV**
**** Akikusa JD**

INTRODUCTION

Children presenting with acute arthritis represent a relatively common problem for the practicing general paediatrician. A large proportion will have underlying conditions that are self limiting in nature and require no more than symptomatic treatment for a short period of time. The challenge in their acute assessment is to identify those with conditions that require more than just symptomatic therapy. This requires a good knowledge of conditions commonly associated with acute arthritis.

A small proportion of children will go on to have chronic arthritis, the commonest cause of which is Juvenile Idiopathic Arthritis (JIA). It is important to understand that this is a diagnosis of exclusion and that mimics need to be considered before making it. This article will review the basic clinical approach to the child with acute and chronic arthritis, covering issues of differential diagnosis and initial management.

The child with acute arthritis

Acute arthritis for practical purposes is any arthritis present for less than 6 weeks. The diagnostic approach to the child with acute arthritis is outlined in Fig 1. It is important to keep in mind that up to 61% of children presenting with 'rheumatologic' symptoms will either not have an underlying 'rheumatologic' disease or will remain undiagnosed[1]. This underscores the importance of keeping a wide differential diagnosis in mind and of ensuring follow-up until such a time as the diagnosis becomes clearer or symptoms resolve.

Trauma as a cause of acute arthritis will usually be obvious, however it is not uncommon for a traumatic event to bring to attention a joint that has actually been swollen for some time. Clues to the presence of an underlying more chronic condition are wasting of the muscles of the ipsilateral limb, joint contracture, and in the lower limb (if present for long enough) leg length discrepancy with the ipsilateral side being longer. Acute traumatic injury as a cause of joint swelling should be diagnosed with caution if the traumatic event was not immediately followed by difficulty in ambulation or refusal to weight bear. Acute painful swelling of lower limb joints in response to minor injury in young boys may also be the first sign of an inherited bleeding disorder.

Septic joints are usually extremely painful and held in a fixed position. In the case of the hip, this is in flexion, abduction and external rotation. The child will usually be febrile and on laboratory testing will have evidence of raised inflammatory markers (Erythrocyte Sedimentation Rate/ C-reactive protein/ leukocyte count). It is important to note that acute arthritis involving the hip joint as an initial manifestation of JIA is extremely uncommon and such a presentation mandates consideration of more common differentials including septic arthritis, slipped capital femoral epiphysis, transient synovitis and Perthes disease. In the

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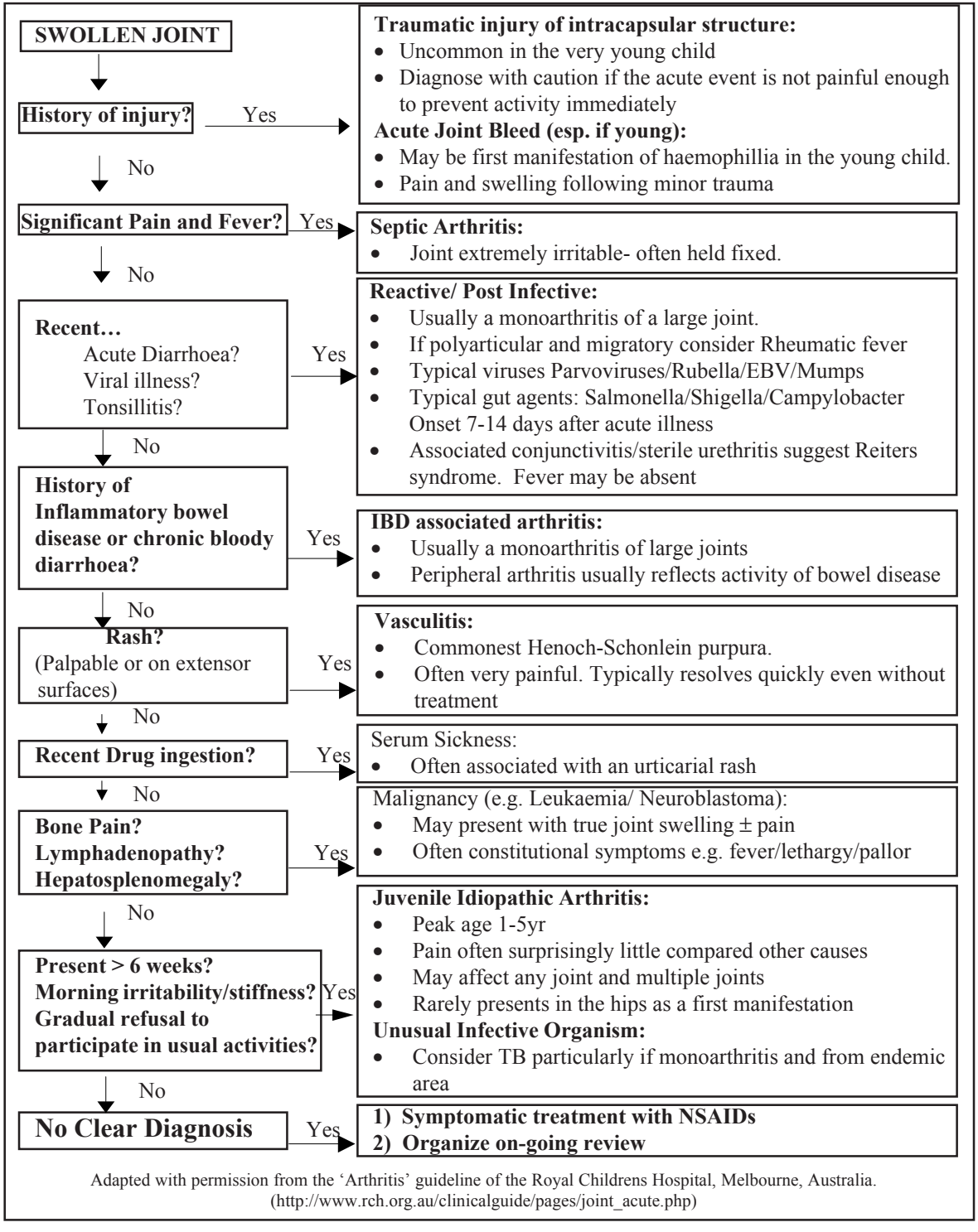

Adapted with permission from the 'Arthritis' guideline of the Royal Childrens Hospital, Melbourne, Australia. (http://www.rch.org.au/clinicalguide/pages/joint_acute.php)

Fig 1: Algorithm for approach to child with acute arthritis.

Table 1: Differential diagnosis chronic arthritis in children*

Juvenile idiopathic arthritis
Connective tissue disorders
- systemic lupus erythematosus (SLE)
- juvenile dermatomyositis (JDM)
- mixed connective tissue disease (MCTD)
- scleroderma
- systemic vasculitis
Childhood sarcoidosis
Inflammatory bowel disease associated arthritis
Other synovial conditions
- pigmented villonodular synovitis
- foreign body synovitis ("plant thorn synovitis")
- synovial hemangioma
- synovial chondromatosis
Infectious arthritis (including tuberculosis)
Reactive arthritis
Periodic fevers
Metabolic diseases
- mucopolysaccharidoses
- diabetes
- mucolipidoses
- hemochromatosis
* some of the causes of acute arthritis listed in the algorithm could also lead on to chronic arthritis

latter two conditions the child will not appear toxic and the acute phase reactants should be normal. Transient synovitis tends to be seen most often in the 3-8 year age group, whereas Perthes is more commonly seen in an older age group (5-10yrs) and is more common in boys. Transient synovitis is typically quite painful and may cause the child significant difficulties in ambulation. Perthes disease is classically described as a painless limp. Slipped capital femoral epiphyses tend to occur in the teenage age group, typically older overweight boys, who present with pain and limp.

Reactive arthritides are perhaps the most common cause of acute arthritis in children. Common agents are viruses such as Parvovirus, Rubella and Epstein Barr virus. In endemic areas hepatitis B should be borne in mind. Many of the bacterial causes of gastroenteritis can be followed by acute arthritis, usually of the large joints and typically quite painful and associated with elevated acute phase reactants on laboratory testing. In such instances it is important to look for joint sepsis, from which this form of arthritis may be hard to distinguish, by arthrocentesis and culture of synovial fluid. Streptococcal infection may give rise to subsequent Rheumatic Fever or Post Streptococcal Reactive arthritis[2]. Typically the arthritis in both of these conditions involves large joints, and in the case of rheumatic fever it is migratory and very sensitive to non-steroidal anti-inflammatory drugs (NSAIDs). Indeed failure to respond to NSAID therapy within 48-72 hours places the diagnosis in question. It is important to remember that between 30% and 60% of patients with their first episode of acute rheumatic fever will not have a history of symptomatic pharyngeal infection[3, 4]. Post Streptococcal reactive arthritis tends to be more persistent and not associated with other features of acute rheumatic fever.

Both serum sickness[5] (most often related to drug ingestion) and vasculitis (the most common being Henoch Scholein Purpura), may give rise to a painful arthritis, typically of the large joints. Associated features of these conditions will usually be the clue to these diagnoses.

Perhaps the most worrying cause of acute arthritis in children is malignancy, of which leukaemia and neuroblastoma are the commonest. While both may cause true acute arthritis[6], they more commonly cause bone pain, which may be localized around joints and which will frequently wake the child from sleep. The pain associated with these conditions may be

Table 2: ILAR classification criteria for juvenile idiopathic arthritis: Durban 1997

Systemic arthritis

Definition: Arthritis with, or preceded by, daily fever of atleast 2 weeks duration that is documented to be quotidian for at least 3 days and accompanied by one or more of the following:

1. Evanescent, non-fixed erythematous rash
2. Generalized lymph node enlargement
3. Hepatomegaly or splenomegaly
4. Serositis

Exclusions: None listed

Oligoarthritis

Definition: Arthritis affecting one to four joints during the first 6 months of disease.

Two subcategories are recognized

1. Persistent oligoarthritis: affects no more than four joints throughout the disease course
2. Extended oligoarthritis: affects a cumulative total of five joints or more after the first 6 months of disease

Exclusions:

a. Family history of psoriasis confirmed by a dermatologist in atleast one first or second degree relative
b. Family history consistent with medically confirmed HLA B-27 associated disease in atleast one first or second degree relative
c. Positive RF test
d. HLA B-27 positive male with onset of arthritis after 8 years of age
e. Presence of systemic arthritis as defined above

Polyarthritis (RF negative)

Definition: Arthritis affecting 5 or more joints during the first 6 months of disease, associated with negative RF tests on 2 occasions atleast 3 months apart.

Exclusions:

a. Presence of RF
b. Presence of systemic arthritis as defined above

Polyarthritis (RF positive)

Definition: Arthritis affecting 5 or more joints during the first 6 months of disease, associated with positive RF tests on 2 occasions atleast 3 months apart.

Exclusion:

a. Absence of positive tests for RF on two occasions atleast 3 months apart
b. Presence of systemic arthritis as defined above

Psoriatic arthritis

Definition:

1. Arthritis and psoriasis or
2. Arthritis and at least two of the following

a) Dactylitis
b) Nail pitting or onycholysis
c) Family history of psoriasis confirmed by dermatologist in at least one first degree relative.

Exclusions:

1. Presence of rheumatoid factor
2. Presence of systemic arthritis as defined above

Enthesitis related arthritis

Definition: Arthritis and enthesitis, or arthritis or enthesitis with atleast two of the following:

1. Sacroiliac joint tenderness and/or inflammatory spinal pain
2. Presence of HLA-B27
3. Family history in atleast one first or second degree relative of medically confirmed HLA-B27 associated disease
4. Anterior uveitis that is usually associated with pain, redness or photophobia
5. Onset of arthritis in a boy after the age of 8 years

Exclusions:

a. Psoriasis confirmed by a dermatologist in atleast one first or second degree relative
b. Presence of systemic arthritis as defined above

Other arthritis
Definition: Children with arthritis of unknown cause that persists for atleast 6 weeks but that either
1. Does not fulfill criteria for any of the categories, or
2. Fulfills criteria for more than one of the other categories

Exclusions:
Patients who meet criteria for other categories

extreme and may result in the child not weight bearing. Under these circumstances it is crucial that the child undergoes a thorough physical examination of the lymphoreticular system and at the very least a complete blood count taken. Other investigations which may be required in order to ensure that a malignancy is not being missed are a bone marrow aspirate, urinary catecholamines and CT or Ultrasound scan of the abdomen.

Clearly some of the conditions associated with acute arthritis discussed above require specific therapy, but a great many require symptomatic treatment only. If there is evidence of true synovitis or joint effusion such treatment should be with NSAIDs at appropriate doses (Table 3). With this therapy the majority of these conditions will settle within 6 weeks. If they do not then consideration must be given to the causes of chronic arthritis in children

The child with chronic arthritis

Chronic arthritis is defined as the persistence of arthritis for 6 weeks or more. Common causes of chronic arthritis are shown in Table 1. Of all the causes of chronic arthritis in children JIA is the most common.

Most connective tissue disorders including lupus, juvenile dermatomyositis (JDM) and scleroderma may have arthritis as one manifestation. Approximately 90% of lupus

Table 3: Standard Anti-inflammatory doses of NSAID

Naproxen	15-20mg/kg/d in 2 divided doses
Ibuprofen	30-40mg/kg/d in 3 divided doses
Indomethacin	2-3mg/kg/d in 3 divided doses

patients and 65% of JDM patients will have arthritis/arthralgia during the course of their illness[7]. A thorough clinical examination looking for other features which might suggest these diagnoses is essential. Such features include Gottron's papules, heliotrope rash, proximal muscle weakness, mucocutaneous changes, alopecia and evidence of serositis.

Classic early onset childhood sarcoidosis is characterized by a triad of arthritis, uveitis and rash. The arthritis of childhood sarcoidosis is characterized by boggy tenosynovitis with relatively painless effusions and good range of movement[8].

Arthritis is the most common extra-intestinal manifestation of inflammatory bowel disease. There are two patterns of joint involvement: peripheral and, less commonly, sacroiliac arthritis (spondyloarthropathy). The peripheral arthritis usually reflects the activity of the underlying bowel disease, while, the sacroiliac arthritis tends to follow an independent course[9]. Uncommonly, the arthritis may precede the bowel manifestations. In this situation the diagnosis is suggested by the presence of abdominal symptoms, occult blood in stools, low haemoglobin, thrombocytosis, a low serum albumin and a positive pANCA (anti-neutrophil cytoplasmic antibody), the latter found in 60-80% of cases.

The differential diagnosis of chronic monoarthritis includes tuberculosis, in endemic areas, and local disorders of synovium. An example of the latter is pigmented villonodular synovitis, a rare condition characterized by

recurrent painless effusions which, on aspiration, are heavily blood-stained. Both T_1 and T_2-weighted MRI studies reveal hypertrophic synovium, with very low signal density as a result of hemosiderin deposition[10]. Synovial hemangioma, most commonly seen in the knee, usually presents as an intermittent hemarthrosis.

The diagnosis of JIA is a clinical one. The use of investigations is primarily to exclude differential diagnoses and, once the diagnosis is made, to aid in classification and prognostication. Perhaps the one exception is a slit-lamp examination of the eye, which can be very helpful in the diagnostic work-up of a child with arthritis. A significant proportion of children with JIA develop clinically silent but potentially blinding chronic uveitis. On average, uveitis is seen in 15-20% of patients with pauciarticular and 5 % of patients with polyarticular JIA[11]. The presence of uveitis in a child presenting with arthritis narrows the differential essentially to JIA and sarcoidosis, of which the former is overwhel mingly more common. The Inter national League Against Rheumatism (ILAR) has classified JIA into seven categories with inclusion and exclusion criteria for each type (Table 2)[12]. It is important to remember that these criteria were proposed mainly to classify patients for research and prognostic purposes, but as with many such criteria, they also serve as a diagnostic tool.

Initial management of chronic arthritis: As with acute arthritis the initial management of a child presenting with chronic arthritis revolves around symptomatic relief, which in most instances will be an NSAID at anti-inflammatory doses (Table 3). Ongoing management will depend on the underlying diagnosis. Whatever the cause, it is important to remember that patient/ parent education and physiotherapy are integral to the successful management of many of the conditions which result in chronic arthritis in children.

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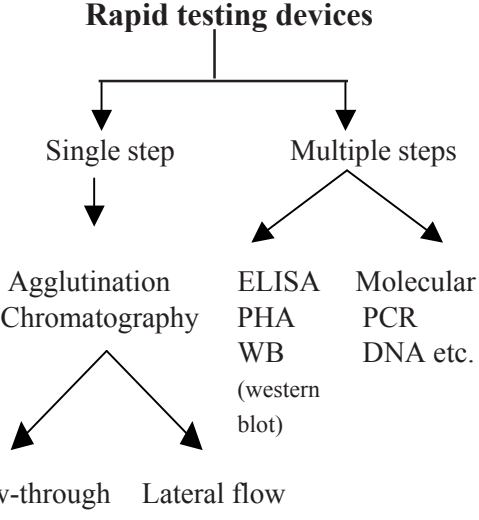
LABORATORY MEDICINE

RAPID DIAGNOSTIC TESTS – BENEFITS AND PITFALLS

**** Saranya N***

The last decade has indeed been the decade of diagnostics. To keep pace with the emergence and re-emergence of several infections, manufacturers have not left any stone unturned in improving the quality of the available kits. In addition, the need for faster and equally accurate, reliable, sensitive and specific rapid kits has been felt more urgently. These rapid testing kits / methods can be broadly divided into two categories those that involve single step and depend on agglutination, flow-through and lateral flow etc. which take a few minutes and those that involve multiple steps like ELISA, Passive Haemagglutination (PHA) and Molecular tools, which may take upto a few hours.



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An ideal diagnostic tool needs to fulfill certain requirements:

- It should be easy to perform
- Should not require expensive equipment
- Should not require electricity if possible, so it can be applied to field situations too
- Results obtained should be repeatable
- It should be highly sensitive and specific
- It should aid in the diagnosis

In the pediatric age group in India, the infections commonly encountered are malaria, typhoid, dengue, leptospirosis, tuberculosis and Hepatitis A. Several other viral and bacterial infections are encountered too, though much less frequently. The rapid tools available for these infections will be dealt with, in reference to their benefits and pitfalls.

Typhoid

A major problem worldwide and is particularly rampant in the developing nations. Early detection is vital for its control. With the more recent blood culture techniques available, it is possible to isolate, identify and give a complete blood culture report within four days. Some of the commercially available blood culture media have an incorporated resin, which absorbs the antibiotic that the patient might have been treated with. Hence the drawback of false negatives in blood culture as a result of antibiotic usage in the patient has been removed. **Table I** lists the merits and demerits of the available diagnostic tests.

Table 1. Properties of diagnostic tests used in typhoid fever

Properties	Culture (Ag)	PCR (Ag)	Widal (Ab)	Rapid tests (Ab)
Quality (single)	Gold standard	Promising	Not useful (single)	Not useful
Utility	First week	Early	Second week	4 – 7 days
Sensitivity	45 – 70%	72%	36%	95%
Specificity	100%	100% (dead bacilli)	Non specific	*High NPV 96.1%
Result	4 days	1 – 2 days	Overnight	1 hour – IgG 3 hours – IgM
Cost	Moderately expensive	Expensive	Inexpensive	Moderately expensive

* Negative Predictive Value

Rapid tests for typhoid are based either on the principles of EIA (IgM and IgG antibody), immuno-chromatography (antigen detection) or agglutination. **A positive test result even if antigen is present, needs ideally to be confirmed with a more specific test, while a negative result does not preclude the presence of infection.** When an IgG test alone is positive, a positive blood culture done a few days later will resolve the issue of re-infection or relapse. Detection of S. typhi infection using labelled probes is 99% specific but a minimum of 500 organisms per ml is required while with PCR it is 10/ml and with nested PCR 1-5 organisms per ml is sufficient to detect an infection[1].

Widal test has outlived its usefulness and more often than not a very ambiguous report is obtained. The test is most often ordered as the initial and often the only diagnostic tool in patients with suspected typhoid and when the result is negative, a diagnosis of typhoid is no longer considered. This test gives numerous false positives that have led to unnecessary and ineffective medication.

Blood culture remains the gold standard and when done with observation of all necessary precautions such as time of sampling, aseptic procedures, volume of blood drawn, maintenance of ratio between blood and media and so on, a definitive diagnosis of typhoid can be reached within a day.

Malaria

Clinical or syndromic diagnosis is often used to identify and treat malaria in remote areas where diagnostic facilities are not available. In addition, symptoms of malaria are often non-specific and result in mis-diagnosis. Four species of malaria that commonly infect man are the Plasmodium vivax, falciparum, malariae and ovale. Of these the P.falciparum causes the most fulminant forms of infection while P.vivax is the most frequently seen in India. Diagnostic techniques include the time honoured blood films both thick and thin, the quantitative buffy coat technique (QBC) and several immuno-chromatographic tests based on the 'Dipstick' format. These are based on the principle of detection of plasmodial histidine rich protein-2 (HRP-2) or parasite specific lactate dehydrogenase (pLDH) that is present in P.falciparum infections. These tests are now being applied for other forms of malaria but the results have not been encouraging[2]. Table II compares the commonly used tests.

Positive results obtained in the IC test need to be confirmed by a more specific test. Rapid

Table 2. Properties of tests used in diagnosis of malaria

Properties	Smear	QBC	IC (Dipstick)
Usefulness	"Gold standard"	Extremely sensitive	Falciparum
Principle	Routine staining	Flourescein stain	Immuno Chromatography (IC)
Parasitic forms	All	All	Falciparum Antigen
Sensitivity	Can be missed	100%	100%
Specificity	100%	False positives	False positives

tests are useful for screening and confirmation especially when,

a) there are very few forms or
b) if an inexperienced person is doing the testing[2].

Other recent field players are Enzyme immuno-assay (EIA) and Multiplex Polymerase Chain reaction (PCR). EIA has been developed and evaluated, including tests for Pf HRP-2 antigen. However they only detect falciparum malaria hence their usefulness is limited. They equal microscopy in sensitivity, but are impractical and expensive to use in the field. If an EIA test that was able to detect all forms of malaria was available, that would perhaps be more useful.

A multiplex PCR has been developed for all four species using the target 18S single stranded rRNA and serum sporozoite stage DNA sequences. The Royal Tropical Institute Amsterdam has developed a qualitative Nucleic Acid Sequence Based Assay (NASBA) method for detection and semi-quantification of as few as 50 parasites per milliliter of blood, which is many times more sensitive than microscopy. However they are expensive to make, difficult to run and need sophisticated equipment**.**

Rapid tests can be used as supplemental tests but can never replace microscopy in the diagnosis of malaria.

Dengue

This infection caused by a member of the Flavivirus family is transmitted to humans through the bite of the Aedes mosquito. Antibody appears within 3-5 days and is detectable for around 90 days[3]. There are several methods used for the diagnosis of Dengue. PCR is used to detect the presence of the viral nucleic acid but is fairly expensive. Serological detection of Dengue infections are based on the principles of haemagglutination inhibition, ELISA (IgM, IgG and IgM and G combined) and the more rapid tests being the Dipstick enzyme immuno-assay (IgM or IgM and G) and immuno-chromatography to detect IgG alone or IgM and IgG combined. **Paired serum sampling is ideal to make a diagnosis of dengue and differentiate between primary and secondary infections.** Certain disadvantages of any IgM test for dengue are that[3]

1) IgM may be undetectable for upto 5 days and so a sample drawn earlier than this period may give a false negative result. A repeat sample drawn a week later will help resolve this issue.
2) False positives in other flavi-virus infections
3) False positives as a result of stimulation by non-flavi viruses.
4) A positive result does not indicate an active infection

All the serological assays can be completed within a working day with the microtitre ELISA taking about three hours and the immuno-chromatographic tests about 15 minutes. Studies done at Singapore have found that the microtitre format capture ELISA for detection of IgM and IgG when used together was superior to the use of IgM or IgG alone, and showed good correlation (sensitivity 99%, specificity 96%)[4] when compared to the haemagglutination inhibition assay which is considered to be the ideal serological test.

In summary, there is no single perfect diagnostic test for dengue. While viral isolation gives the best chance of a definitive diagnosis, it takes time and cannot be performed in all laboratories. **Clinical judgement therefore is very important particularly in dengue** and simple laboratory tests like a platelet count or haematocrit should be used to institute the appropriate supportive treatment without any loss of vital time[3].

Leptospirosis

A geographically widespread spirochetal infection caused by members of the genus Leptospira, this infection has assumed endemic proportions in certain states namely Andamans, Gujarat, Tamilnadu and Kerala. More than 230 serovars have already been identified. The organism is shed in the urine of the reservoir host into the environment and man acquires the infection when the organism enters through cracks in the skin and mucous membranes. Anicteric presentations account for 90% of human leptospirosis. Icteric and anicteric cases follow a biphasic course. Weil's syndrome can be caused by any serovar in its severe form. All forms of leptospirosis begin the same way and at the start of infection it is not possible to predict the outcome[5]. While almost 85% to 90 % of infections clear spontaneously with no residual problems, it is the remaining 10%-15% of patients in whom early and rapid diagnosis is even more imperative. Like in malaria, symptoms are non-specific and can mimic any viral infection hence this infection is often under-reported.

Rapid diagnostic tests for leptospirosis can be divided into two groups:

Those based on the presence of antigen

a) Dark field microscopy (DFM) and special stains

b) Molecular techniques like PCR, RAPD, hybridisation methods and PGE

These are ideal tools for the early diagnosis of leptospirosis. Molecular techniques are extremely sensitive, very expensive and are not available for routine use. Microscopy has been a severely under-utilised tool and while the risk of false positives does exist, if done by a trained microscopist it can be extremely specific[6].

Those based on antibody presence

a) IgM detection assays like ELISA and Dipstick

b) Agglutination tests like the PSAT, MAT, IHA

c)Immuno-blotting assays like the Dot Blot assay

A commercially available IgM ELISA kit has been evaluated against the gold standard of the MAT and found to have a sensitivity of 100%[7]. The IgM –PK ELISA with 89.9% sensitivity and 97.4% specificity and the Leptotest-S with an 89.9% sensitivity and 94.8% specificity have been found to be ideal for early diagnosis in most laboratories according to another study[8].

Pitfalls of antibody detection in leptospirosis:

a) Paired sampling done 10-14 days apart is a must to demonstrate a rise or fall in titre.

b) A single positive titre is of no significance as raised IgM antibody levels are detectable even a year after infection.

c) Prior treatment with antibiotics may delay, blunt or supress antibody production.

IgM ELISA tests are able to detect antibody presence on an average five to seven days after onset of an infection, however while an initial sample might be negative, a second sample taken a week later might show a significant rise in titre. A practical problem that clinicians face is accessibility of the patient after the initial visit. Hence the search continues for a test that can give a conclusive diagnosis with a single sample.

The MAT test has until recently been considered the cornerstone for leptospirosis diagnosis, however, the focus of researchers the world over is now shifting towards antigen based molecular methods of detection. A simple, inexpensive, molecular tool that does not require skilled personnel and that can be used in any resource poor setting would be ideal. Ironically enough, most of diagnostic research in the field of leptospirosis has been done by the western world, where leptospirosis is not as large a problem as in tropical countries where it is endemic in some.

The MAT test is an excellent epidemiological and research tool but is not suitable as a rapid screening or diagnostic test[5].

Tuberculosis

Pulmonary TB is among the foremost killer diseases in India. According to estimates of the WHO, 90 million new active cases have been identified worldwide of whom a third have already died. With AIDS having assumed gigantic proportions, the situations can only worsen. Sputum culture remains the gold standard for the diagnosis of TB. Cultures are 81% sensitive and 98.5% specific for active disease. However reporting takes anywhere between 10 days with some of the newer techniques to three to four weeks with the more conventional methods, and hence when an immediate diagnosis is required, culture cannot be used. Rapid indication of drug resistance is also possible by using MTB specific mycobacteriophages to reflect the presence of viable tubercle bacilli in the presence or absence of rifampicin[9]. The need for early, rapid diagnosis is essential for prompt institution of treatment.

Rapid tests for TB can be divided into two main groups:

Direct

a) Sputum smear microscopy

b) Continuous automated mycobacterial liquid cultures (CAMLiC)

c) Molecular techniques

Indirect

a) Line immuno-chromatographic serological assays (LISA)[10]

b) ELISA

The best method for diagnosing pulmonary TB is the sputum smear. PCR is indicated in smear positive individuals who have not had treatment for longer than seven days. While it takes 10000 organisms to produce a positive smear, even a few are sufficient to give a positive PCR report[11]. However, the PCR does not differentiate between dead and live bacilli and hence a PCR report should be interpreted with caution. Rapid serological tests for the diagnosis of tuberculosis have sensitivities between 13-92% and specificities between 66-100%[12]. A negative rapid diagnostic test in a patient with low clinical

suspicion and a positive AFB smear will be helpful to eliminate the presence of active infection. Conversely a positive rapid test, when the level of suspicion is moderate with a positive smear will clinch the issue[12].

Hepatitis A

Commonly referred to as infectious hepatitis, this is caused by a picorna virus. This spreads almost exclusively through faeco-oral contact, from person to person through contaminated food or water. IgM Antibody to the virus is detectable five days after exposure and remains detectable for 3-6 months. During the convalescent phase individuals produce IgG antibody, which usually remains as a lifelong marker. **Diagnosis is usually made on the basis of clinical symptoms and signs and the need for testing more for a confirmation of diagnosis and identification in those situations where the "ink-filler" principle operates.** The affected individual has two or three infections simultaneously and the clinical picture is totally confusing. Serological diagnosis is by detection of IgM antibody or total antibody to Hepatitis A virus. Several commercially available ELISA kits are used and usually take about three hours to perform. These tests are extremely reliable and offer good degrees of sensitivity and specificity[13].

HIV

An emerging area of great concern is that of vertical transmission of HIV. This is possibly one situation where rapid tests are most indicated. Rapid tests for HIV are based on different principles like particle agglutination, membrane immuno-concentration, immunochromatography and ELISA. The sensitivity of these devices is around 97-100% with specificity of 96%[14]. Rapid tests are indicated in certain situations[15]:

a Pregnant women whose HIV status is unknown, during the time of delivery so as to prevent vertical transmission

b People who may have exposed themselves to an occupational risk (medical and nursing staff)

c Screening before providing medical attention.

A negative rapid test result in an area of low prevalence does not pose a problem. Any patient with a positive test result on a rapid test needs to have it confirmed by a western blot.

A HIV antibody positive report in a newborn needs to be interpreted with caution. In the newborn's blood, maternal IgG is present as, a)during pregnancy, there is a passive transfer of maternal IgG antibody to the newborn, b) there is admixture of small amounts of maternal and foetal blood and c) there are placental leaks. This antibody remains detectable in the blood of the newborn even up to one year, hence these results should be correlated with the maternal HIV status when possible. If a conclusive diagnosis of HIV is required in the newborn, a qualitative polymerase chain reaction is ideal. With a qualitative PCR, the sample can be reported conclusively as either being negative or positive for copies of the virus.

In adults, rapid testing of saliva and urine for HIV antibody has become common over the counter tests in some of the developed countries. The saliva tests have a sensitivity of 99.5% and those of urine are 98.7% sensitive and 99.1% specific. However at a "HIV point of care testing workshop in Canada in March 99"[16], it was underlined that since 2/3rd of people who test positive on rapid testing devices subsequently tested negative for HIV by the western blot, **rapid testing devices need to be used only in certain specific situations** as the benefits of easy testing are far outweighed by the enormous anxiety the individual undergoes before his/her HIV status is confirmed.

Rapid testing devices are a great innovation, do save considerable time and can be used in certain places where sophisticated equipment or trained personnel are not available. **However wherever and whenever indicated they need to be confirmed before the report is disclosed to the patient.** They need to be interpreted after taking into account the prevalence of that particular infection/disease in the population under study. All laboratory tests are only guides to a diagnosis and should be clinically correlated in all situations.

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LABORATORY MEDICINE

NEONATAL METABOLIC SCREENING

**** Nair PMC***

Every parent wants to bring a healthy baby into the world. The advances in medical sciences has led to a reduction in infectious diseases, so that genetic and metabolic disorders are remaining as a major group of disorders responsible for morbidity and mortality, especially in neonates. Newborn screening program identifies biochemical or other inherited conditions that may produce mental retardation, other disabilities and/or death. There are 2 types neonatal screening for high risk neonate, mass newborn screening. The latter is decided by discord prevalence in a particlar area and by the availabilty of laborotary facility reservoiers. The most commonly accepted diseases needing neonatal screening are[1] Hypothyroidism, Phenyl ketonuria, Maple syrup urine disease, Biotinidase deficiency, Galactosemia, Tyrosinemia, Histidinemia, G6PD deficiency, Sickle cell disease, Cystic fibrosis, Congenital adrenal hyperplasia, Homocystinuria

Around 500 metabolic diseases are known today. Approximately 24 children per one lakh births have a disease involving amino acids, organic acids, primary lactic acidosis, galactosemia or a urea cycle disease[2]. Recent advances in the diagnosis and treatment of inborn errors of metabolism have improved the prognosis for many of these conditions[3,4,5,6]. Even with untreatable disorders, it is important to establish the diagnosis in the index case in order to allow prenatal diagnosis in subsequent pregnancies. Hence it is imperative that practicing paediatricians and neonatologists be familiar with the clinical presentation and approach to these disorders.

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Clinical recognition of metabolic disease in the neonatal period

An important key to diagnosis is a high index of suspicion. The signs and symptoms are quite nonspecific and subtle in onset or can be stormy. Consider the possibility of a metabolic disease in any infant with non-specific symptoms that are not explicable by another cause.

Look for history of 1) consanguinity (the majority of metabolic diseases presenting in the newborn period are autosomal recessive), 2) positive family history of similar disease / unexplained neonatal deaths in siblings, mental retardation, developmental delay or intolerance to certain foods. 3) Most often it is a full term baby born after an uneventful perinatal period. Prior to delivery, the fetus is "protected" from any ill-effects of a metabolic disease by virtue of the function of the placenta in providing fuel and filtering toxic metabolites. It takes some time for the toxins to build up, so that for the first few days after birth, the baby is usually asymptomatic. 4) Acute onset with progressive course- starting with some subtle symptoms like lethargy, poor feeding, vomiting, hiccoughs, respiratory distress, apnea, and jaundice that soon progress to coma, seizures, multi-system failure and death. 5) Not to forget some metabolic diseases like Long Chain Hydroxy Acyl CoA dehydrogenase

Table I.Unusual odour or smell of urine

Odour	Disorder
Musty or mousy odour	Phenylketoneuria
Boiled cabbage smell	Tyrosinemia
Smell like burnt sugar (Maple syrup)	Maple syrup urine disease
Sweaty feet smell	Isovaleric acidemia Glutaric acidemia (TypeII)
Cat urine smell	Multiple Carboxylase deficiencies
Rotten fish odor	Trimethylaminuria

deficiency (LCHAD) in the fetus affecting the mother with Acute fatty liver of pregnancy.

Physical examination may yield nonspecific findings like hypotonia / hypertonia, seizures, jaundice, hepatomegaly, cardiomyopathy, dysmorphism or coarse facial features, abnormalities of the skin, hair, eyes, joints, unusual urine color, unusual odour of sweat or urine (Table 1). Acute symptoms maybe indistinguishable from those of sepsis, cardiorespiratory failure or CNS disease. Neutropenia, thrombocytopenia and sepsis particularly with E.coli may be present. Chronic symptoms are failure to thrive, developmental delay or neurological defects.

Patterns of presentation of metabolic disease in the neonate and clue to diagnosis

Three types of presentation[7,8]

1) Intoxication type with a window period and progressive encephalopathy. Neurological presentation with a symptom-free interval, followed by lethargy, poor feeding, altering of conscious state, seizures and coma, is typical of a) Organic acidemias including Maple syrup urine disease b) Urea cycle disorders.

2) Energy deficient type with no window period. Encephalopathy, seizures and apnea without a symptom-free interval is typical of

a) Primary lactic acidosis
b) Non-ketotic hyperglycinemia (NKH)
c) Sulphite oxidase deficiency (SOD)
d) Pyridoxine dependency

If associated with profound hypotonia, dysmorphism and / or congenital anomalies, myopathy think of a) Peroxisomal disorders b) Mitochondrial disease

3) Storage type: Hydrops, jaundice, hepatosplenomegaly and dysmorphism may be present. eg: Mucolipidoses, Niemann Pick disease

Cardiac disease: Cardiac failure and cardiomyopathy, can occur in association with mitochondrial, lysosomal or fatty acid oxidation disorders or Pompe's disease (GSDII).

Liver dysfunction: Persistent hyperbiliru binemia (conjugated +/- unconjugated) may be indicative of a metabolic disease, in particular, galactosemia but also hypothyroidism, tyrosinemia, alpha-1-antitrypsin deficiency and others[8].

Dysmorphism: Metabolic diseases associated with dysmorphic features include peroxisomal disorders (Zellweger syndrome), disturbances of energy metabolism(Pyruvate dehydrogenase deficiency) defects in cholesterol biosynthesis (Smith-Lemli-Optiz syndrome, CDG-Carbohydrate deficient glycoprotein syndromes) and storage disorders[8].

Fetal hydrops: A number of metabolic diseases can cause fetal hydrops but rare.

Approach to the diagnosis of a metabolic disease (Fig.1)

1. History and clinical information
2. Initial Screening or Primary laboratory tests (Table II)

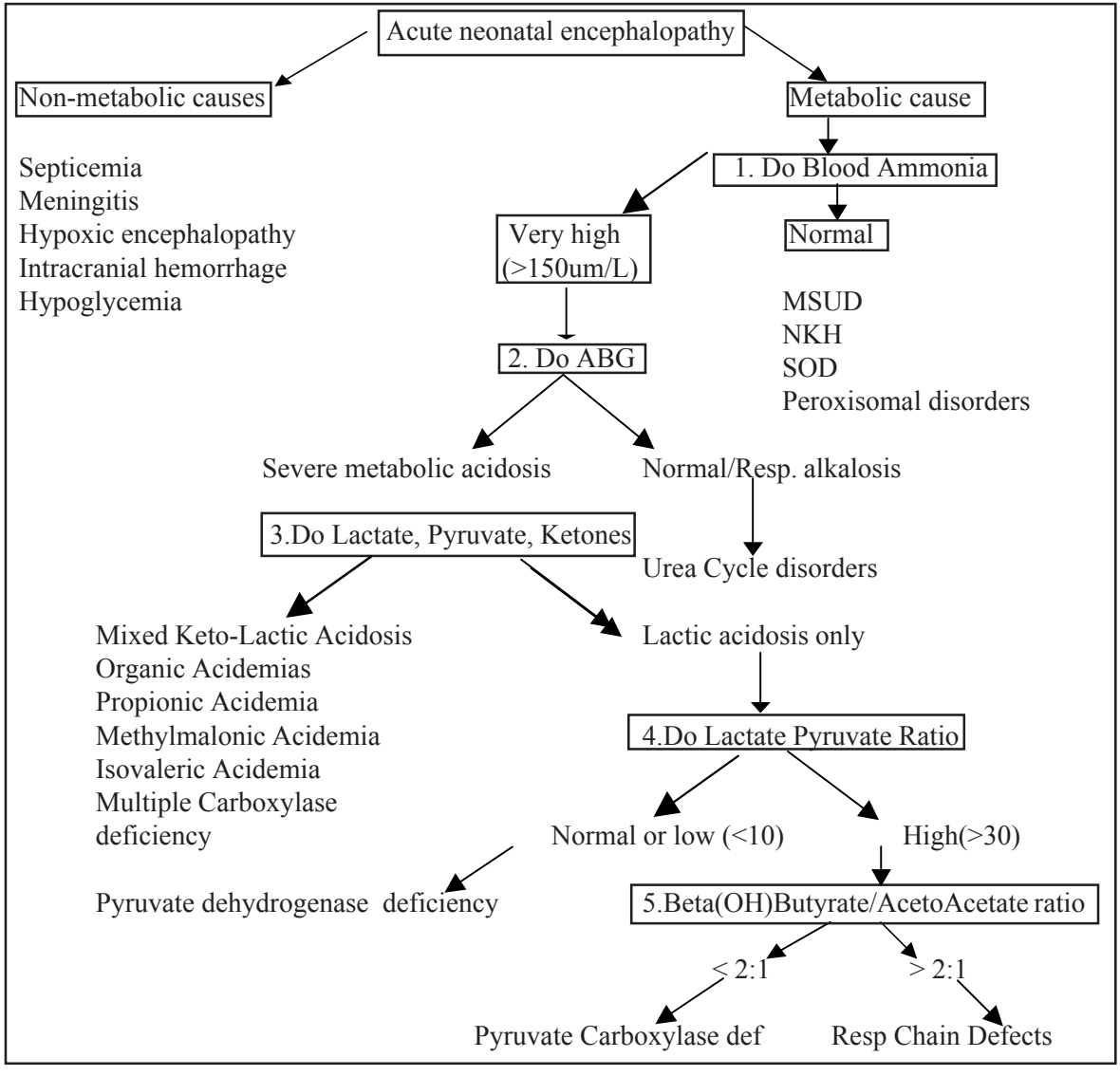

Fig 1. Approach to diagnosis – Algorithm

i) CBC for neutropenia and thrombocytopenia

ii) Electrolytes and arterial blood gas – to evaluate for metabolic acidosis and anion gap

Anion gap = $(Na^+ + K^+) – (Cl^- + HCO3^-)$

Normal value = < 15 mEq/L

Metabolic acidosis with increased anion gap, is suggestive of organic acidemias and primary lactic acidosis

iii) Blood sugar. Hypoglycemia indicates either glycogen depletion +/- inadequate gluconeogenesis (premature or SGA infant) or hyperinsulinism (infant of a diabetic mother); occasionally hypoglycemia will be a manifestation of a metabolic disease eg; fatty acid oxidation defect, glycogen storage disease

iv) Urine for ketones, reducing substance and ferric chloride test. Presence of urinary ketones is suggestive of organic acidemia and absence of which may denote fatty acid oxidation defects. If reducing substance in urine is positive, interpret it carefully, because of the chance of high false positivity. Remember that glucose is a reducing substance. So if the clinitest is positive (Clinitest detects all reducing substances including glucose), check the urine specifically for glucose using a glucose oxidase strip. Urine dipsticks detect glucose only. Ferric chloride test for ketoacids is positive in Phenyl ketonuria, Tyrosinemia, Maple syrup urine disease, Histidenemia, and Alkaptonuria. The test is non-specific and not used in modern laboratories.

v) Low blood urea: Signifies urea cycle disorders

vi) Uric acid is elevated in glycogen storage type Ia and low in molybdenum co factor defects.

vii) Serum ammonia : If hyperammonemia (>150umol/L) is detected in a newborn less than 24 hours of age, think of transient hyperammonemia of newborn, if preterm and Pyruvate dehydrogenase deficiency (PDH),if full-term. After 24 hours of age, hyperammonemia associated with keto-acidosis, is suggestive of Organic acidemias and with normal blood gas or alkalosis is suggestive of Urea cycle disorder.
For accurate values, rapidly flowing blood (arterial stab) should be collected, placed in ice and carried to the lab immediately. It should be done within 1 hour. Hence prior notification to the lab is necessary.

viii) Blood lactic acid, pyruvic acid and lactate pyruvate ratio.
If arterial lactate is persistently high (>3mmol/L), the differential diagnosis is:

Table 2. Laboratory tests

Disorders	Screening Laboratory Tests				Confirmatory Tests	
	Blood gas Anion gap	Urine Ketones	Lactic Acid	Serum Ammonia	Blood TMS AA & Acyl carnitine	Urine GCMS (Organic Acids)
MSUD	-	+	-	-	+	Not indicated
Organic Acidemias	Severe acidosis	++	+	+	+	+
Primary Lactic Acidosis	Severe acidosis	+/-	+++	+	+	+
Urea Cycle Disorders	Resp alkalosis	-	-	+++	+	Not indicated
Non-ketotic hyperglycin -emia	-	-	-	-	+	Not indicated

(+) abnormal test (-) normal test
AA-Amino acids; MSUD- Maple Syrup Urine Disease
TMS- Tandem mass spectrometry
GCMS - Gas chromatography & mass spectrometry

Table 3. Differential diagnosis of common metabolic disorders:

Diseases	Clinical features	Biochemical abnormalities	Confirmatory tests
Maple Syrup Urine disease	Urine smell, Neuro-intoxication, tone changes, seizures (in first wk of life)	Urinary ketones++ Hypoglycemia+/-	Di-nitro phenylhydrazine; Aminoacid profile; TMS
Organic acidemia	Neuro-intoxication (within first month)	U.Ketones++ Acidosis+++ Ammonia+ Lactate+ Pancytopenia	TMS Urine GCMS
Urea cycle disorders	Intoxication type (in first week of life)	No ketosis Respiratory alkalosis Ammonia+++	TMS Aminoacid profile; Urine Orotic acid
Cong Lactic Acidosis	Energy deficiency (since birth)	Acidosis++ Ketosis++ except in PDH	Lactate Pyruvate ratio; B-OH.B/AA ratio; Urine GCMS
NKH SOD Peroxysomal Disorders	Energy deficient type, Myoclonic seizures, Severe hypotonia (since birth)	Normal	CSF & Blood Amino acid profile, TMS, Urine Sulfitest; Plasma very long chain fatty acids
Galactosemia Fructosemia Tyrosinemia	Hepatomegaly Hypoglycemia Jaundice, Fanconi syndrome (in first few months of life)	Hypoglycemia Cholestatic jaundice; Urine reducing substance	Enzyme studies Urine GCMS
Glycogen storage disease	Hepatomegaly Hypoglycemia No jaundice	Hypoglycemia Lactate++ Uric Acid+	Enzyme studies
Fatty acid oxidation defects	Energy deficiency Hepatomegaly (in first year)	Non ketotic acidosis Hypoglycemia	TMS

TMS- Tandem Mass Spectrometry, GCMS-Gas chromatography mass spectrometry;
B-OH-B/AA – Beta hydroxy butyrate and aceto acetate ratio;
NKH- Non-ketotic hyperglycinemia; PDH- Pyruvate dehydrogenase deficiency;
SOD- sulphite oxidase deficiency

a) severe organ dysfunction leading to decreased tissue perfusion/oxygen delivery or increased metabolic demand as in perinatal asphyxia, congenital heart disease (duct dependent lesions), sepsis or untreated seizures.

b) Primary lactic acidoses like disorders of pyruvate metabolism, mitochondrial disorders

c)Secondary lactic acidoses – Other metabolic diseases may be associated with lactic acidosis like fatty acid oxidation defects, organic acidoses etc.

ix) Urine for metabolic screen : 5-10 ml freshly-collected urine in a sterile container with no preservatives; can be frozen prior to analysis if necessary.

Filter paper technique for collection of capillary blood by heel prick: Spot 1 to 2 drops of blood onto each of the 3 circles on the specific filter paper provided, until the circles are filled completely. Then let the blood spots to dry in air. Blood spots can now be used for the diagnosis of a large number of inherited metabolic disorders.

Before doing the primary investigations, ensure that the patient is well fed with an adequate protein diet 2-3 hours before. Neonates should be given milk feed. Primary investigations for inborn errors of metabolism must be carried out as a matter of urgency and if indicated out of hour also. The specimens should be collected during the acute episode before starting treatment.

If the above simple primary investigations are normal in a patient that is well fed, the chance of a metabolic disease as the cause of illness is low.

Advanced Screening tests (Table 2)

1. Tandem Mass Spectrometry (TMS)
2. Plasma Amino acid and urine Chromatography
3. CSF analysis for organic and amino acids

Tandem mass spectrometry is the most significant advance in newborn screening in the past 30 years[9]. While gas and liquid chromatography is time consuming, using tandem mass spectrometry, more than 30 disorders can be easily detected from a drop of blood on filter paper in a single test within 1 to 2 minutes. It detects molecules by measuring their weight (mass) electronically and display results in the form of a mass spectrum (graph showing each specific molecule by weight and how much of each molecule is present)[10].

Definitive diagnostic tests include specific enzyme analysis, assays for galactose 1-phosphate uridyl transferase , DNA testing on liver, muscle, or skin biopsy specimens.

Emergency management of a suspected metabolic disease

It is essential that the treatment of patients with inborn metabolic disease is started without delay in order to avoid irreversible damage to vital organs, especially the brain, and fatal outcome in neonates where the clinical course can be rapid.

1. Stop all oral feeds after collecting the necessary tests. Collect 3 drops of blood on filter paper for Tandem MS. Collect 10 ml urine and deep freeze immediately for organic acids by gas chromatography mass spectrometry (GCMS).

2. Monitor vital signs and biochemical parameters periodically

3. Treat sepsis if indicated.

4. Prevent dehydration and catabolism by giving full maintenance fluid as 10% glucose with electrolytes

5. Start next day intralipids and a small amount of amino acid mixtures (maximum 0.25 to 0.5

gm/kg/day) to prevent endogenous protein breakdown.

6. Treat metabolic acidosis if pH <7.2

7. Hyperammonemia (Ammonia >150umol/L) always warrant urgent treatment, as every minute delay can cause neuronal damage.

Priming (stat) dose :

Sodium benzoate 250mg/kg; Phenyl acetate 250mg/kg; Arginine 660mg/kg (in urea cycle disorders only) – all diluted in 25ml/kg of 10%Dextrose and infused over 90 minutes.

Maintenance dose: Same dose and dilution but infused over 24 hours.

8. IV Carnitine. Useful in organic acidemias by removing toxic organic acids and restoring mitochondrial functions.

9. Use of soluble insulin is anabolic and prevents hyperglycemia from use of high glucose concentrations (0.1 units/kg/hr with monitoring of blood sugar)

10. Specific treatment include cofactor biotin and Propimex-1 formula for Propionic acidemia, Thiamine and Ketonex-1 formula for Maple syrup urine disease, High carbohydrate diet and biotin for Pyruvate carboxylase deficiency etc.

Conclusion : IEM is an extremely challenging area. For successful management, awareness, early suspicion, and a good regional center with facilities for accurate early diagnosis and prompt treatment including availability of special milk formulas, are mandatory.

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ERRATUM

In the issue 2003;5(1), in page 81, under questions and answers column in the Answer 4 regarding need for Tet Vac, it should be read as Skunks instead of snakes and Ferrets instead of parrots.

LABORATORY MEDICINE

LABORATORY DIAGNOSIS OF PERSISTENT AND CHRONIC DIARRHEA

*** Shinjini Bhatnagar***

Persistent Diarrhea

The duration of acute diarrhea forms a continuum, most episodes terminating within 7 days and progressively smaller proportions persisting beyond 14, 21 or 28 days. The delineation of persistent diarrhea from acute diarrhea is arbitrary. The most commonly used definition is an episode that begins acutely, is of a presumed infectious etiology and persists for 14 days or more. The pathogenesis is multifactorial with persistent mucosal injury being the hallmark of the disease. The common etiological factors are persistent or recurrent infection with enteropathogens namely Shigella, Salmonella, enteroadherant E.coli or small bowel bacterial overgrowth. Secondary lactose or carbohydrate intolerance due to a combination of macro and micronutrient deficiency and enteric infection, and infrequently secondary milk protein intolerance further perpetuates the mucosal injury and prolongs diarrhea. Several randomized controlled studies have shown that antimicrobials offer modest or no clinical benefit in persistent diarrhea. Nutrition is the mainstay of treatment. A dietary algorithm using a stepwise elimination of carbohydrates is recommended by the WHO and the National Task Force on diarrhea[1].

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Lab diagnosis of persistent diarrhea

Patients with persistent diarrhea can be managed without elaborate laboratory tests using the above algorithm with very high levels of success. Stool microscopy helps in identifying trophozoites of E.histolytica and G.lamblia, which are present in a very small proportion of children. Majority of children who have cysts of E.histolytica are now known to have non-pathogenic E.dispar. Large number of pus cells (> 20 /HPF) in stool suggest invasive diarrhea but the specificity of this test is low and a majority of children with persistent diarrhea do not have these.

Stool cultures are expensive and not warranted in all cases. They should be ordered only when there is a high index of suspicion for Shigella or Salmonella especially in very young infants. Isolation of E.coli is not helpful as most laboratories cannot characterize for virulence properties.

In a non-hospital setting, detecting reducing substances is often impractical as tests cannot be done promptly and several stools need to be examined for sufficient sensitivity. In these settings it is, therefore, more practical to use clinical criteria to decide on change in diet as shown in the algorithm (Fig.1). The fact that diet-A has reduced lactose already assumes that some secondary lactose intolerance exists in children with persistent diarrhea[2]. However, wherever possible stools should be tested for pH and reducing substances (see details of methods below) as it documents carbohydrate intolerance.

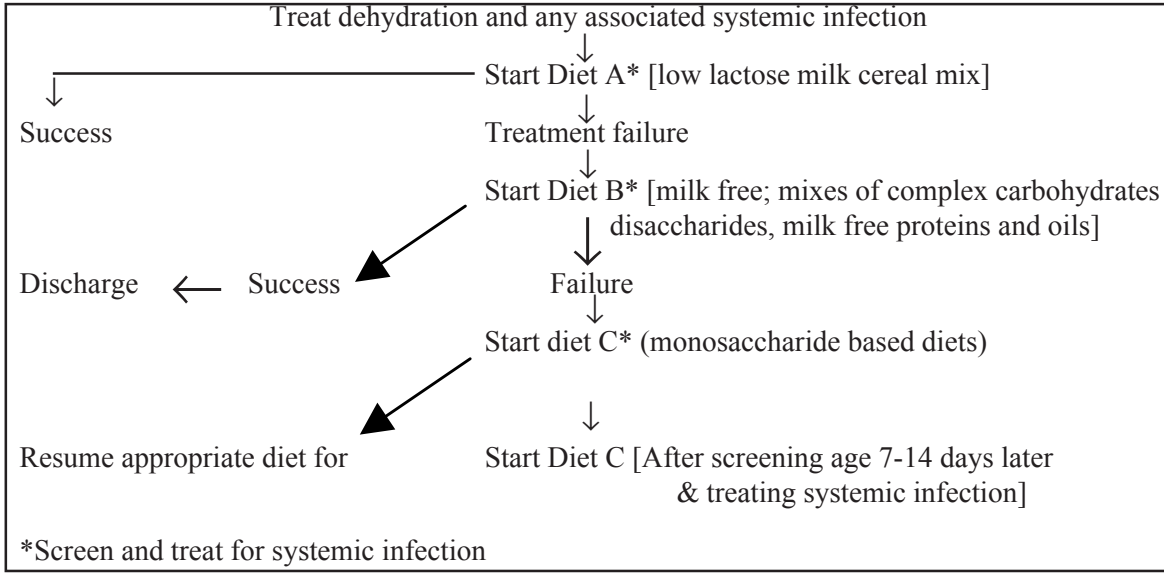

Fig 1. Dietary algorithm for treatment of persistent diarrhea

Chronic Diarrhea

Diarrhea that has persisted beyond 6-8 weeks is defined as chronic and the etiology may differ by age[3].b (Table 1)

IMPORTANT LABORATORY DIAGNOSTIC STUDIES

Initial screening tests - Stool examination

The initial studies would include stool examination for blood, leucocytes, protozoa and reducing substances. Identification of fecal leukocytes, red blood cells or occult blood suggests an inflammatory condition of the lower colon. Fecal leukocytes are detected on examining direct smears or after staining with 3% Loeffler's methylene blue. The smear should be allowed to stand for two or three minutes for good nuclear staining. All differential counts should be made under high power, counting 200 cells when possible. Only those cells clearly identified as either mononuclear or polymorho nuclear are included in the differential count.

A skilled microscopist and careful attention to the collection and preservation of stool samples is important for diagnosing enteric parasites. Presence of radio contrast material like barium, antacids, mineral oil or antibiotics may interfere with the detection of protozoa and a period of 2 weeks without any of these substances would be advisable before collecting the stools. Further, contamination with water or urine can result in lysis of trophozoites. Examining multiple samples obtained on separate days increases the sensitivity of detection because of variable shedding of cysts and trophozoites[4]. Sensitivity of detecting Giardia trophozoites, cysts or antigens increases by about 20% (about 70% if a single stool sample is examined) if three stool samples are examined. Giardia is detected on direct smear or after concentration with 10% formol-ether. Examination of a fresh stool is ideal for identification of motile trophozoites.

Routine "ova plus parasite" examinations do not include tests for Cryptosporidium parvum and other new enteric spore forming protozoa like isospora and cyclospora and need to be specially asked for. Cryptosporidium parvum occurs in

Table 1. Causes of chronic diarrhea in different age groups

Neonatal diarrhea
Anatomic causes
Congenital short-bowel syndrome
Malrotation with partial blockage
Hirschsprung's disease
Congenital microvillus atrophy
Tufting enteropathy
Neonatal lymphangiectasia
Inherited transport defect
Glucose-galactose malabsorption,
Congenital chloridorrhea,
Bile-salt malabsorption
Milk enterocolitis
Age 1 mo to 2 y
Post viral or bacterial gastroenteritis e.g. lactose intolerance, zinc and other nutrient deficiency
Persistent infection with Shigella, Salmonella, enteroadherant E.coli, Giardia lamblia, Cryptosporidium, small bowel bacterial overgrowth
Cow's milk, soy and other allergy
Celiac disease
Irritable colon of infancy (chronic non-specific diarrhea)
Cystic fibrosis
C. difficile, (antibiotic-associated diarrhea)
VIP secreting tumors
Immunodeficiency: common variable, severe combined, X-linked agammaglobulinemia, transient hypoglobulinemia
Autoimmune enteropathy
Age 2 y to 18 y
Celiac disease
Inflammatory bowel disease
Post-infective persistent diarrhea with Shigella, Salmonella, enteroadherant E.coli, Giardia lamblia, Cryptosporidium, small bowel bacterial overgrowth
Chronic non-specific diarrhea (Irritable bowel syndrome)
Primary acquired lactase deficiency
Tropical sprue
Chronic pancreatitis/exocrine pancreatic deficiency
Primary or secondary lymphangiectasia, hypo/abetalipoproteinemia
Acquired immunodeficiency
Constipation with encopresis
Antibiotic-associated C. difficile
VIP secreting tumors7

upto 12% of immunocompetent children with diarrhea and upto 24% in immunocompromised hosts especially those with AIDS in developing countries[5]. At least 5-6 stools should be collected in 10% formalin or sodium acetate-acetic acid-formalin (SAF) on separate days. Staining with modified Kinyoun's acid-fast stain is usually the method of choice for clinical microbiological laboratory while negative staining with Giemsa and concentration methods are restricted for research purposes[6]. A stool is considered positive for Cryptosporidium parvum if typical oocysts 4-6 µm in diameter are identified while the cyclospora and isospora oocysts are larger and vary from 10-30 ìm in diameter respectively.

Kinyoun acid fast stain

Freshly passed stool is emulsified in 5 ml of 10% normal saline and filtered through two layers of gauze. 4 ml of solvent ether is added to the filtrate, mixed well and centrifuged at 1500 gyrations for 5 minutes. The supernatant is decanted leaving 1-2 drops with the sediment. Smears are made from the thoroughly mixed sediment on glass slides, fixed in methanol after air drying and are examined under oil immersion.

Enzyme linked immunoassay tests for antigens in stool for Giardia and Cryptosporidium

are highly sensitive and specific but are not routinely available.

Clostridium difficile diarrhea is uncommon in children but wherever the index of suspicion is high, stool should be examined for the pathogen. The tissue culture assay for cytotoxin B is the gold standard but is expensive and cumbersome. Rapid toxin ELISA assay has comparable sensitivity and specificity to those of the tissue culture assay and can be read within hours.

Acidic stools with pH of less than 5.5 and/ or positive for reducing substances usually indicate carbohydrate malabsorption and proximal small bowel damage. Small bowel mucosal injury results in malabsorption of carbohydrates. The unabsorbed carbohydrates in the small intestine are fermented by colonic bacteria producing organic acids, carbon dioxide and hydrogen gas. The organic acids get oxidized and absorbed in the colon. This fermentative action, which reduces the osmotic load of malabsorbed carbohydrates and may benefit the host by salvaging calories, is known as the colonic salvage mechanism. Therefore the liquid stool seen in carbohydrate intolerance is characterized by an acid pH due to organic acids, mainly lactic acid and by the presence of unabsorbed sugars. The tests for identifying acidic stools are valid only if the child's diet contains sufficient quantities of carbohydrates. Stool pH provides an indication to the amount of organic acids in stool while the increased amounts of reducing substances indicate the presence of unabsorbed sugars. Sucrose is a non-reducing sugar and will react in this test only after it has been acted upon by the colonic bacteria. Detection of stool pH and reducing substances is an important diagnostic tool in infants but may not be helpful in older children as they have a better colonic salvage mechanism. Presence of reducing substances in stool of neonates particularly those who are exclusively breast-fed and pass liquid stools may be normal because of a physiological malabsorption of lactose during the neonatal period which has no nutritional significance.

Detection of reducing sugars in stool

1 ml distilled water is added to 0.5 ml liquid stool and shaken well. Eight drops of this solution is added to 5ml of pre-boiled benedicts solution and is boiled for 1 minute. The solution is cooled and the colour of the precipitate is examined:

The reducing sugars in stool are graded as follows:

No colour change: nil

Green precipitate: 0.5%

Yellow precipitate: 1.0%

Orange precipitate: 1.5%

Brick red precipitate: > 2.0%

For **detection of non reducing substances** in stool 1 ml N/10 HCl (instead of distilled water) is added to 0.5 ml liquid stool and boiled for 1 minute. The HCl splits the non-reducing to reducing sugars. The subsequent steps are as shown above.

Lactose hydrogen breath test that detects the presence of hydrogen in the breath after giving a lactose dose of 2g/kg (to a maximum of 50g) is another useful diagnostic tool for documenting carbohydrate malabsorption. A rise in hydrogen excretion greater than 20ppm 1-3 hours after the oral dose represents a positive peak and is produced by the fermentation of unabsorbed carbohydrates by the colonic bacteria.

Stool osmotic gap can be measured to determine the osmotic nature caused by unabsorbed carbohydrates. The osmolality (mOsm/kg) and the fecal concentrations of sodium and potassium (mEq/l) of a fresh liquid

stool sample is measured and the osmotic gap is calculated as:

Osmotic gap = stool osmolality (approximately 290 mOsm/kg) –2 (stool sodium + stool potassium). There is an osmotic gap due to the malabsorbed carbohydrates when the difference is greater than 50 mOsm/kg. Stool sodium concentrations greater than 90 mEq/L and an osmotic gap less than 50 mOsm/kg indicates a secretory diarrhea. These are specialized tests and maybe used in hospital settings in more complicated cases to differentiate conditions leading to osmotic (e.g. secondary carbohydrate intolerances, infrequently intestinal transport defects) or secretory diarrhea (infections, infrequently congenital chloride and sodium diarrhea or neural crest tumors).

Sudan III stains fat globules in stool and is a quick and simple way to screen for fat malabsorption (Drummey's method). It is a qualitative test and indicates gross steatorrhea. Chemical analysis of fat in stool per 24 hours collected over 72-hours using Van de Kamer' method gives an accurate quantitative measurement of fat malabsorption. The child should be on a high fat diet (at least 50g/day) during the test. Co-efficient of fat absorption/ retention can be calculated if the 72 hour dietary intake of fat is available as:

$$\frac{\text{(Dietary fat – fecal fat)}}{\text{Dietary fat}} \text{ X } 100$$

The reference limits for fecal fat losses are < 7% of daily fat intake for children > 6 months of age and < 15% of intake for younger infants.

Presence of severe steatorrhea would suggest an exocrine pancreatic deficiency. Mild or moderate fat malabsorption may be present in chronic infections like giardiasis or in celiac disease and other enteropathies.

Iron deficiency anemia is common in conditions where there is iron malabsorption or chronic intestinal blood loss particularly in celiac disease, inflammatory bowel disease and cystic fibrosis. Megaloblastic anemia maybe present in untreated celiac disease due to chronic malabsorption of folate and B12. Inflammatory bowel disease may have anemia of chronic disease. Low levels of total protein and albumin may reflect the nutrition status. Hypoalbuminemia may be seen in intestinal lymphangiectasia. and inflammatory bowel disease. An elevated erythrocyte sedimentation rate suggests an inflammatory bowel disease.

Sudan III staining for fat malabsorption

2 drops of normal saline is added to one drop of stool on a clean glass slide and is mixed well with a stirring stick. Two drops of 95% ethyl alcohol is added to this mixture followed by two drops of Sudan III stain. :Neutral fats appear as orange or red drops.

A rough grading is as follows:

Severe	:	> 100 big (> 6 ìm in diameter) droplets / hpf
Moderate:		< 100 big droplets /hpf
Mild	:	< 100 small (< 6 ìm in diameter) droplets /hpf

Fatty acids and soaps do not stain but appear as amorphous flakes or coarse crystals

Blood and urine d-xylose

D-xylose is a pentose sugar, which is absorbed passively across the proximal intestinal mucosa without requiring intestinal brush border or pancreatic enzymes and bile salts. Its absorption is a measure of the functional surface area of the intestinal mucosa. A standard dose of 14.5g/m² body surface up to a maximum of 25 g is given by mouth. About 50% is metabolized in the liver and the remaining is

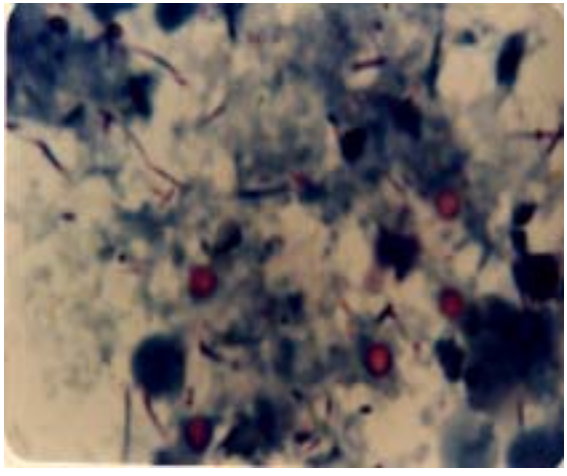

Fig 2. Cryptosporidium oocysts seen in modified acid-fast stain

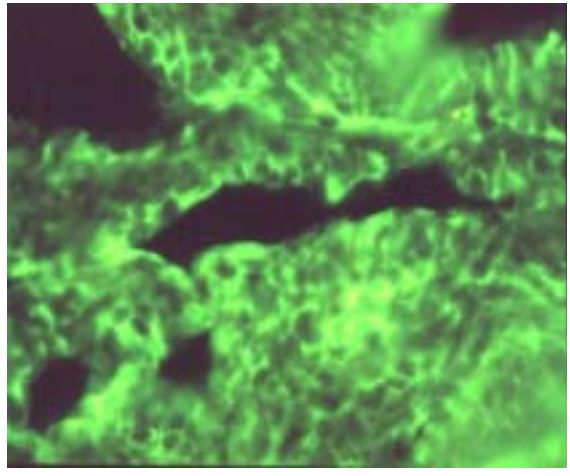

Fig 3. Characteristic fluorescent honey-combing seen around the smooth muscle bundles on the monkey esophagus indicating a positive antiendomyseal test on IFA assay

excreted in the urine. The serum d-xylose levels of 25g/L at one hour and excretion of > 20% of the oral d-xylose dose in urine collected for 5 hours after giving the oral dose indicates a normal functioning mucosa (Reiner's method). Although d-xylose is a non invasive screening method for assessing proximal intestinal mucosal surface area, its low sensitivity and specificity limits its use. It would be a good test for differentiating between exocrine pancreatic dysfunction and an abnormal intestinal mucosa. A normal d-xylose test in the presence of decreased serum pancreatic enzymes like trypsinogen would suggest a pancreatic dysfunction.

SECOND PHASE TESTS

Intestinal biopsy

Endoscopic biopsies are obtained from the first part or mid–duodenum as compared to the earlier capsule biopsies, which were taken from the dudeno-jejunal flexure. Intestinal biopsy is an essential diagnostic tool in chronic diarrhea and evaluates the crypt villus structure, epithelial abnormalities and mucosal inflammation. Characteristic histological features of celiac disease include partial or total villus atrophy, elongation of the crypts, increased crypt mitotic index, increased intra-epithelial lymphocytes with a lymphocytic mitotic index above 0.2%, infiltration of plasma cells, lymphocytes, mast cells and eosinophils in the lamina propria, loss of nuclear polarity with pseudostratification of epithelial cells and absence of a brush border[7]. Well-defined histological features are seen in intestinal lymphangiectasia, giardiasis, cryptosporidiosis (Fig 2.), abetalipoprotenemia, acrodermatitis enteropathica. Cryptosporidium oocysts are identified on hematoxylin and eosin stained sections as rows or clusters of spherical structures attached to the microvillus border of the epithelial cells. In the small intestine the lateral aspects of the villi have the maximum number of oocysts. Significant mucosal inflammation indicates infections, immunode ficiency, autoimmune enteropathy or protein sensitive enteropathies. In the absence of an abnormal mucosal histology or inflammation, exocrine pancreatic deficiency, hormonally mediated secretory tumors, colonic causes or

primary transport defects should be considered. Colonic biopsies are essential for diagnosing inflammatory bowel disease.

Serology

Serological tests are important adjuncts in the diagnosis of celiac disease and are available in reference laboratories in our settings. Serum IgG and IgA anti gliadin antibodies (AGA) were the first generation serological antibodies and are detected in an ELISA using crude gliadin extract. The specificity of both IgG and IgA AGA is about 80% in studies done at our centre but the sensitivity of IgA is higher (90%) than that of IgG (76%). IgA anti reticulin detected by immunoflorescence (IFA) on rat kidney are highly sensitive (>90%) and specific (>90%) but cumbersome and expensive. Serum anti IgA anti endomyseal antibodies (EMA) directed against the reticulin like tissue around the smooth muscle fibres are detected in an IFA assay using the monkey esophagus (Fig 3). The sensitivity (91%) and specificity (95%) of these antibodies is high in our settings and is consistent with the west. Human umbilical cord is now being used as a substrate instead of the more expensive and inaccessible monkey esophagus with similar results. Because the test for EMA uses IFA it can be operator dependent and needs specialized laboratories and experienced hands. It may also be less reliable in children less than 2 years. IgA AGA and EMA are IgA dependent antibodies and will be negative in individuals with selective IgA deficiency, which is present in 3% of celiac disease. The most recent anti transglutaminase (tTG) antibodies, which is now considered the main autoantigen for EMA, is measured by ELISA, a more objective and easily available test than the IFA[8]. Both guinea pig and human tTG have been used as antigens in the ELISA with results comparable to those of EMA in IFA assay.

Serological tests for detection of circulating pANCA are a useful diagnostic tool for ulcerative colitis and helps in differentiating it from other colitides and also Crohn's disease.

Testing for exocrine pancreatic insufficiency

Quantitative measurement of 72-hour fecal fat collection that demonstrates less than 90% absorption of the fat ingested is a simple test to document exocrine pancreatic insufficiency. These patients would have a normal d-xylose and intestinal mucosa on biopsy[9]. Measurement of fecal concentrations of the pancreatic enzymes trypsin or chymotrypsin is an indirect measure of pancreatic function but these measurements are limited by proteolytic degradation. The ELISA for human fecal elastase is an alternative fecal test of pancreatic dysfunction. It is decreased in exocrine pancreatic deficiency. It has been seen that values > 100 μg /g stool have 99% predictive value for ruling out pancreatic insufficiency[10]. Serum concentrations of immunoreactive trypsinogen. determined by radio immunoassay is a highly sensitive test for establishing pancreatic insufficiency but is not very specific. Values < 28 ng/ml are suggestive of pancreatic insufficiency. The gold standard remains the estimation of duodenal fluid enzymes and bicarbonate collected after stimulation with secretin-pancreozymin or liquid feeding. Marked reduction of the enzymes reflects severe damage to the acinar cells, usually when 60% of the exocrine function is lost. Decreased levels of fat-soluble vitamins and cobalamin indicate chronic pancreatic insufficiency.

Elevated concentrations of sodium and chloride in sweat stimulated by the pilocarpine iontophoresis is an important diagnostic tool for cystic fibrosis. However in infants and during the cold winter months collection of sweat maybe a problem. Further molecular diagnostic techniques are used for confirming the diagnosis of cystic fibrosis.

THIRD PHASE TESTS

Serum immunoglobulins and other extensive immunological tests to determine immunodeficiency, measurement of anti-intestinal epithelial antibodies in the serum in suspected autoimmune enteropathy and circulating VIP levels for neural crest tumors may be required for a small number of patients. Special staining of biopsies and electron microscopic evaluation is useful for diagnosis of microvillus inclusion disease and tufting enteropathy.

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NEWS AND NOTES

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LABORATORY MEDICINE

LABORATORY EVALUATION OF HYPERTENSION

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Introduction

The interest of pediatricians in hypertension has increased markedly in the last two decades essentially due to recent developments in the field of medicine. Primary hypertension, which was considered a disease of an adult, is also being documented in children. Essential hypertension in adults may be preceded by high BP of childhood. Control of blood pressure in children and hence, prevention of end organ damage in adulthood can be done easily. Lifestyle modification in terms of diet, salt restriction, exercise and stress can be introduced early in childhood to have full benefit in adulthood. Hence, measuring BP regularly as a part of routine care of each child and adolescent should be the rule in pediatric care. Finding out the cause for hypertension is the most important aspect of management. Detailed clinical history, essential clinical examination, initial investigations followed by appropriate investigations based on clues obtained from the previous steps are needed. Cause of hypertension in children should be always considered secondary unless proved otherwise and every step should be taken to find out the cause. Management of the cause is mandatory in addition to management of hypertension. Treating elevated BP without managing the cause if treatable will not make proper sense.

Blood pressure is an important basic physical sign as are the body temperature, pulse rate and respiratory rate. The measurement of blood pressure is now firmly established as an essential component of routine pediatric physical examination. It is mandatory for every child, three years of age and older to have as a part of routine continuing medical care, a yearly blood pressure measurement. In addition acutely ill children, regardless of age should have a blood pressure reading performed at the time of evaluation. Investigation of a child with hypertension depends not only on the severity of hypertension but also whether the child is symptomatic and hypertension is the suspected cause. Possible investigatory procedures range from routine tests available in most hospitals to more refined invasive procedures available in specialized units[1].

Goals of evaluation

There are five major goals of initial evaluation of hypertension in children[2,3].

1. To establish whether hypertension is sustained and might benefit from treatment
2. To identify coexisting diseases
3. To characterize the risk factors
4. To identify the presence and severity of target organ damage
5. To identify curable causes of the hypertension

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Definition of hypertension[4]

Normal BP: Systolic blood pressures (SBP) and diastolic blood pressures (DBP) below 90th percentile for age, sex and height.

High normal BP: Average SBP and/or average DBP between 90th and 95th percentile for age, sex and height.

High BP (Hypertension): Average SBP and/or average DBP above 95th percentile for age, sex and height on three occasions.

Causes of hypertension in children

One should know the common causes of hypertension in various age groups to decide on diagnostic evaluation (Table 1)[4]. Laboratory evaluation should be preceded by detailed history and clinical evaluation to get clues on the cause and hence to decide on investigations.

95% of hypertension in children is acute hypertension, wherein the cause is obvious. In sustained hypertension, i.e., hypertension persisting for more than 6 weeks and/or with echocardiographic evidence of left ventricular hypertrophy, 95% are secondary to an underlying renal/extrarenal cause. It is this group which needs evaluation for diagnosis. In the majority of them, the diagnosis will be obvious with a good clinical history and thorough physical examination. More often, investigations are necessary to confirm the clinical diagnosis and in only about 5% of patients, investigations are necessary for diagnosis itself. Hence, the clinician must lay emphasis on proper history elicitation and complete physical examination which is outside the purview of this review. History should include family history of hypertension, cerebrovascular accidents, renal death and sudden death. Physical examination should include skin changes like café-au-lait macules, neurofibromatosis, renal and bladder mass.

Table 1. Common causes of childhood hypertension

Neonate
Renal malformation
Coarctation of aorta
Renovascular hypertension following umbilical artery catheterisation
Bronchopulmonary dysplasia
Infancy to 6 years of age
Renal parenchymal disease
Renal artery stenosis
Coarctation of aorta
6-10 years of age
Renal parenchymal disease
Renal artery stenosis
Endocrine causes
Primary or essential HT
Adolescent hypertension
Renal parenchymal disease
Essential hypertension

Measurement of blood pressure in all the 4 limbs is vital and auscultation for bruit, however obvious the diagnosis may be, should not be ignored.

Investigations in hypertension[1,4,5]

In clinical practice, the following investigations are necessary and more often sufficient to make a diagnosis.

i. Urine analysis
ii. Urine culture (with proper precautions)
iii. Serum creatinine
iv. Serum electrolytes
v. Ultrasonogram of abdomen
vi. Echocardiogram

vii. Renal biopsy (in the event of diagnosis of chronic glomerular disease)

The rest of the investigations discussed below along with common investigations mentioned above need the assistance of pediatric nephrologist.

Urinalysis

Severe proteinuria and hematuria suggests glomerulonephritis. Hypertension of long standing nature can produce mild to moderate proteinuria without hematuria. Low specific gravity or osmolality may be seen in chronic tubulointerstitial disease, chronic renal failure, renal cystic disease and dysplasia. Urinalysis may be normal in renovascular hypertension. Transient urinary findings, may make one miss the diagnosis in PIGN.

Blood count

Microangiopathic hemolytic anemia is a feature of hemolytic uremic syndrome and normocytic normochromic anemia is seen in chronic renal failure.

Routine serum chemistry

Serum creatinine and blood urea estimation help in identifying renal impairment of renal parenchymal disease. Elevated blood glucose can be seen in pheochromocytoma. Serum cholesterol and triglyceride estimation are important, as they are cardiovascular risk factors.

Normal serum electrolyte rules out adrenal hormonal disturbance as a cause for hypertension. Low serum sodium with elevated potassium suggests hypoaldosteronism or congenital adrenal hyperplasia. Hypokalemia, metabolic alkalosis and high normal serum sodium indicate hyperaldosteronism. Hyperkalemic metabolic acidosis is a feature of renal failure.

X-ray chest and abdomen

Cardiomegaly and left ventricular hypertrophy are the important features of sustained hypertension. X-ray abdomen may show features of renal stones and pointers for metabolic renal bone disease.

Echocardiography

On documentation of sustained hypertension the child should undergo echocardiography to assess the end organ effect of hypertension, left ventricular hypertrophy. Further, coarctation of aorta as the cause for sustained hypertension can be identified. Serial echocardiographic evaluation periodically is mandatory to ascertain the effect of therapy.

Ultrasonogram of abdomen

This imaging modality is popular for documenting the renal size, gross anatomy and intrinsic details of kidney structure. Multiple communicating cystic structures, large renal pelvis and visible parenchyma are features of hydronephrosis. Diffuse echoes or echogenic mass within the vessels may denote renal artery or renal vein thrombosis. Reflux nephropathy shows irregular small kidneys. Chronic pyelonephritis due to both reflux and non-reflux causes can show small and irregular kidneys. Bilateral smooth and small kidneys indicate chronic glomerulonephritis or renal artery stenosis, hypoplasia or dysplasia involving both kidneys. Unilateral small regular kidney indicates unilateral renal artery stenosis. Infantile polycystic kidneys are identified by echogenic enlarged kidneys with small cysts. Nephromegaly with multiple large cysts denote autosomal dominant polycystic kidney disease.

Intravenous urogram

This imaging modality is important for assessing renal size anatomy and function of

individual kidneys. A conventional IVU is of little value and only minute sequence IVU is found useful in childhood hypertension. In conventional IVU we take the first picture after the contrast only at 5th minute. On the contrary if we do minute sequence (rapid sequence) IVU with pictures after contrast at 1, 2, 3 and 5 minutes followed by regular IVU pictures one can document the ischemia effectively. Distal branch artery stenosis may not be picked up in IVU. On documenting ischemia selective renal angiography can be done using concerned modalities. Unilateral renal artery stenosis can be identified by diminished size of the kidney, delay in appearance of nephrogram and delayed excretion of the contrast by the ischemic kidney, the kidney with renal artery stenosis. Apart from these three major criteria for ischemic kidney there are many minor criterias. Decrease in the size of the pelvicalyceal system, ptosis of the kidney, notching on the ureters due to collaterals developed following renal ischemia are some of them.

Apart from renal ischemia, reflux nephropathy can be documented by abnormal renal contour and deformed calyx indicative of renal scars which is also the feature of chronic pyelonephritis due to non-reflux causes. Opaque striations running into cortex indicative of autosomal recessive polycystic kidney disease and distorted, splayed calyces due to multiple cysts denoting autosomal polycystic kidney disease can be noted in IVU.

Voiding cystourethrogram (VCUG)

This important imaging modality is needed to document posterior urethral valves (PUV) and vesicoureteric reflux (VUR) without ambiguity. Reflux nephropathy causing hypertension and PUV related chronic tubulointerstitial disease are some of the common causes of hypertension in children. In conventional VCUG urethral anatomy is delineated and is useful for PUV detection. We can also grade the VUR but the test cannot be repeated frequently, as ionizing radiation is more. If Dimercapto Succinic Acid Scan (DMSA) is indicative of pyelonephritis but voiding cystourethrogram (VCU) failing to show VUR the child may need direct radionuclide cystogram (DRNC), which is more sensitive than VCU to detect VUR. Direct radionuclide cystogram can be repeated frequently, as ionizing radiation is less.

Radio nuclide imaging

Radio nuclide scintigraphy may be used to image genitourinary tract and to examine renal perfusion and functioning. Radionuclide scintigraphy uses pharmaceutical compounds that can assess renal function and anatomy by measurement of GFR, tubular secretion or tubular integrity by measurement of isotope retention. Radionuclide renal scans have greatly reduced the need for intravenous urogram as an investigation in childhood hypertension. In this modality the child is exposed to only a small dose of ionizing radiation. Information on renal blood flow and split renal function can be obtained. Even in children with compromised renal function this test can be done. This test has completely replaced the need for IVP in neonates. IVP in newborns is associated with poor concentration of the radio-contrast by the kidneys. But one should note that urinary tract anatomy is not better described by radionuclide scan.

In children with renovascular hypertension the renal radionuclide scan (DTPA) shows reduction in renal blood flow and GFR on the affected side in the renogram. On doing captopril renogram after one hour of challenge dose of captopril, the reduction in blood flow and GFR are found accentuated in children with renovascular hypertension. Bilateral

renovascular disease is difficult to diagnose with captopril enhanced renal scan as the blood flow is symmetrically diminished on both sides.

In DTPA the delay in tracer reaching the collecting system as noted by delayed intrarenal transit time suggest i) renal insufficiency ii) renal vein thrombosis iii) pyelonephritis iv) renal artery stenosis and v)dysplastic kidney. When there is normal transit time but delay in drainage the likely possibility could be PUJ obstruction or VUR. In ureteropelvic junction obstruction delay in excretion noted in the excretory phase not abolished by diuretics is indicative of organic obstruction.

Cortical function defects seen in pyelonephritis, infarction, scarring and fetal lobulation are identified by DMSA. Reflux nephropathy is the common condition associated with scarring. It also helps in identifying the cortical function both in acute and chronic pyenonephritis even in children with renal failure.

Computerised tomography of kidneys

This essential modality of imaging is very useful in picking up tumours associated with hypertension and perirenal collections causing ischemia to the kidney as in "Page kidney". The tumours like neuroblastoma and pheochromocytoma can be identified.

Doppler flow ultrasound

This study is attractive by being non-invasive but is not sufficiently sensitive to be the final diagnostic imaging study when renovascular disease is suspected. Positivity is very useful but negativity does not rule out renal ischemia. Increased peak velocity, spectral widening distal to the stenosis are the features documented in renal artery stenosis and in renal transplant artery stenosis.

Selective renal angiography

This study is essential to localize the site of renovascular disease and to predict the type of disorder causing the renovascular hypertension. Fibromuscular dysplasia which is a common etiology of renovascular hypertension is characterized by stenotic lesions in the main renal artery and post-stenotic aneurysmal dilatation. Beaded appearance in the renal artery is possible if several segments are involved. In aortoarteritis the renal arteries are usually involved at the origin from aorta.

Digital substraction angiography can replace selective angiography as the radio contrast is injected intravenously in a large vein and the arterial phase of renal vasculature is obtained by digital substraction methodology. This method needs larger volumes of radio-contrast material and cooperation of the patient. Because of smaller sized renal arterial tree, this method is not fully useful in children.

Classical aortogram done with contrast followed by selective renal angiography was the gold standard investigation for renovascular hypertension in adults. This investigation was done with great difficulty in children above 5 years of age. The advent of doppler study, CT angiography and MRI angiography has revolutionized the investigation for evaluating a child with renovascular hypertension.

MRI arteriogram

It is useful in the evaluation of renal arterial vasculature and aorta and to assess the function of renal hypoperfusion. It helps to identify renal arterial narrowing due to intraluminal and extraluminal causes. Advantage of MRI arteriogram is that contrast needed is much less and hence less nephrotoxicity. The sensitivity and specificity is less when compared to CT angiography.

CT angiography

The sensitivity and specificity of this important imaging modality is 98% and 94% respectively. It is very safe procedure in children and is less invasive than digital substraction angiography.

Renal vein renin assay

This assay is usually done along with renal angiographic study. Renal vein renin level is 25% higher than peripheral venous renin level. In children with unilateral renal or renovascular disease, renal vein renin levels on the affected side is exceedingly high. Renal vein renin level from the diseased side should be above 50% than renin level of inferior venacava and then only full benefit will be present after intervention.

Peripheral plasma renin activity

Elevated levels are seen in renovascular hypertension, renal parenchymal disease and some of those with essential hypertension. A very low peripheral plasma renin activity is seen in mineralocorticoid excess hypertension. Elevated plasma renin levels is associated with renal artery stenosis and 21 hydroxylase deficiency. Primary reninism is caused by renin secreting tumours, benign or malignant, which can be intrarenal or extrarenal. All of them have hypokalemia with elevated plasma renin levels and can be diagnosed with angiography and CT scan.

Plasma aldosterone

Elevated aldosterone level is associated with elevated plasma renin in renal artery stenosis. In hyperaldosteronism, the elevated aldosterone is noted with normal renin level. Low aldosterone along with high plasma renin is noted in 21 hydroxylase deficiency. Low aldosterone and low renin levels are seen in 11 beta hydroxy steroid dehydrogenase and 11 hydroxylase deficiencies. Hypoaldosteronism with hyporeninemia along with hyperkalemic hypertension, hyperchloremia and normal renal function may point towards Gordon's syndrome. With hypoaldosteronism with hypokalemic hypertension one should think of psuedohyperaldosteronism, Liddle's syndrome.

Serum cortisol and 24 hours urine 17 hydroxy corticosteroid

Elevated free serum cortisol and 24 hours urinary 17 hydroxy corticosteroids are suggestive of hypercortisolism. Following dexamethasone (3.75 mg/m^2/day x 2 days) if the level falls it is suggestive of ACTH induced adrenal hyperplasia (Cushing disease).

Urinary and plasma catecholamine levels

Elevated plasma epinephrine or norepinephrine or increased urinary metanephrine levels suggest pheochromocytoma and neuroblastoma.

Meta iodo benzyl guanidine (MIBG) scan

It is both sensitive (86%) and specific (95%) in identification of catecholamine secreting tumours like pheochromocytoma. A reimaging after 48 hours of injection of radionuclide material can also identify extrarenal location.

Approach to investigation in hypertension[4,6]

- Confirm BP on three occasions. If normal BP is documented (BP < 90th percentile), we are going to maintain the health surveillance. If hypertension is confirmed (BP > 95th percentile) we go to the next stage.
- History of drug intake, decongestant nasal sprays or oral decongestants (sympathomimetics) for the common cold and glucocorticoids will give the clue towards drug induced hypertension. Stop the drug and reevaluate after adequate period. If hypertension is resolved, a drug

induced/related hypertension is the diagnosis made. If hypertension is not resolved, child needs investigations for other secondary etiologies. Similar step also should be taken when there is no history of drug intake in the hypertensive child.

- Documentation of BP in all four limbs is an important step. Upper extremity hypertension only, will give us the clue towards coarctation of aorta. Documentation of pulses in peripheral, palpable and accessible blood vessels is mandatory. Hypertension in all the four limbs will indicate the need for investigatory approach for other secondary causes for hypertension. ECHO evaluation, doppler studies and aortogram may be needed as per the diagnosis.
- If plasma renin activity is low, one should consider mineralocorticoid excess. If it is high one should think of renovascular etiology (or even renal disease causing hypertension). Renal ultrasound, captopril scan, renal vein renin, doppler study and renal angiography are the investigations needed in this situation. IVU will give positive findings of ischemia in the kidney that has affected blood vessel. But assessment of plasma renin and renal vein renin are not routinely available in many centers. Discrepancy of kidney size by USG and ischemic changes in the affected kidney by minute sequence IVU will point towards renal artery stenosis.
- Renal function tests like estimation of blood urea, serum creatinine and serum electrolytes are mandatory. If the child has normal renal function but hypokalemia one should think of mineralocorticoid excess. Even renovascular hypertension can have hypokalemic hypertension. If the child has abnormal renal function the diagnosis is essentially renal parenchymal hypertension. History and clinical examination by this time also would have pointed towards the etiology of renal parenchymal disease either glomerulonephritis or the other group including chronic pyelonephritis, renal dysplasia and cystic renal disease.
- Investigations needed in glomerulonephritis are:

  24 hours urine protein, creatinine and creatinine clearance

  Serological evidence for infection in acute HT like ASO

  Complements C3, C4 in immune related hypertension

  Serological tests for SLE

  Peripheral blood smear for microangiopathy for acute HT

  Renal biopsy in non-contracted kidneys for confirming the diagnosis of chronic glomerular disease
- Investigations for chronic pyelonephritis, renal dysplasia and cystic renal disease include:

  Renal ultrasound, Radionuclide renal scan, DTPA and/or DMSA scans, VCUG in chronic pyelonephritis
- In children showing abnormal urinalysis (hematuria and/or proteinuria or defective urinary concentration) renal disease as the cause of hypertension should be considered and investigations for glomerulonephritis and the group of chronic pyelonephrits, renal dysplasia and cystic renal disease should be done depending on the presentation of other features.
- A clinical suspicion of pheochromocytoma should make the clinician do the relevant

investigations. Sustained or labile hypertension, poor weight gain, episodes of shock like features needing intravenous fluids, excessive appetite, hypertensive crisis on palpation of abdomen are some of the features that make one think of pheochromocytoma. Relevant investigations include urinary catecholamines and metabolites, plasma catecholamines, computerized tomography of the abdomen and ^{131}I metaiodobenzyl guanidine (MIBG) scan to confirm the cause of HT.

Conclusion

Hypertension in children is no longer an uncommon disease. Causes are many. Hypertension in children should be always considered secondary unless proved otherwise. Essential hypertension is also possible in children and is being increasingly documented in adolescents. High normal BP of childhood is a pointer towards adult hypertension. All possible investigations should be done as per history, clinical examination and initial laboratory evaluation before defining hypertension as essential.

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NEWS AND NOTES

Lakeside Education Trust, Twenty First Annual CME

Subject: "Recent trends in pediatric practice"

Date: - Sunday, July 27th, 2003. **Venue: Hotel Atria, Bangalore.**

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LABORATORY MEDICINE

CLINICAL NEUROPHYSIOLOGY IN PEDIATRIC PRACTICE

**** Ayyar SSK***
**** Suresh Kumar***
***** Vasanthi D***
****** Sangeetha V***

The vast advances in medical electronics and computer technology have made several sophisticated but essential investigations possible in the diagnosis, management and prognosis of neurological disorders.

A well-equipped neurophysiology laboratory caters to a multitude of test protocols, the common among them being EEG (electroencephalography), EMG (electromyo graphy), NCS (nerve conduction study- motor and sensory), VEP (visual evoked potentials), BSEP (Brainstem auditory evoked potentials), BERA (Brainstem evoked response audiometry), SSEP (Somatosensory evoked potentials – both neural and dermatomal stimulation), RNS (Repetitive nerve stimulation study for myasthenia), Facial nerve and blink reflex studies and SSR (sympathetic /galvanic skin response).

Such an array of tests demand precise knowledge of neuroanatomy and neurophysiology on the part of the technician and hands-on experience in the performance of the tests in order to reach a degree of perfection. The clinical neurophysiologist on the other hand should have adequate training in the different modes of testing and the interpretation of the test results and aid in advancing and clinching the diagnosis. In short, any neurophysiology test should be considered as an extension of the clinical neurological examination.

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EEG (Electroencephalography):- Chief role is in the diagnosis of epilepsy and definition of the seizure type. Epileptiform discharges are recorded in about 45-50% cases of epilepsy; with activation techniques such as hyperventilation, photic stimulation, sleep deprived and sleep induced recordings the yield of information can be increased (Fig 1 and 2). Nevertheless it should be remembered that a normal EEG does not exclude epilepsy and diagnosis of epilepsy should always be clinical at the first instance. Advances in technology have made it possible to integrate EEG and video imaging of the patient so that the epileptic discharge can be synchronized to the epileptic fit as observed on the video (synchronized video EEG). Such precise correlation between the seizure and epileptic discharge has become mandatory and a prelude to the consideration of epilepsy surgery.

EMG (Electromyography) uses a needle electrode inserted into the muscle which records the electrical potentials generated in the muscle at rest and during graded muscular contraction. A comparison is then possible between normal pattern and values and those obtained in diseases of the muscle such as muscular dystrophy, myopathy (congenital, acquired), motor neuron disease and peripheral nerve diseases. Fig 3 and 4 compare the findings in motor neurone disease and myopathy.

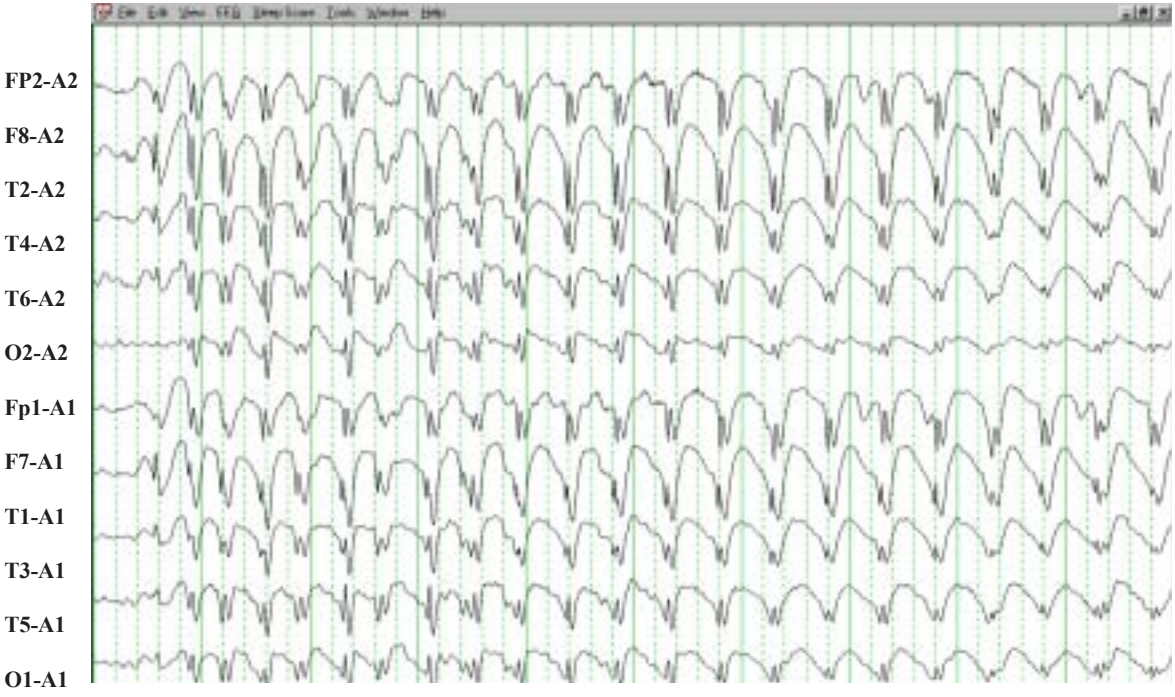


Fig 1. 3Hz spike and slow wave discharge elicited on hyperventilation in petitmal seizures

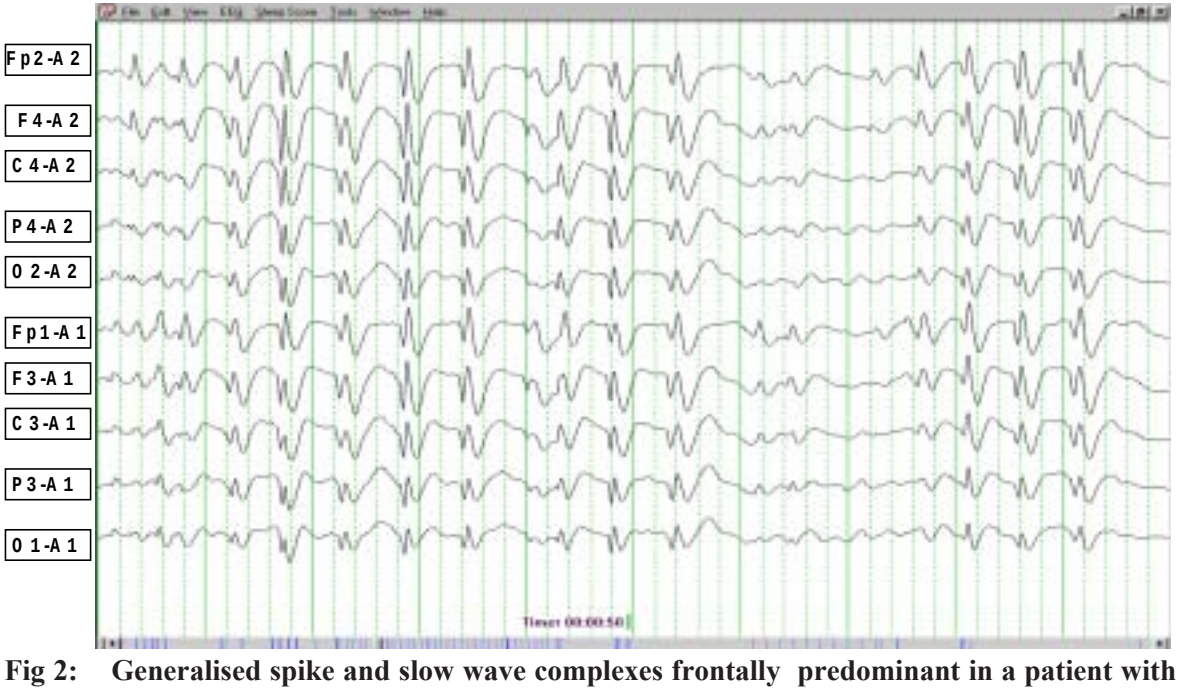


Fig 2: Generalised spike and slow wave complexes frontally predominant in a patient with generalised tonic clonic seizures

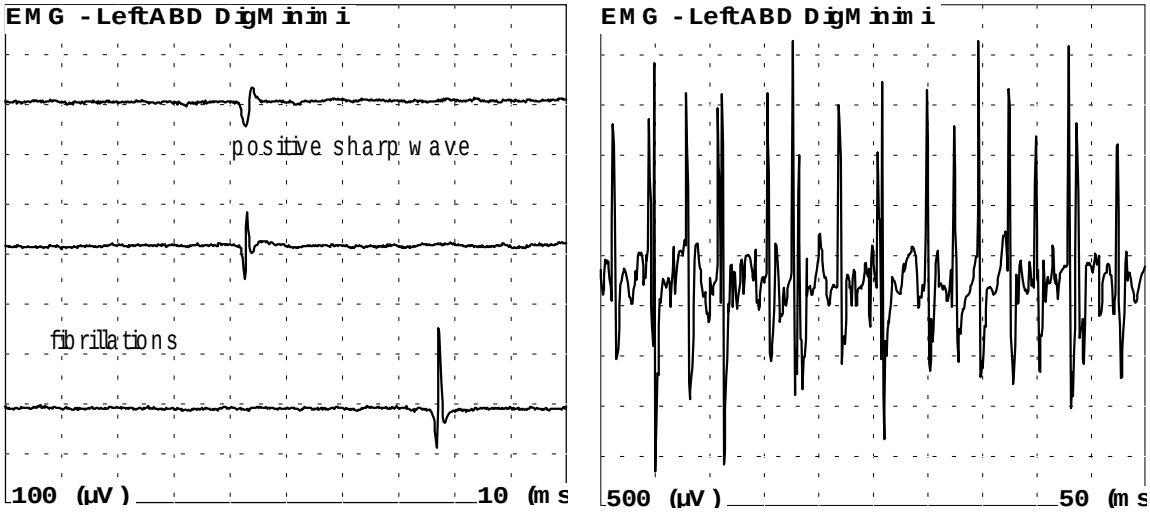
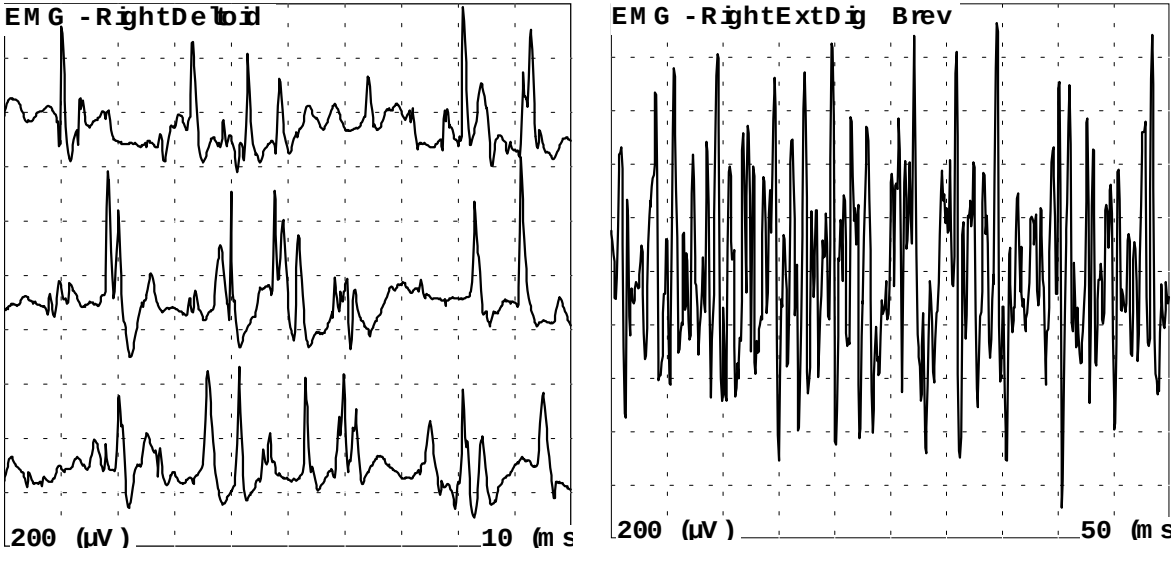


Fig 3: EMG in motor neurone disease – classical findings are fibrillations, positive sharp waves, long duration high amplitude motor unit potentials, delayed recruitment and reduced interference pattern



short duration MUPS

low amplitude interference pattern

Fig 4: EMG in myopathy: The characteristic finding is motor unit potential (MUP) of short duration and low amplitude. As all motor neurons are intact the interference pattern is full. The recruitment of motor units is early in these cases

NCS (Nerve conduction study): The peripheral nerves for the four limbs and trunk emanate from the spinal cord and the cranial nerves from the brainstem. The motor fibres in these nerves conduct impulse to the muscles and end organs and the sensory fibres conduct impulse from the peripheral sense organs to the central nervous system. Nerve conduction study evaluates the

conduction of the nerve impulse in terms of latency (time from stimulus to the onset of response), velocity of conduction and amplitude (voltage of the motor or sensory action potentials generated). The conduction in proximal portions of the peripheral nerves and roots can be measured by the late response studies (ie, F wave and H reflex). NCS is the most common neurophysiological evaluation in neurological practice and is useful in a variety of peripheral nerve disorders such as diabetic neuropathy, nutritional neuropathy, Guillain Barre Syndrome, toxic and hereditary neuropathies. (fig 5, 6 & 7)

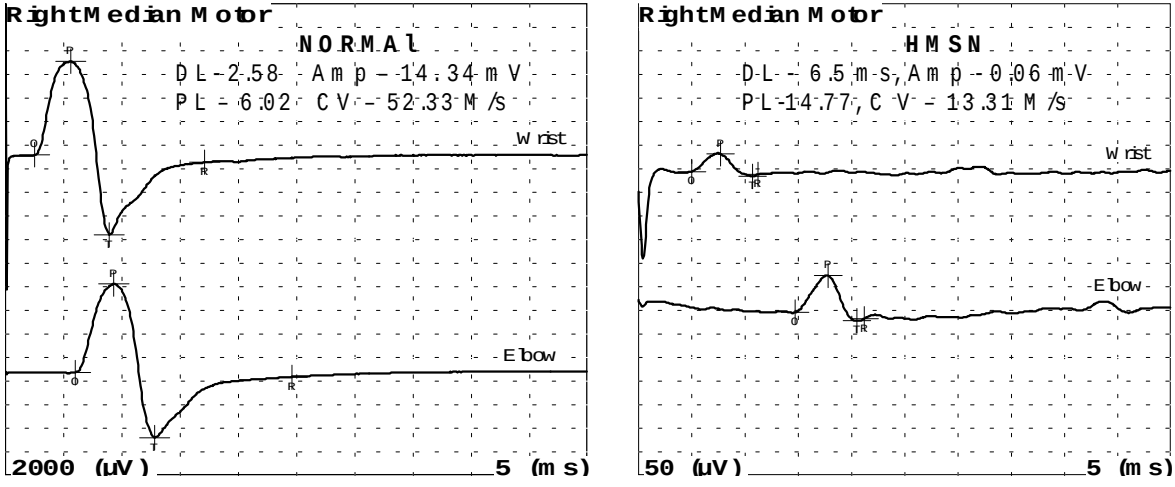


Fig 5: Hereditary Motor Sensory Neuropathy (HMSN) Type 1 in a girl aged 6 yrs; Note prolonged distal latency, grossly reduced amplitude and grossly decreased motor conduction velocity. Normal response and values are depicted on the (L) side

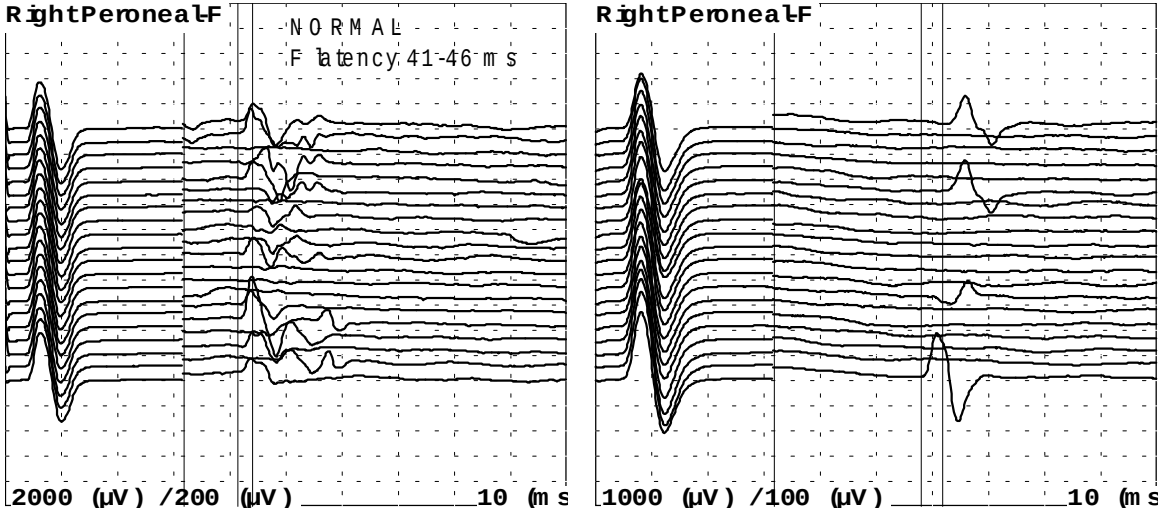


Fig 6 : Guillain Barre Syndrome (GBS) – boy of 16 yrs; the earliest abnormality is prolongation, absence or infrequency of F wave response and this is the hall mark of GBS in the typical clinical setting

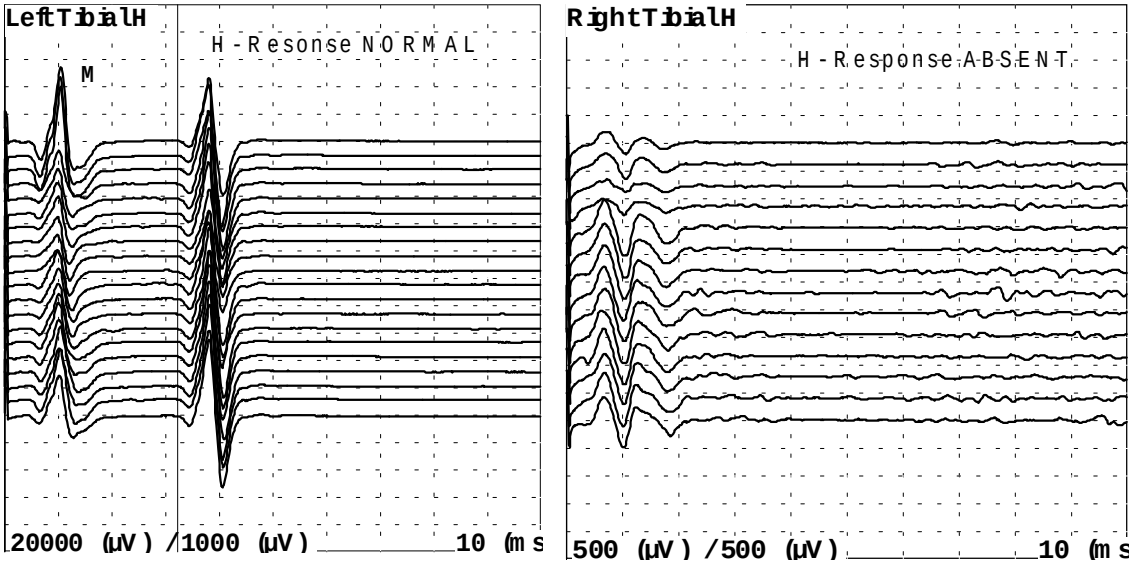


Fig 7 : H reflex response from a normal subject compared to absent H response in sciatic nerve injury following gluteal injection in a boy of 6 yrs

EP (Evoked Potential Studies): Advances in electronic and computer averaging techniques have made it possible to measure very tiny signals of the order of microvolts (one millionth of a volt) from the visual, auditory and somatosensory pathways in the central nervous system. Measurement of the artifact-free biological signal obtained is made in terms of latency (time period from stimulus to response) and amplitude of the signal. Sequential recordings from different levels of the spinal cord (spinal evoked potentials) makes it possible to assess conduction in segments of the spinal cord and helps in the localization of the spinal lesion.

VEP (Visual Evoked Potential): Consists of presenting a reversing chess board pattern of dark and light stimulus to the eyes from a TV monitor placed one meter away from the eyes of the subject and recording the visual response from the occipital area of the brain through surface electrodes placed over the scalp at relevant sites. Normally it takes about 100 milliseconds (1/10 sec) for a light impulse from the retina of the eye to reach the visual area of the brain concerned with normal perception (P100 latency). This test is of immense value in assessing the visual pathways in conditions such as optic neuropathy (Fig 8), multiple sclerosis, pituitary and other brain tumours.

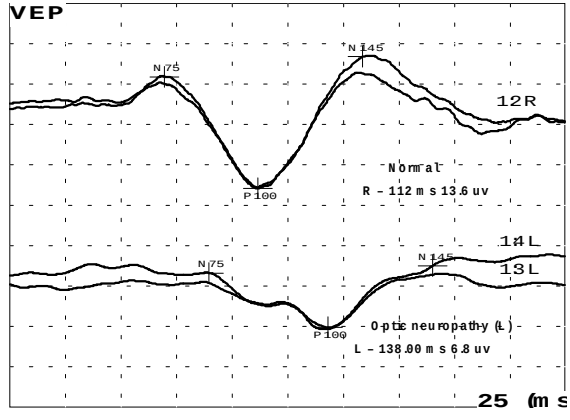


Fig 8 : Visual Evoked Potential (VEP) : Normal on the right compared with abnormal on the left. Note the moderate-to-marked prolongation of the P100 latency with reduced amplitude in optic neuropathy (L)

BAEP (Brainstem Auditory Evoked Potential): In this modality click sounds are presented to each ear separately at different decibels and rates of stimulation while blocking the opposite ear with white noise. Recording is made from an active electrode placed over the mastoid and referenced to the vertex with opposite mastoid acting as the ground. As a standard practice about 2000 averages are made to obtain a artifact-free signal consisting of five major peaks named waveform I to V, each waveform representing the generator of the potential as auditory impulse passes sequentially along the auditory nerve to the auditory cortex. Waveforms VI and VII which are believed to be generated in the auditory cortex are inconsistent and inconstant and therefore are not included in the measurement. Latency to waveform I, III and V and interpeak latencies I-III, III-V and I-V as well as amplitudes of waveform I and V are measured. Auditory nerve function is represented by the latency and amplitude of waveform I. The interpeak latencies I-III and III-V give a measure of conduction and integrity of lower and upper brainstem auditory pathways respectively. This test is useful in assessing auditory nerve function in children and adults and in lesions such as multiple sclerosis and stroke affecting conduction in the brainstem auditory pathways.

BERA (Brainstem Evoked Response Audiometry) is a modification of BAEP test and is widely used in assessment of auditory function in high risk neonates suffering / recovered from hyperbilirubinaemia, hypoxic ischaemic encephalopathy (Fig 9), meningitis, convulsions and in preterm low birth weight babies and children with hearing deficiency.

SSEP (Somatosensory Evoked Potentials): The sequential conduction of a nerve impulse through the peripheral nerves (such as the median, ulnar, tibial and peroneal) to the spinal cord and from there through the spinal somatosensory pathways, the brainstem and thalamic pathway to the cerebral sensory cortex can be recorded and the latency and response in terms of voltage

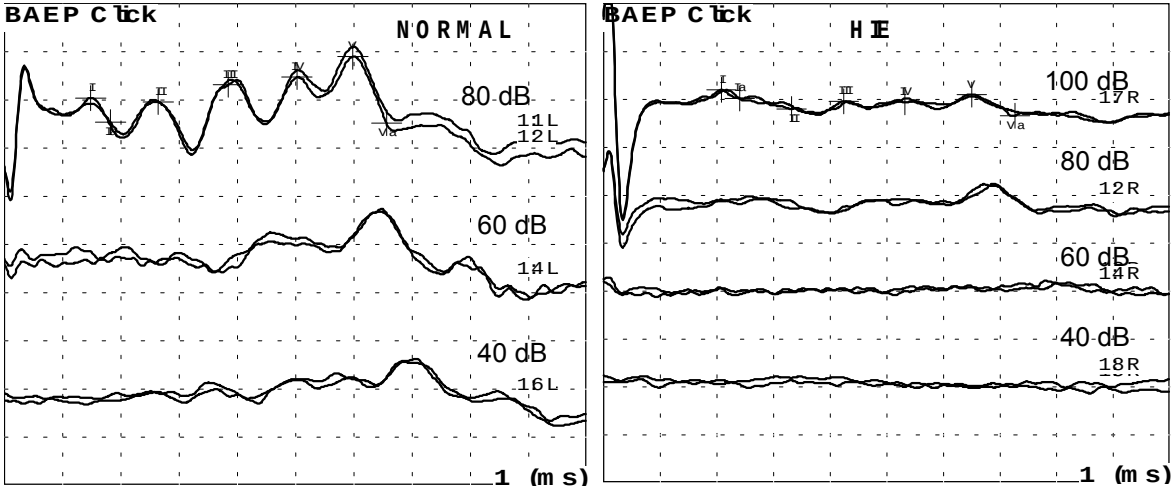


Fig 9: Brainstem Evoked Response Audiometry (BERA): Left – Normal response consists of waveform V elicited at 40 dB and I to V waveforms with normal latency and amplitude at 80 dB Right – waveform V elicited only at 80 dB indicating severe hearing deficit. This finding is supported by delayed waveform I with very low amplitude of waveforms I to V

measured. The peripheral nerve is stimulated and recording is made from surface electrodes placed over the limbs, spine or scalp region overlying the sensory cortex. This gives a measure of the sensory conduction in each of the segments and helps to locate lesions in the spinal cord, brainstem or cerebral cortex. The test is useful in multiple sclerosis, stroke, brainstem lesions, spinal cord tumours, transverse myelitis etc.(Fig 10, 11)

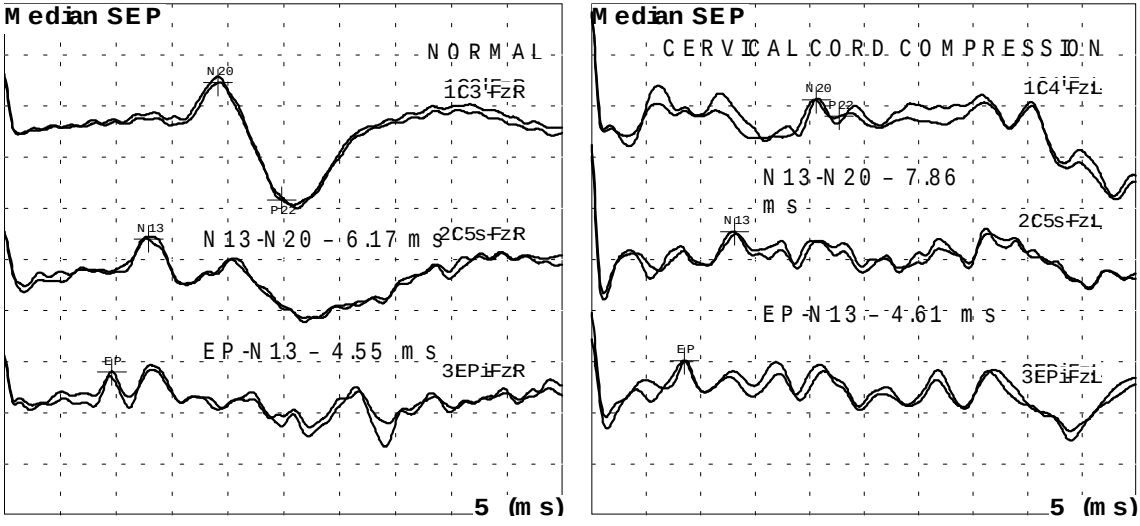


Fig 10: Somatosenspry Evoked Potentials (SSEP) from upper limbs (median nerve stimulation). Recording made from Erb's point, C5 spine and contralateral scalp area (C4). EP, N13 latency normal but N13-N20 interlatency (normal upto 7 ms) is prolonged due to cervical cord compression.

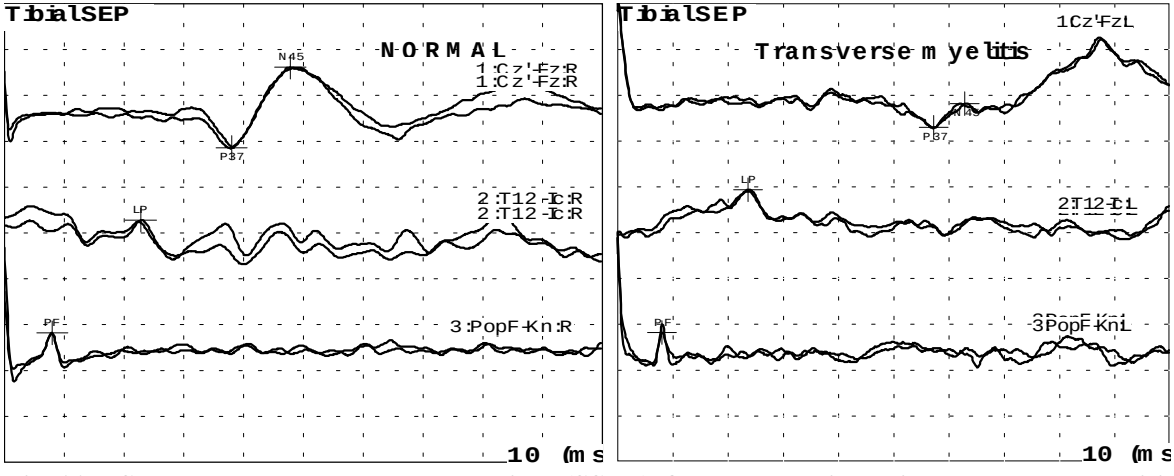


Fig 11 : Somatosensory Evoked Potentials (SSEP) from lower limbs in transverse myelitis compared to normal. Note the marked prolongation of the P37 latency and decreased amplitude recorded from the scalp overlying leg area of the cortex. The N22 – P37 latency is prolonged (28 ms) in transverse myelitis indicating delayed conduction in spinal somatosensory pathways (normal 15 ms).

An extension of this test is dermatomal SEPs in which the dermatome is stimulated and the conduction along the particular root subserving the dermatome is studied as in cervical or lumbosacral radiculopathies and brachial plexopathies in children and adults. Entrapment of the peripheral nerves such as the lateral femoral cutaneous nerve of the thigh can be studied by stimulating the dermatomal area of the nerve and recording from the scalp. The delay in latency between normal and affected side clinches the diagnosis.

Polysomnography (PSG) is a fairly recent modality of investigation in which overnight recording (for 8-12 hours) is made of EEG waveforms, respiratory and cardiac parameters and any abnormal limb movements during sleep. The study is useful in obstructive sleep apnoea, excessive day time sleepiness due to different causes, narcolepsy (sleep attacks), restless legs syndrome, sleep walking, sleep talking, nocturnal seizures, enuresis, sleep terrors etc. Sleep centres are very few in our country, but is an important requirement in the comprehensive study of sleep related medical problem in children.

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NEWS AND NOTES

PEDINEUROCON-2003
5th NATIONAL NEUROLOGICAL CONFERENCE &
31st RAJASTHAN STATE IAP CONFERENCE-2003
HOST: RAJASTHAN STATE BRANCH – IAP

A three day conference is being organized on 7-9th Nov 2003 at Pink City Jaipur

Highlights: Core group meeting on development of protocols for common pediatric neurological illnesses.

Workshops on EEG, Neuroimaging, Electromyoneurodiagnosis

Guest orations, Poster presentations, Award papers, Panel discussion

Registration Fee	Up to 30 June'03	31 Aug'03	6 Nov'03	Spot
IAP Member	Rs 700	Rs 900	Rs 1200	Rs 1500
Non IAP Member	Rs 800	Rs1000	Rs 1300	Rs 1600
Assoc. Member	Rs 500	Rs 700	Rs 1000	Rs 1500
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NUTRITION

SMART NUTRIENTS AND BRAIN DEVELOPMENT

**** Elizabeth K E***

The expression of the genetic potential for growth and intelligence is the sum total of the interplay of the genetic/host factors with nutrition and environment. Brain is the soul of the human being, the key area concerned with our intelligence, personality, emotions, well-being, spirituality and probably our existence. As most of the brain growth occurs in utero and early postnatal period, the role of maternal nutrition, breast-feeding and complementary feeding cannot be underestimated. The nutrients that help in the development of brain can be called as 'smart nutrients'.

The number of neurons is almost fixed by mid - gestation and it is difficult to malnourish a foetus during this period. Most of the malnutrition occurs in the third trimester of pregnancy. The migration of the neurons to the respective areas, the connections, the proliferation of synapses, receptors and dendrites progress in the perinatal period and early postnatal period, especially first 2-3 years of life. These are modifiable to a great extent through diet, specific nutrients especially micronutrients, stimulating environment, tender loving care (TLC), parental interaction and play[1,2].

The weight of a baby at birth is 3 kg and is only 5% of the adult weight, whereas the weight of the brain is 350 g, almost 25% of that of the adult brain. The average adult weight is around 60 kg and brain weight is 1400 g, thus the body grows 20 times compared to the four fold increase in brain growth. The interesting point is that most of the brain growth occurs in the first few years of life. In the first half of infancy, brain growth becomes 50%; by 2 years it becomes 80%, 90% by 5-6 years and almost 95% by 10 years of age. By 2 years of age, body growth becomes only 20% of that of the adult, but brain growth becomes almost 80%. Thus it is clear that most of the brain growth is directly influenced by breast feeding and complementary feeding. The human brain consists of 100 billion neurons, almost 1000 billion glial cells as supporting cells and their connections.

Two third of the weight of the brain is due to phospholipids and long chain polyunsaturated fatty acids (LCP). Breast milk is the best for brain growth, neuromuscular development and myelination. Thus milk is now found to be 'species specific'. Low birth weight premature babies (LBW) fed on preterm milk secreted by the mothers are found to have 10 IQ points more than artificially fed babies[3,4]. Hence milk is also 'baby specific'.

The smart nutrients that promote brain growth are variable and belong to various food groups. The food that we eat also influence our memory, concentration, comprehension, judgment, intellect, mood, emotions etc. There are over 50 neurotransmitters that are affected by the food and the micronutrients that we take.

Carbohydrate

Among the carbohydrates, lactose is credited as a smart nutrient. It promotes the synthesis of cerebrosides and myelination. It is a 'prebiotic

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substance' that promotes lactobacilli and thereby digestion. It also promotes the absorption of calcium and magnesium. The lactose content of breast milk is double that of cow's milk.

Protein

Sulphur containing amino acids are brain friendly. Cysteine to methionine conversion is low in the brain of the infant and so high cysteine: methionine ratio in breast milk is advantageous for CNS development. Amino acids are the main precursors of neurotrans mitters. High tryptophan to neutral aminoacid ratio in breast milk is beneficial to the brain. Tryptophan is the precursor of serotonin. Serotonin is important for mood and sense of well-being. Choline, a vital amine, is crucial for brain development and is the precursor of acetylcholine, which is important in neurotrans mission and memory. Serotonin is the 'feel good neurotransmitter' and acetylcholine is the 'memory-boosting chemical'. Tyrosine is the precursor of dopamine and is functional in motor coordination. Taurine is instrumental in brain growth and maturation of retina. Taurine is an important neurotransmitter and neuromodulator of brain and retina. The low content of aromatic amino acids like tyrosine and phenylalanine, which are less utilized by small babies, also seems to be protective to the brain. Moreover, the amino acids in trans-form are brain- friendly whereas those in cis-form as in micro waved formula are neurotoxic.

Lipids

Over 60% of the brain weight is due to phospholipids and long chain polyunsaturated fatty acids. The derived lipids, docosahexaenoic acid (DHA) and arachidonic acid (ArA) are essential for brain and neuromuscular development. ArA is the precursor of prostaglandin. DHA increases the level of serotonin and acetylcholine. DHA is derived from omega 3 fatty acid, linolenic acid and ArA is derived from omega 6 fatty acid and linoleic acid. These are 30 times more in breast milk than in cow's milk. Infants are unable to convert the short chain omega 3 fatty acid, alpha linolenic acid into DHA. The requirement of DHA is found to be 20 mg/kg/day during brain growth. Fish and fish oils are important sources of omega3 fatty acids and DHA. These are seen to maintain integrity of cell membrane in the brain. Almost half of the lipid in brain cell membrane is DHA. DHA is the building block for cell membrane and synaptic connections. Long chain polyunsaturated fats (LCP) are being tried in comorbid conditions like hyperactivity, attention deficit disorders, dyslexia etc. Ketogenic diet is considered the final answer in intractable myoclonic seizures.

Micronutrients

These are the vitamins and minerals that are required only in small quantities, but serve key functions in the body and brain. Micronutrients are cofactors in metabolic pathways and are essential for production of several enzymes and brain development [5,6].

Among the B complex factors, B1,B2,B3, B6, B11 and B12 are important for the synthesis of various neurotransmitters. Thiamin (B1) is essential in the function of brain and peripheral nerves. B1 deficiency decreases the ability to utilize glucose. Deficiency is also associated with insomnia, loss of memory, visual acuity, Wernicke's encephalopathy, Korsakoff's psychosis and absent knee jerk. Dry beriberi is known to cause neuropathy, aphonia etc. Riboflavin (B2) deficiency is associated with neuromotor incoordination, personality changes and impaired performance in psychomotor tests. Niacin (B3) deficiency leads to pellagra with dementia and impaired cognition. Pyridoxine (B6) is essential for the synthesis of GABA, the

inhibitory neurotransmitter and its deficiency may cause convulsions and peripheral neuropathy. B6 deficiency is also associated with sideroblastic anemia. Folic acid (B11) is essential for neural tube development and periconceptional supplementation of folic acid can prevent neural tube defects. Folic acid deficiency is also associated with chronic diarrhoea, attention deficit disorder, stroke and autism. Folic acid and choline are also important for myelin synthesis. Cobalamine (B12) deficiency is associated with subacute combined degeneration of spinal cord, dementia and probably emotional instability. B11 and B12 deficiency produce megaloblastic anaemia. Deficiency of folic acid (B11), B12, B6 and choline leads to elevated levels of homocysteine that may result in thromboembolic episodes and stroke. Vitamin A is important in integrity of the eyes and vision.

Vitamin C deficiency is attributed to reduced resistance power, reduced IQ score, altered behaviour and increased incidence of stroke. Vitamin E is the potent antioxidant; its deficiency is concerned with transient ischaemic attacks (TIA), stroke, oxygen toxicity and probably Alzheimer's disease.

Among the minerals, iodine deficiency is the prototype of mental deficiency caused by a nutritional deficiency. Iodine deficiency leads to reduced physical activity, growth and development and is referred to as endemic cretinism. And iodine supplementation leads to substantial improvement if undertaken early. Iron deficiency is known to cause irreversible changes in the growing brain. It results in neuromuscular incoordination, reduced physical activity, attention and cognition. It also leads to headache and lack of concentration and impaired auditory and visual brain stem evoked potentials. Cytochrome oxidase in mitochondria is an iron dependent enzyme and oligodendrocytes require iron for the synthesis of myelin. Iron deficiency results in deficiency of dopaminergic D2 receptors leading to reduced dopamine and thereby relative increase in opiates. This shift is the cause of reduced learning ability in iron deficiency. The balance between dopamine and opiates influences learning ability. When opiates take the lead, this ability comes down. Iron is also important in serotonin and GABA levels. Iron deficiency is also known to make the RBCs rigid thereby increasing the chance of thrombosis. Conventionally, polycythemia is said to increase the incidence of thrombosis and stroke. Increased iron content is also not desirable. It is connected to Parkinson's disease in adults and Hallervorden Spartz disease. Similar to iron, copper is an important component of cytochrome oxidase and also another enzyme called super oxide dismutase. As iron and copper share several properties copper is aptly called the "iron twin". Both iron and copper deficiency are known to produce microcytic, hypochromic anaemia. Copper deficiency leads to Menkes kinky hair disease and excess is associated with Wilson disease, Indian Childhood Cirrhosis (ICC) and probably amyotrophic lateral sclerosis and dementias like Alzheimer's. Aluminium excess is also suspected in the pathogenesis of Alzheimers disease. Zinc is the constituent of about 200 metalloenzymes with high activity in the brain. Zinc deficiency is associated with diarrhoea, infertility, growth retardation and neuropsychological problems. Selenium deficiency is attributed with anxiety, oxidant stress, depression, low mood etc. It is a powerful antioxidant. Chromium deficiency is said to reduce glucose tolerance. Cobalt is useful in iodine utilization.

Antioxidants

Brain is the seat of abundant metabolic activity and hence abundant waste products. Brain consumes 20-30% of entire energy in spite of having only 2% of body weight. It utilizes

maximum amount of glucose and oxygen. In the bargain, lot of oxygen free radicals and reactive oxygen species (ROS) are produced as byproducts. These bullets attack the cell membrane, mitochondria and damage even the DNA. It leads to shrinkage and dissolution of dendrites and synapses and disrupts the communication system in the brain. The content of fat in the brain makes it vulnerable to lipid per oxidation by these oxidants. Antioxidants, both endogenous and dietary are the only answer to this disaster. Beta-carotene, vitamin C, vitamin E, selenium and other phytonutrients act as scavengers and antioxidants. Copper, iron, vitamin B complex factors are functional in the endogenous antioxidant systems like glutathione peroxidase, superoxide dismutase, catalases, ceruloplasmin etc[7].

Others

Non-protein nitrogens like urea, amino acids, peptides, nucleic acids, nucleotides, choline, creatine, creatinine, uric acid, ammonia, polyamines, N Acetyl glutamine, N Acetyl neuraminic acid are **"bioactive factors"**. These are seven times more in breast milk than in cow's milk. The exact role of each of these is under study. Other bioactive factors in breast milk are lactoferrin, enzymes, hormones, growth factors, oligosaccharides, mucins and probiotic factors. Probiotic factors help in digestion, eg, lactic acid, lactobacilli, bifidus factor etc. Polyamines like spermine, spermidine and putrescine promote cell growth and differentiation. Putrescine is the precursor of GABA. Epidermal growth factor, nerve growth factor, betacasomorphin, thyroxine, growth hormone releasing factor etc play a role in CNS development. Colostrum is rich in enzymes like lysozyme, peroxidase, xanthine oxidase which promote cell maturation. Carnitine is another substance important in lipid oxidation and various other functions.

Apart from the specific deficiencies, protein energy malnutrition (PEM) is known to cause growth arrest, arrest of milestones, regression of social smile, inability to explore and master the environment, irritability and apathy. PEM leads to functional isolation as in the case of hibernation adapted by certain animals to tide over adverse situations. This functional isolation in the child will evoke less interaction from the mother; caretakers and peer group, resulting in poor stimulation, TLC and play.

Fish is aptly called a 'brain friendly food' second only to breast milk. This is now made more available through the 'blue revolution'. Fish and fish oils are the source of the omega3 fatty acids, DHA, iodine, zinc and taurine. The so called fast food and junk food are called 'brain busting food' due to the deficiency of protective factors and the presence of excess omega 6 trans fatty acids which make the cell membrane of the brain more rigid and less pliable. The omega 6 to omega 3 fatty acid ratio should be kept <5:1.

Greens are the other sources of omega 3 fatty acids. Green leafy vegetables and green, yellow orange vegetables and fruits are rich sources of micronutrients and antioxidants. These are now more available through the 'rainbow revolution'.

Breakfast should be considered the 'brain's food'. After 8 hours fast, the body reaches the lowest or basal levels of nutrients and energy in the morning and so breakfast is like the petrol for the vehicle in reserve. Unfortunately and unknowingly many children skip the breakfast and start the race for the day. Mothers should take balanced diet during pregnancy and lactation. She should deliberately take extra nutrients for the growth and intelligence of her baby. No baby should be denied the merits of breast feeding and optimum complementary feeding during early part of life.

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NEWS AND NOTES

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National Training Project Workshops in
PRACTICAL PEDIATRIC ONCOLOGY - 2003

Two day workshops in practical aspects of pediatric oncology for practising pediatricians, pediatric surgeons and pediatric postgraduates will be held this year at - Hyderabad, Vadodara, Kolkata, Jaipur & Bhopal (proposed). Registration is now open on first come and zonal basis. Prior registration approximately two months before the workshop is mandatory. A reference manual of Practical Pediatric Oncology will be provided free to the delegates about one month before the workshop. This course will help the delegates to participate in managed shared care of pediatric cancer. For details contact the national co-ordinator or trhe respective workshop co-ordinators:

NATIONAL CO-ORDINATOR:

Dr. Bharat R. Agarwal
Head of Department, Division of Pediatric Hematology - Oncology, B.J. Wadia Hospital for Children, Parel, Mumbai - 400 012. Telefax : 00-91-22-26431902, 26426846 Email: prul@bom5.vsnl.net.in

Workshop at Hyderabad: on 22nd & 23rd August 2003:

D. Raghunadharao, MD DM
Professor and Head, Department of Medical Oncology, Room Number #607, 6th Floor, 'E' Block
Nizam's Institute of Medical Sciences, Panjagutta, Hyderabad 500 082. Andhra Pradesh
Tel: 040 23371747, Fax: 040 55669049, Mobile: 040 56871537
Emails: telerama@hd2.dot.net.in and telerama@rediffmail.com

Workshop at Bhopal: dates to be finalised

Dr. Shyam Agarwal
Navodaya Oncological Research Center, 108, Zone II, M.P. Nagar, Near Bhopal Eye Hospital,
Bhopal - 462 011.M.P. Tel. No. Off. 272220-19, Res: 551488, Mobile: 98270-55790

Workshop at Kolkata:

Dr. Ashish Mukhopadhyay
Ideal Tower, Flat 7C & 8, 57, D.H. Road, Kolkata - 700 023. Tel.No.Off. 4567050-59, Res: 4486362
Email: ashism2002@yahoo.co.in / somashis1@rediffmail.com

Workshop at Jaipur: Dr. Rajiv Kumar Bansal, 12, Rathapuri, Sodala, Ajmer Road, Jaipur - 302 006. Rajasthan

Workshop at Vadodara:

Dr. Vibha Naik
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IJPP-IAP CME

RECOGNITION OF A CRITICALLY ILL CHILD

**** Ramachandran P***

- How to identify a critically ill child?
- What are the predisposing conditions?
- What is the initial management of critically ill child?

"Critically ill child" means a child who is in a clinical state which may result in respiratory or cardiac arrest or severe neurologic complication, if not recognised and treated promptly. This term does not refer to any particular disease, but many diseases can lead onto "critically ill state". Whether a child presents with a primary cardiovascular, respiratory, neurologic, infectious or metabolic disorder, the goal is early recognition of respiratory and circulatory insufficiency. In clinical practice, there are three common situations that characterise a critically ill child:

1. Respiratory distress
2. Shock
3. Altered sensorium .

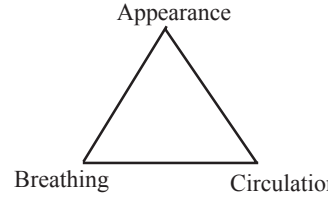
Early intervention is geared towards preventing the progression of hypoxemia and hypoperfusion to full cardiorespiratory arrest.

It is easy to recognise a critically ill child when there is an obvious problem like severe trauma or unconsciousness. On the other hand it is important to identify a child with physiological derangement in its early stages when signs are subtle. The "golden hour" concept applies to all children with illnesses presenting as emergency. Early recognition of a "critically ill child" requires a systematic and rapid clinical assessment with a background knowledge of age appropriate physical signs.

There are many methods to assess an acutely ill child. A very simple and quick way of assessment of overall illness and injury severity is by:

1. Appearance of the child
2. Breathing
3. Circulatory status

These three parameters comprise "Pediatric assessment triangle"



Appearance of the child

Appearance basically denotes the neurological status. It is determined by the oxygen and blood supply to the brain which are dependent on cardiopulmonary status and the structural integrity of the brain. The parameters assessed in appearance are alertness, distractibility or consolability, eye contact, speech or cry, motor activity and color of the skin. In addition, seizures, abnormal posturing, muscle tone and pupillary reaction are noted.

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1. Alertness: Normal children exhibit awareness and interest in surroundings. Determine if the child is confused, irritable, lethargic or totally unaware of environment. Changes in level of conscious can also be rapidly assessed by AVPU method.
    - Awake
    - Responsive to voice
    - Responsive to pain
    - Unresponsive
2. Distractibility or consolability by parent is a normal phenomenon in infants and young children.
3. Eye contact with parents or physician is noted normally at 2 months of age. Failure to do this, is an early ominous sign of cortical hypoperfusion and brain dysfunction.
4. Speech / cry: Whether the cry is normal or whimpering or moaning or high pitched
5. Motor activity: Normal movements of limb, trunk and neck.
6. Colour of the skin: denotes respiratory and circulatory status. Skin of palm and fingers may be pink (normal), pale, cyanosed, mottled or ashen grey.

Other features in appearance are:

Seizure activity: Seizures with altered sensorium is a critically ill state as it may lead onto cardiorespiratory compromise or neurologic sequalae if not treated.

Posturing: Intermittent flexor (decorticate) or extensor (decerebrate) posturing occur with prolonged cerebral hypoperfusion.

Muscle tone: Hypotonic limp child is a bad sign.

Pupil size: Pupils may be small but reactive in cerebral hypoperfusion. Unequal pupils is a medical emergency; may indicate ICP.

Breathing

1. Respiratory rate: Tachypnoea is an early sign of respiratory distress. Tachypnoea without increased work of breathing (Quiet tachypnoea) is seen in shock, heart disease and acidosis. A slow or irregular respiratory rate in an acutely ill child is ominous.
2. Work of breathing: Increased work of breathing (IWB) indicates respiratory distress or potential respiratory failure. IWB is assessed by nasal flaring, grunting, intercostal, subcostal and suprasternal retractions. Head bobbing and see saw respirations (severe chest retraction with abdominal distension) are more advanced signs of respiratory distress and impending respiratory failure.
3. Air entry: Effective tidal volume is assessed by chest expansion and auscultation of breath sounds.
4. Pulse oximetry: Oxygen saturation assessment is an important adjunct to identify oxygenation state in acutely ill child.

Circulatory Status

Circulation is assessed to find out if the cardiac output meets the tissue demand. Shock is defined as circulatory dysfunction in which there is inadequate delivery of oxygen and substrates to meet the metabolic demands of tissues. Circulatory status is assessed by heart rate, skin perfusion, systemic perfusion and blood pressure.

1. Heart rate: Tachycardia is a common response to a variety of stresses including shock. Hence its presence mandates further evaluation. Bradycardia in a critically ill child is ominous
2. Pulses: Comparison of central (femoral, carotid and brachial) and peripheral (radial,

dorsalis pedis and posterior tibial) pulse volume. In early shock peripheral pulses are weak. Loss of central pulse is a premorbid sign and is to be treated as cardiac arrest.

3. Skin perfusion
   a. Temperature: When ambient temperature is warm, hands and feet should be warm. Hands and feet become cold when cardiac output falls.
   b. Colour: Normally the colour is pink over the palms upto the fingers. Pallor or cyanosis or mottling denote decreased perfusion.
   c. Capillary refill time (CRT): Normal is less than 2 seconds. Delayed CRT is again a feature of early shock.
4. Organ perfusion
   a. Brain perfusion: Brain perfusion can be assessed by features already described in appearance i.e. changes in level of consciousness, pupil size, muscle tone and posturing.
   b. Renal perfusion: Urine output may not be useful in initial assessment in a critically ill child, but is useful in monitoring the child and evaluation of renal perfusion. 1-2 ml/kg/hour of urine output is normal
5. Blood pressure: Shock can be present with normal, increased or decreased blood pressure. In early compensated shock, BP is normal. In late or decompensated shock there is hypotension.

Lower limit (5th percentile) of Blood pressure

Newborn	60 mm Hg systolic
Upto 1 year	70 mm Hg systolic
2 years and above	70 + (2 x Age in years) mm Hg

Based on the appearance, breathing and circulatory status, physiologic status of a critically ill child is characterised as:

1. Stable
2. Respiratory distress characterised by IWB
3. Respiratory failure characterised by cyanosis, altered sensorium, poor muscle tone and poor respiratory efforts.
4. Early shock – Peripheral signs with normal BP
5. Decompensated shock – Peripheral signs with brain dysfunction and hypotension
6. Cardiorespiratory failure – Shock + respiratory failure

Conditions characterising a critically ill child requiring rapid cardio pulmonary assessment

1. Tachypnoea Respiratory rate > 60 in newborn
   > 50 in infants
   > 40 in 1-5 years
2. Bradycardia or Tachycardia

Newborn	< 80 and > 200
1 month - 8 years	<80 and > 180
> 8 years	<60 and > 160

3. IWB and decreased tidal volume
4. Cyanosis
5. Altered level of consciousness
6. Seizures
7. Fever with bleeding
8. Fever > 41°C in less then 3 months or fever in immuno compromised child.
9. Trauma
10. Burns totaling > 10% body surface area
11. G1 bleeding
12. Poisoning

Initial Management of a critically ill child

When a child is assessed to be critically ill, initial management comprises of taking care of airway, breathing and circulation. Recognition of acuity of illness determines the urgency of intervention. Aggression in response is driven by degree of physiologic compromise.

1. Airway is kept patent – if necessary by positioning, suctioning and intubation.
2. Breathing: In respiratory distress with increased WOB, only supplemental O_2 is given in a nonthreatening manner.

   If respiratory failure is present, ventilation is done with maximal supplementary oxygen.
3. Vascular access and volume expansion with isotonic fluids such as RL or NS.
4. Avoid oral feeds in a critically ill child.
5. If partial airway obstruction is suspected, allow the child to assume position of comfort and avoid any painful procedure.
6. If child presents with seizures, take care of airway and breathing and control seizures with IV diazepam or lorazepam. In office practice, IM midazolam 0.15 mg/kg is safe, effective and fast.
7. In polytrauma or head trauma – open and maintain airway with cervical spine stabilisation carry out volume expansion with early administration of blood and control bleeding.
8. In acute severe asthma, nebulisation with salbutamol and if necessary ipratropium.
9. Plan for transport to a centre where child can be managed further.

Common predisposing factors for a child becoming critically ill:

1. Age: Younger the age, more the risk
2. Malnutrition / impaired immune status
3. Underlying anatomic / functional defect
4. Nature of illness
5. Bad child rearing / traditional practices
6. Type of medical care received
7. Parent's knowledge / awareness

Preparedness to manage critically ill child

1. Oxygen source
2. Oxygen delivery system -
   Oxygen mask, (infant, child size)
   - Nasal cannula
3. Suction apparatus / suction catheters / mucus sucker (De Lee)
4. IV cannula 20, 22, 24 size

   Scalp vein needles 21, 22, 23, 24 size
5. Intraosseous needles – 15 and 18 G
6. Fluids: Normal saline, lactated Ringer, 25% Dextrose
7. IV sets
8. Self inflating bag (500 ml, 750 ml), valve, mask with O_2 reservoir
9. Drugs: Diazepam, Lorazepam, Hydrocortisone, Dexamethasone,

   Inj Adrenaline 1:1000, Midazolam injections
10. Nebuliser solution: Salbutamol, Ipratropium
11. Laryngoscope, blades
12. Spine board
13. Drug dosage chart

Do's and don'ts in management of critically ill child

Do's

1. Be aware of age specific emergencies
2. Know about current epidemic in your area
3. Keep emergency drugs ready and resuscitation equipment in good condition
4. List the nearest hospital for referral, telephone numbers of hospitals and ambulance
5. Inform parents about the problem and what is being done

Don'ts

1. Don't fail to monitor periodically
2. Don't give only IV fluids without taking care of airway and breathing
3. Don't give drugs by inappropriate route
4. Don't panic.

Suggested reading

1. Pediatric Advanced Life Support Guidelines 1997

   American Heart Association and American Academy of Pediatrics.
2. Pediatric Emergency Medicine Course guidelines, Chennai 2001.
3. Pediatric Critical Care, 2nd Edn., Eds Fuhrman BP, Zimmerman JJ, St.Louis, Mosby 1998

NEWS AND NOTES

VII RAJNEOCON - 2003 - KOTA

Date : 20-221, September, 2003

Host : IAP Hadoti Branch Kota & NNF Raj State Chapter

The IAP Hadoti branch is organising VII Rajasthan Neonatology Conference on 20-21st September, 2003. at IMA House, M/B.S. Hospital Campus, Nayapra, Kota. The theme is "Better-Newborn care- Need of the Millenium".

Highlights : Faculty includes eminent neonatologists and intensivists of India.

Programme : Common neonatal problems with practical approach protocols and recent advances in form of guest lectures, Panel discussion and NALS workshop.

Topics : Persistent hyperbilirubinemia. Newer guidelines on neonatal resuscitation, Mec asp. Syndrome-newer management stratigies, neonatal sepsis, Neuroprotection in HTE, refractory neonatal sizures and fluid-electrolyte balance in NICU etc.

Registration fee	upto 31-08-03	from 1-9-03	Spot
IAP/NNF member	300	400	500
Non member	400	500	600
Accompanying member	200	300	400
NALS workshop	400	500	–

(Payment through, demand draft only in favour of "VII Rajneocon, 2003 Kota")

Correspondence :

Dr. C.B. Das Gupta, Organising Chairperson, 1, Gulab Bari, Arya Samaj Road, Kota - 324 006.
Phone : 0744-2381723, 2322703 Email - ekatmgupta@yahoo.co.in

Dr. Ashok Sharda, Organising Secretary, Sharda Children Hospital, 4-B-14, Talwandi, Kota - 324 005.
Phone : 0744-2428393, 2420066(H), 2426088(R) Email - shardachildhosp@rediffmail.com

RADIOLOGIST TALKS TO YOU

OBSTRUCTION IN URINARY TRACT

**** Vijayalakshmi G***
**** Natarajan B***
***** Ramalingam A***

In this issue we will discuss problems pertaining to dialatation of the urinary collecting system. Dilatation of the collecting system usually means a block somewhere along the pathway of flow. This basic inference solves many clinical problems like urinary tract infection, a palpable kidney or colic. The commonest obstruction that is now increasingly been diagnosed because of the widespread use of antenatal ultrasound is pelvi-ureteric junction obstruction.

Fig 1 Shows a dilated pelvicalyceal system (PCS) consisting of round, black or cystic pelvis and calyces. The ureter is not dilated. So it tells you the level of obstruction is at the PUJ. Now look at Fig 2. Is this a dilated pelvicalyceal system? Here also you see a number of cystic spaces like the dilated calyces of a hydronephrotic kidney. But this is a multicystic kidney. In this condition the kidney shows a number of cysts. Unlike PUJ obstruction these do not communicate with each other. In PUJ obstruction there is a central large, cystic pelvis and peripherally situated smaller calyces which all communicate with the pelvis.

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Sometimes you may see the dilated upper moiety in a duplex system as in Fig 3. When you see double moiety, look for associated abnormalities of ureters like a ureterocele or ectopic ureter. If the ureter is also dilated then one should expect a block at the appropriate level. Fig 4 shows a ureter that is dilated. Look for the cause. The commonest is a calculus. Sometimes the dilation may extend upto the vesico-ureteric junction. This happens in conditions like a ureterocele or primary megaureter. The ureterocele is seen as a rounded, smooth, black structure projecting into the bladder (Fig. 5).

In primary megaureter the distal part of the ureter is very narrow and shows frequent peristalsis. The diagnosis is confirmed with IVU. All structural abnormalities need to be subjected to IVU before surgery. If there is bilateral ureterohydronephrosis it is rightly lower urinary tract obstruction. The important condition that one has to be alert to is the posterior urethral valves. In this the posterior urethra is dilated (Fig. 6).

This structure can be imaged from the transabdominal position and perineal route. A large ureterocele, a vesical diverticulum or a presacral mass can cause bladder outlet obstruction as also, a urethral calculus. So you see that ultrasound is the first investigation in suspected urinary tract obstruction.

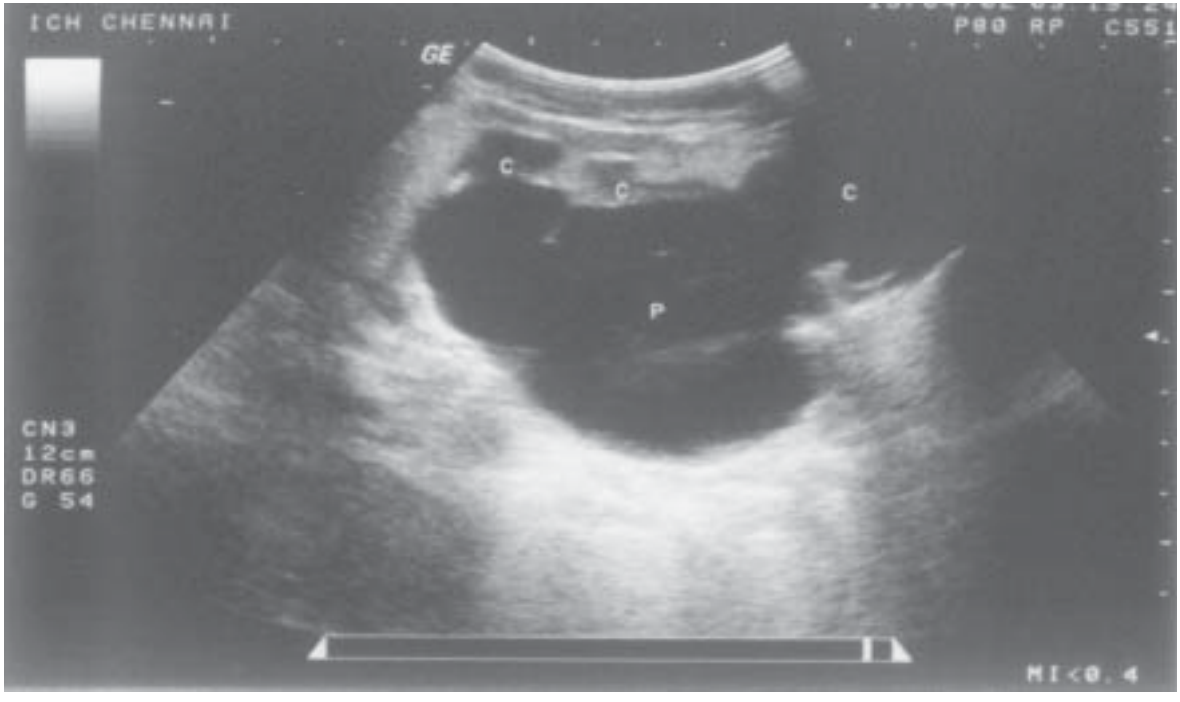

Fig 1. PUJ obstruction

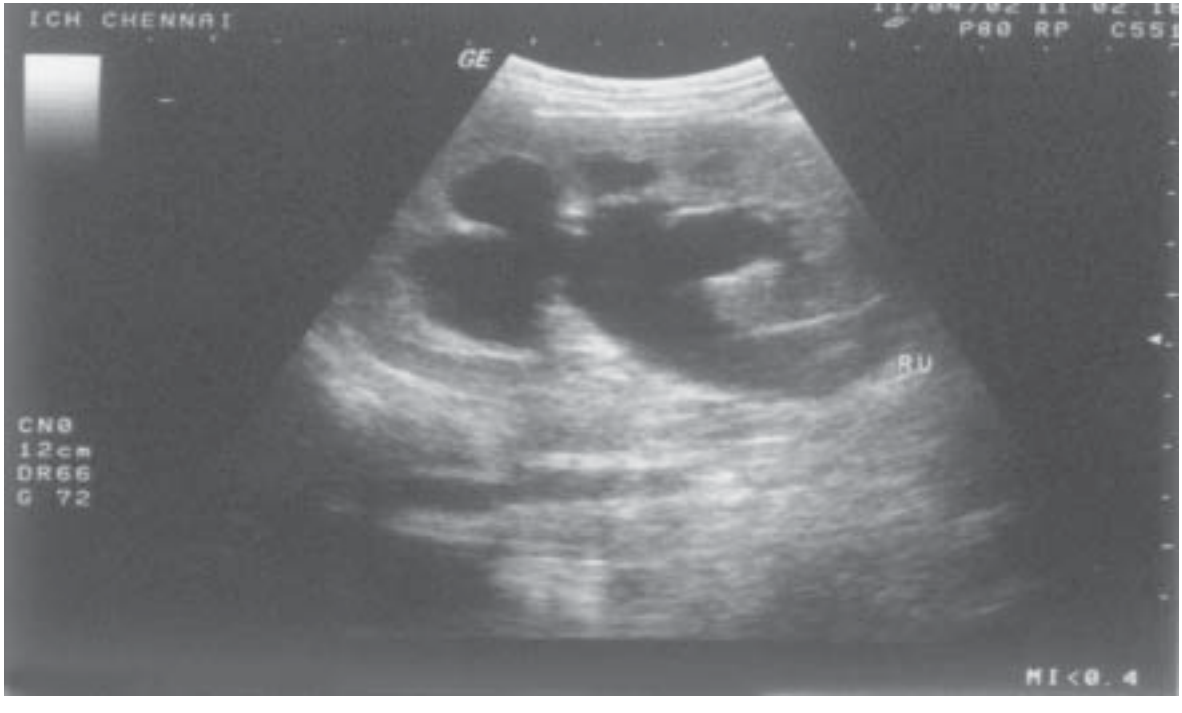

Fig 2. Multicystic kidney

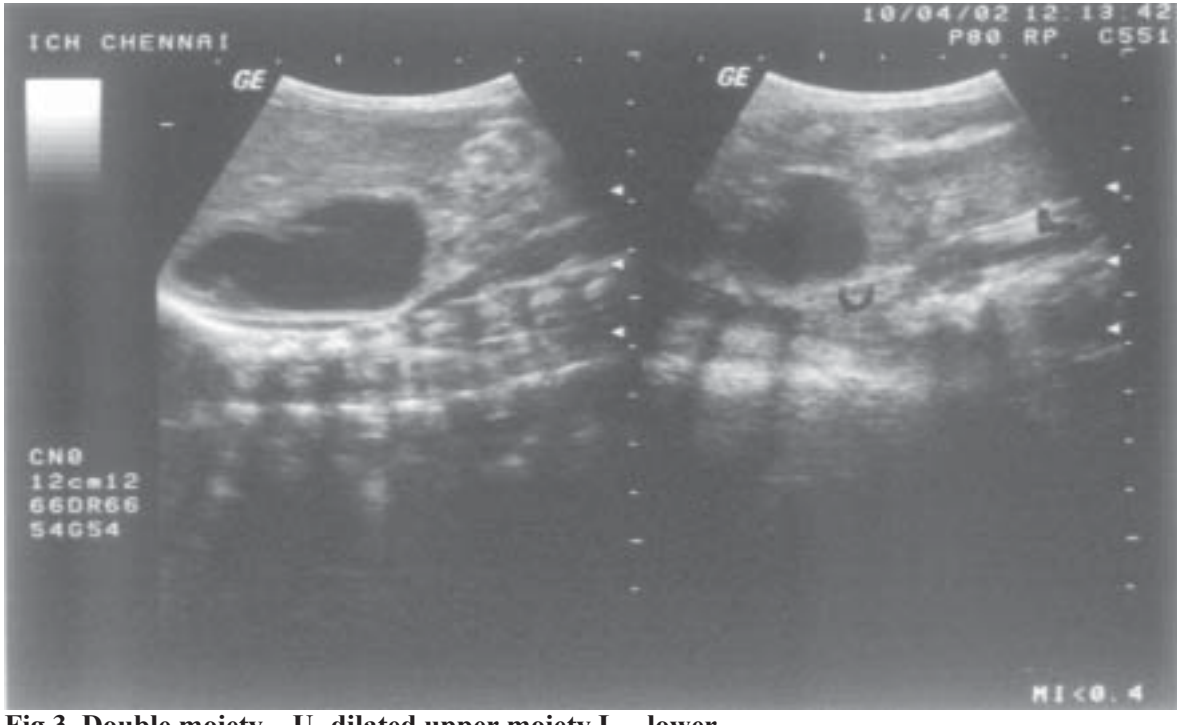

Fig 3. Double moiety – U- dilated upper moiety L – lower

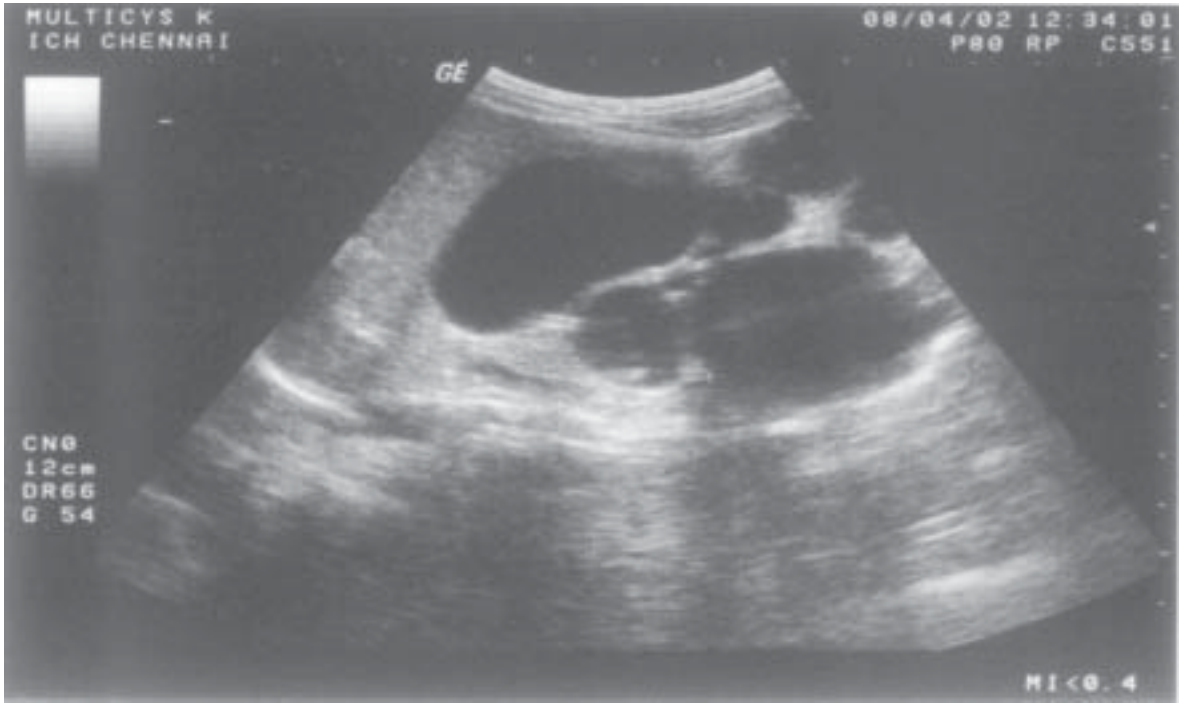

Fig 4. Dilated PCS and ureter (RU)

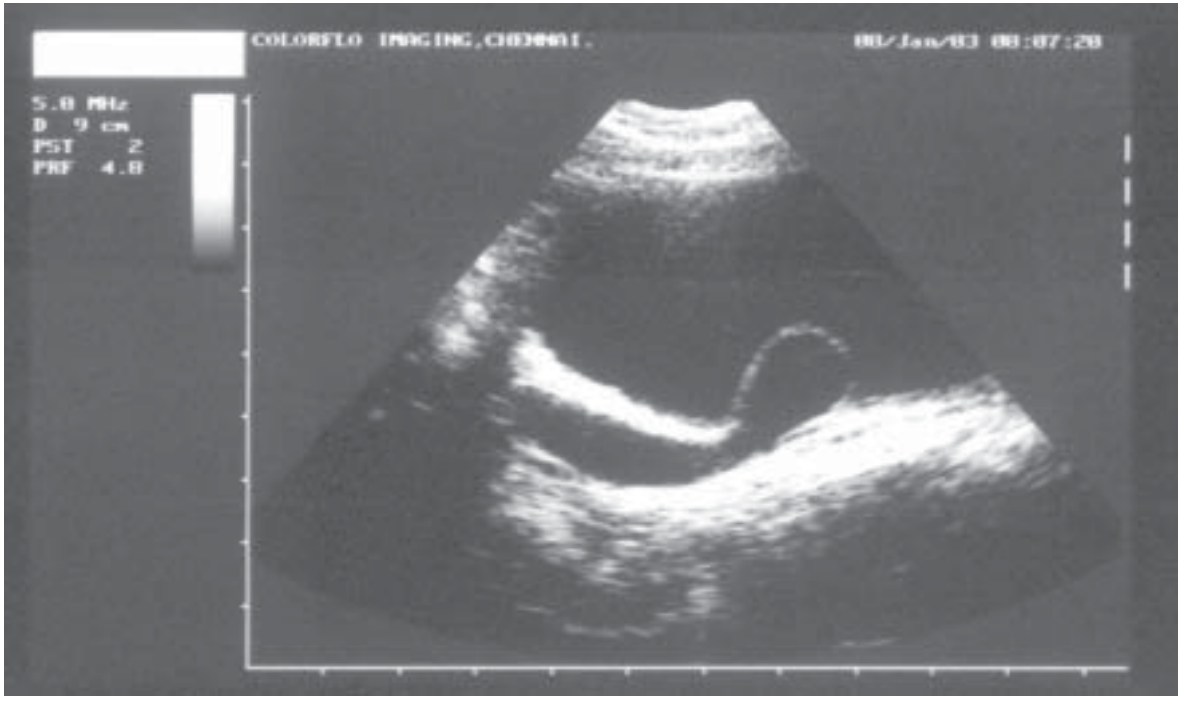

Fig 5. Ureterocele

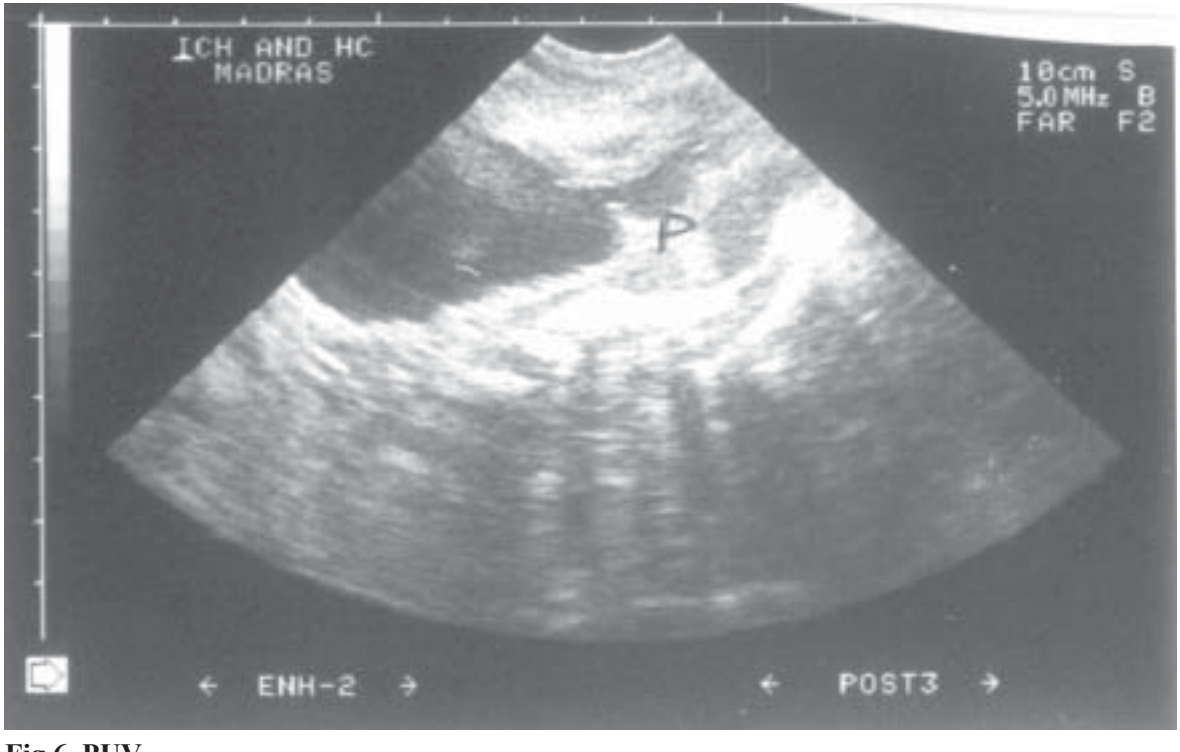

Fig 6. PUV

CASE STUDY

DENGUE HAEMORRHAGIC FEVER IN A BOY WITH BOMBAY BLOOD GROUP – A RARE COINCIDENCE

***Janani Shankar**
****Adhisivam B**

Dengue fever is an acute febrile viral disease frequently presenting with headache, bone or joint and muscular pains, rash and leucopenia as symptoms. Dengue haemorrhagic fever is characterized by four major clinical manifestations : high grade fever, haemorrhagic phenomena, often with hepatomegaly and in severe cases, signs of circulatory failure[1]. Some of these children with significant clinical bleeding may require transfusion of blood or blood products as an emergency. Sometimes a pre-existing condition of the child may interfere with the management of the current problem. We present here one such child with Bombay blood group who developed dengue haemorrhagic fever – a rare coincidence not reported in literature so far.

Case report

A four year old boy from Chennai born to non consanguinous parents was brought to the emergency room with history of high grade continuous fever with severe myalgia for two days following which he started passing black tarry stools and then developed drowsiness and cold extremities. On examination, he was in shock as evidenced by absent peripheral pulses, cold and clammy skin, unrecordable BP, and a prolonged capillary refill time. Liver was enlarged 4 cm below the right costal margin. Melena was the only bleeding manifestation. Examination of the other systems was normal. A diagnosis of dengue shock syndrome was made and he was immediately given appropriate IV fluids and oxygen by mask.

His lab investigations revealed thrombocytopenia (Platelet 45,000 / cu.mm), hemoconcentration (PCV : 42%), raised liver enzymes (SGOT : 524 IU/L, SGPT : 304 IU/L), prolonged APTT and serology for dengue – both IgM and IgG were positive. Even with the use of adequate volume crystalloids for 3 hours, he was still in shock and was losing excessive blood from the body in the form of melena. Hence it was decided to transfuse him with fresh whole blood and a blood sample for cross matching was sent.

In the blood bank, a forward typing showed the blood group as "O". However there was no agglutination with anti – H serum and a back typing confirmed the blood group to be of the Bombay phenotype (Oh). Being a rare blood group, finding a suitable donor was very difficult. Fortunately, a close relative of the boy was identified to have Bombay blood group and his blood was transfused to the patient with no reactions. After the transfusion he improved hemodynamically and was discharged after a week of hospitalization.

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Discussion

The Bombay phenotype (Oh) is a rare blood group. Though it was first reported by Dr.Bhende and Bhatia from Bombay in 1952, it is also found in Caucasians. In India, it occurs with a frequency of 1 in 7,600 and a high level of consanguinity has been observed among the parents of Bombay phenotype. The cause of this group is predominantly a mutation in the H gene on chromosome 19 that causes a non functional H glycosyl transferase. Individuals with this group fail to express A, B or H antigens on their red cells or other tissues and hence no agglutination is noted with anti A, anti B and anti H typing sera. These individuals have all three antibodies – anti A, anti B and anti H in their serum [2]. though in front typing they appear as "O" blood group, the presence of anti H in their serum (a potent hemolysin of H positive red cells) makes their blood incompatible with "O" blood group individuals. Hence a patient with Bombay blood group should be transfused only with the same blood group [3].

Blood grouping should be done routinely by both front typing (cell grouping) and back typing (serum typing). The serum grouping serves as a recheck for the front typing, as proper ABO grouping is vital in the prevention of disastrous hemolytic transfusion reactions. It is also important to use Anti H lectin in front typing of blood for the presence of H antigen in cells giving the reaction of O group. Usage of Anti H lectin in front typing and meticulous back typing with known A,B,O cells and serum of the individual is the only way in which patients or potential blood donors with Bombay blood group (Oh) can be identified. Sadly, this is not done routinely in many laboratories.

The implications are

1. Hemolytic transfusion reactions due to transfusion of normal O group (with H antigen) blood to Bombay group (without H antigen) may occur, as the Anti H in the Oh individuals is a very potent hemolysin. This will occur especially in situations in which blood is issued without crossmatching, as in emergencies.
2. The exact incidence of the Bombay blood group which is more prevalent in India will not be known and hence availability of blood donors of this rare group may not be identified. In our hospital which is an exclusive pediatric hospital, over the past five years we have had three Bombay groups out of about 18,000 blood groupings done for patients and two Bombay group donors out of 4,500 blood donors.

In the above case, had the agglutination test not been done with anti H and the back typing the patient's blood would have been mistaken for "O" group and transfusion with that group could have been disastrous.

Acknowledgement

We herewith acknowledge the work of all blood bank technicians of Kanchi Kamakoti CHILDS Trust Hospital and the kind donor without whose blood we would have lost the patient.

References

1. WHO manual "Dengue haemorrhagic fever – diagnosis, treatment, prevention and control" – 2nd edn. Published by Ashok Ghose, Prentace Hall of India, New Delhi,1997, p1.
2. Frances K Widmann, Technical manual of the American Association of Blood Banks, 9th edn. published by American association of Blood banks, Arlington,Virginia, 1985, pp 177-120.
3. Mollison PL, Engelfriet CP, Marcela Contreras. Blood transfusion in clinical medicine – 9th edn.1993, p154.

CASE STUDY

CAFFEY'S DISEASE (INFANTILE CORTICAL HYPEROSTOSIS)

**** Mohammed Thamby***
**** Nagarajan M***
***** Ram Saravanan R***

Caffey's disease is a very rare pediatric orthopedic problem of infantile age group. It is spontaneous, self-limiting and with no definite etiology. It has no sex or racial predilection.

Report

A female child, third of three siblings, presented at 2 months of age with swelling and discolouration of skin of short duration (few days) over the upper half of left tibial region. The child was reluctant to move the limb and there was tenderness on palpation. The child was highly irritable with mild to moderate fever and other systems were normal. The child had absolutely normal birth history and no trauma since birth. Other siblings were normal.

Blood counts of the child showed, elevated TC (22500 cells / cu.mm), elevated ESR (½ hour - 55mm, 1 hour - 97mm), positive CRP (6 mg/L) and negative VDRL test. Radiological investigations revealed abnormal cortical thickening confined to diaphysis of tibia in the upper part with coarse elevated periosteum. USG - reported periosteal thickening. CT Scan showed abnormal periosteal elevation.

* Senior consultants

** Junior Resident in Pediatrics
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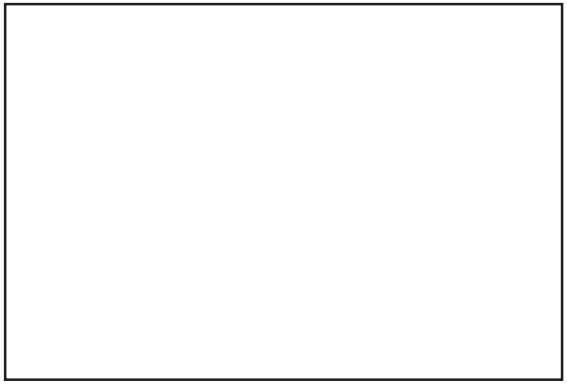
Based on the above picture the child was diagnosed as having 'acute osteomyelitis' and was treated for around 1 month period, but there was no response. The child developed same type of swelling with discolouration over both sides of cheeks. Radiology also revealed the same features over the mandibles. It made the pediatricians to suspect the diagnosis of Caffey's disease.

DISCUSSION

In this type of clinical presentations, "infantile cortical hyperostosis" is usually kept last in the list of differential diagnosis like acute osteomyelitis, hypervitaminosis A, scurvy, syphilis and trauma, since it is rare and all other conditions need immediate intervention. In acute osteomyelitis radiological changes occur only if they are left untreated for 2-3 weeks and it usually involves the medullary cavity first, then progresses to the cortex and periosteum ,whereas in Caffey's disease the pattern of involvement is reverse.

'Infantile cortical hyperostosis' is a self-limiting disease of early infancy, characterised by swelling of soft tissue, cortical thickening of underlying bone and hyperirritability.It has no definite etiology. Inherited defect of the arterioles of the periosteum, allergy and infective theories have been postulated in the cousation of caffey's disease.

Usual age of onset is ninth week of postnatal life, but cases have been reported even at birth and as early as twenty fourth week of intra uterine life. It starts with sudden swelling which is deep and firm with mild to moderate fever and



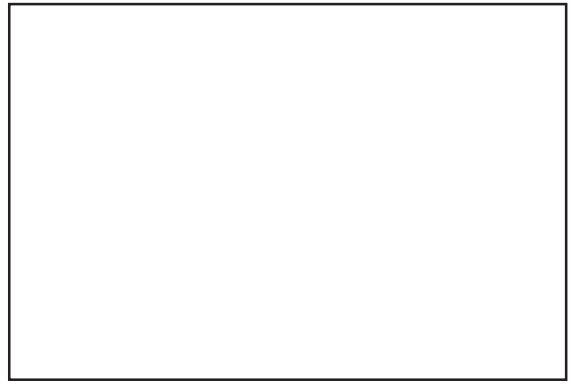


Fig 1 and Fig 2. Radiogram shows marked involvement of tibia with cortical hyperostosis and deep soft-tissue swelling.

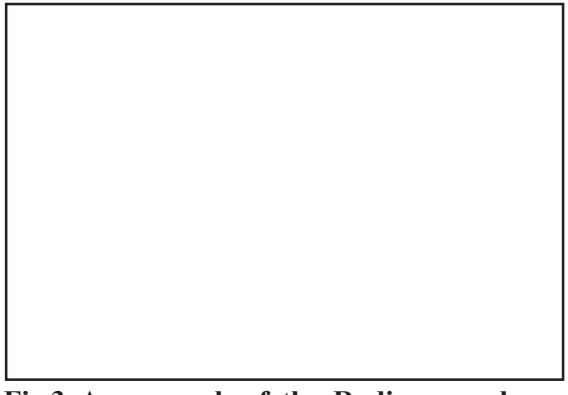


Fig 3. Arrowmark of the Radiogram shows involvement of mandible both sides.

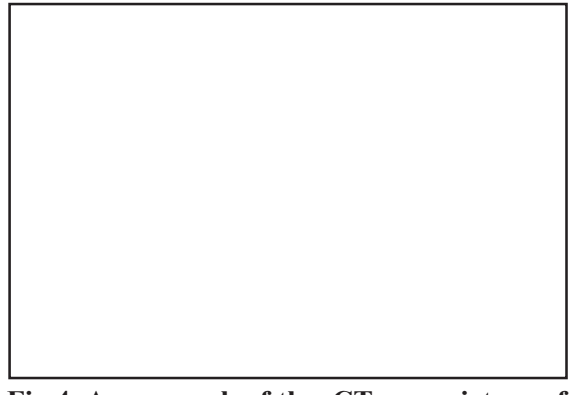


Fig 4. Arrowmark of the CT scan picture of leg shows marked involvement of tibia with cortical hyperostosis.

hyperirritability; commonly involves mandible and then ulna, tibia, clavicle, scapula and ribs are involved. Neither phalanges nor vertebrae are involved which differentiates it from hypervitaminosis A.

X-ray usually shows periosteal hyperostosis confined to diaphysis of long bones. In due course it becomes homogenous with the underlying cortex(Fig 1,Fig 2,Fig 3 & Fig 4). It takes several months and even a year to resolve. Laboratory values like elevated ESR, elevated alkaline phosphatase and positive CRP test have been reported. Sometimes child may report with anemia. But culture will not grow any infectious agent.

There is no specific treatment, complete resolution in 6 – 9 months is the rule. Spontaneous remission and exacerbation may occur. Corticosteroids are effective in alleviating acute symptoms but has no role on reverting bony changes.

CASE STUDY

NEUROFIBROMATOSIS TYPE I WITH CONGENITAL PSEUDOARTHROSIS AND HOLOPROSENCEPHALY

*Preetha Prasannan
**Veerendra Kumar
***Jayakumar
***Sukumaran TU

Neurofibromatosis type I (NF-I) is a neuro cutaneous syndrome with diagnostic criteria including distinct cutaneous and osseous lesions[1]. This includes congenital pseudoarthrosis of tibia, a rare anomaly with incidence of one per two lakh live births[2] and which when present is a strong pointer to NF–I. Here we present an infant with NF–I with congenital pseudoarthrosis who on further evaluation had a developemental malformation of brain, holoprosencephaly.

A five month old female baby presented with multiple café au lait spots, more than six in number with greatest transverse diameter more than five millimeters. She also had a swelling in lower end of right leg noticed since three months.On examination, there was anterolateral bowing of lower leg with abnormal mobility, simulating a joint, being elicited at the junction of middle and distal thirds of tibia and fibula. X-rays taken three months back and presently on admission revealed a fracture at the junction of middle and distal thirds of tibia and fibula, with no signs of union along with sclerosis and obliteration of medullary cavity. Orthopaedic consultation confirmed that this was the typical presentation of congenital pseudoarthorosis. There was no positive family history.

Since admission, the infant was getting myoclonic seizures of increasing severity. EEG showed a hypsrrhythmia pattern and CT scan revealed holoprosencephaly. The infant was put on temporary bracing of the leg to prevent further displacement of ununited fracture segments and is awaiting corrective surgery. Seizures were controlled with high doses of sodium valproate and prednisolone.

Discussion

Neurofibromatosis type I (Von Recklinghausen disease) is an autosomal dominant disorder which results from an abnormality of neural crest differentiation and migration during early stages of embryogenesis.

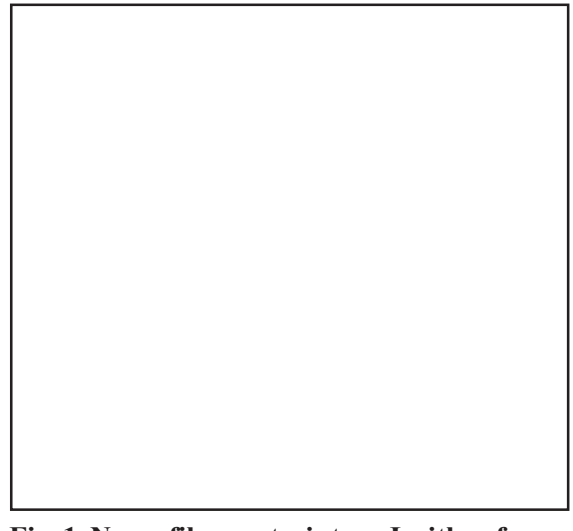


Fig. 1. Neurofibromatosis type I with cafe-au-lait spots and congenital pseuarthrosis MBIA

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First clinical and pathological account of the disease was given by Von Recklinghausen in 1882. Tilesius gave the first description of a patient with multiple fibrous skin tumors in 1793. Incidence is 1/4000 and is diagnosed if two out of the following are present[1].

1. Six or more café au lait spots of more than 5 mm. transverse diameter which may be present at birth. They are present in almost 100% of NF- I.
2. Axillary or inguinal freckling – manifest around puberty.
3. Two or more Lisch nodules - These iris hamartomas increase with age, incidence being 5% below three years to 100% above 21 years.
4. Two or more neurofibromas or one plexiform neuro fibromatosis. Neurofibromas are small rubbery lesions which appear around adolescence. Plexiform neuro fibromatosis involves diffuse thickening of nerve trunks which may produce overgrowth and deformity of an extremity. This may be present at birth.
5. A distinct osseous lesion such as sphenoid dysplasia or congenital pseudoarthrosis tibia.
6. Optic nerve gliomas in around 15% which give rise to an afferent pupillary defect.
7. A first – degree relative with NF-I. 50% of NF- I are inherited, rest result from sporadic mutations.

As 2 out of 7 diagnostic criteria are satisfied in this baby, a diagnosis of NF –I was made.

Congenital pseudoarthrosis of tibia, is a specific type of nonunion, that at birth may be present or incipient. Incidence is one in two lakh live births[2]. Cause is unknown, but occurs almost always with NF-I, the favoured site being distal third of tibia and fibula. Boyd's classification includes six types, the commonest being type – II which is due to anterior bowing and hourglass

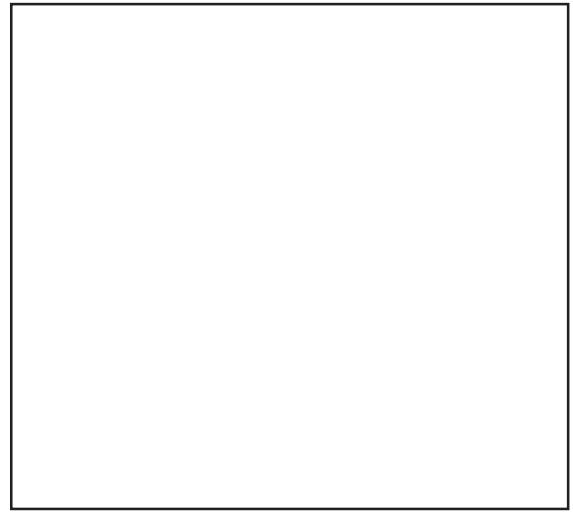

Fig. 2. Neurofibromatosis type II with cafe-au-lait spots and congenital pseuarthrosis MBIA

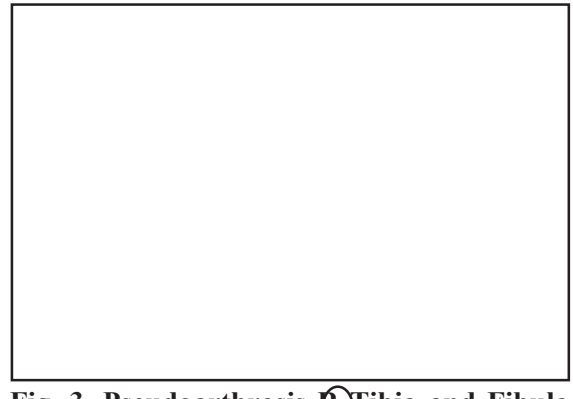

Fig. 3. Pseudoarthrosis R Tibia and Fibula inneurofibromatosis

constriction of tibia present at birth. Spontaneous fracture or fracture following minor trauma occurs before two years. In the other types, there may be a congenital cyst, sclerotic segment, dysplasia or intra-osseous neuro fibroma which fractures and heals poorly. Treatment consists of early bone grafting and intra-medullary fixation. Congenital pseudoarthrosis responds poorly to treatment with multiple failed surgical procedures and repeated fractures which may necessitate amputation.

Fig. 4. Congenital Pseudoarthrosis (R) Tibia and Fibula

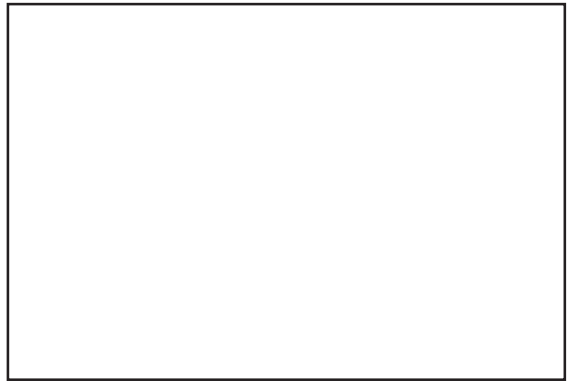

Fig. 5. Holoprosencephaly in neurofibromatosis I

NF –I patients are susceptible to neurological complications including neuronal migration disorders and cerebral heterotopias. Various brain tumours including astrocytomas, meningiomas, optic gliomas, schwannomas and cerebral vessel thrombosis, stenosis and hydrocephalus have been described.

This infant had seizures with holoprosencephaly being detected on CT scan brain. It is a developemental defect of brain which results from defective cleavage of the prosencephalon[3,4]. It is characterized by a globular brain with absence of inter hemispheric fissure, absent falx, fused ventricles, fused basal ganglia. Incidence ranges from 1/5000 to 1/ 16000. Cause is unknown in majority of cases, with certain chromosomal aberrations accounting for a minority. Affected infants die during infancy**.**

As there is no definite treatment for NF, supportive treatment in the form of correction of pseudoarthrosis and control of seizures can be offered to this infant[5]. But the ultimate prognosis appears grim due to the associated brain anomaly.

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GLOBAL CONCERN

SEVERE ACUTE RESPIRATORY SYNDROME (SARS)

Introduction:

Severe Acute Respiratory Syndrome (SARS) is an acute respiratory illness that has recently been reported in Asia, North America, and Europe. The majority of patients identified as having SARS have been adults aged 25 - 70 years who were previously healthy. Few suspected cases of SARS have been reported among children aged <15 years.

Agent suspected to cause SARS:

Scientists at CDC and other laboratories have detected a previously unrecognized coronavirus in patients with SARS. Genetic analysis suggests that this new virus belongs to the family of coronaviruses but differs from previously identified coronaviruses .While the new coronavirus is still the leading hypothesis for the cause of SARS, other viruses are still under investigation as potential causes.

Spread of SARS:

The principal way SARS appears to spread is through droplet transmission; namely, when someone sick with SARS coughs or sneezes droplets into the air and someone else breathes them in. It is possible that SARS can be transmitted more broadly through the air or from objects that have become contaminated.

Droplet transmission refers to the spread of viruses contained in relatively large respiratory droplets that people project when they cough or sneeze. Because of their large size, droplets travel only a short distance (usually 3 feet or less) before they settle. Droplet transmission can occur either directly when droplets are inhaled by another person, or indirectly when droplets land on an object or surface (such as a doorknob or telephone) that are then touched by another individual.

Information to date suggests that people are most likely to be infectious when they have symptoms, such as fever or cough. However, it is not known how long before or after their symptoms begin that patients with SARS might be able to transmit the disease to others. Cases of SARS continue to be reported primarily among people who have had direct close contact with an infected person, such as those sharing a household with a SARS patient and health-care workers who did not use infection control procedures while caring for a SARS patient.

Clinical features:

The incubation period for SARS is typically 2-7 days; however, isolated reports have suggested an incubation period as long as 10 days. The illness begins generally with a prodrome of fever (>100.4°F [>38.0°C]). Fever often is high, sometimes is associated with chills and rigors, and might be accompanied by other symptoms, including headache, malaise, and myalgia. At the onset of illness, some persons have mild respiratory symptoms. Typically, rash and neurologic or gastrointestinal findings are absent; however, some patients have reported diarrhea during the febrile prodrome.

After 3-7 days, a lower respiratory phase begins with the onset of a dry, nonproductive cough or dyspnea, which might be accompanied by or progress to hypoxemia. In 10%—20% of cases, the respiratory illness is severe enough to

require intubation and mechanical ventilation. The case-fatality rate among persons with illness meeting the current WHO case definition of SARS is approximately 3%.

The severity of illness might be highly variable, ranging from mild illness to death. Although a few close contacts of patients with SARS have developed a similar illness, the majority have remained well. Some close contacts have reported a mild, febrile illness without respiratory signs or symptoms, suggesting the illness might not always progress to the respiratory phase.

Investigations:

Early in the course of disease, the absolute lymphocyte count is often decreased. Overall white blood cell counts have generally been normal or decreased. At the peak of the respiratory illness, approximately 50% of patients have leukopenia and thrombocytopenia or low-normal platelet counts (50,000—150,000/μL). Early in the respiratory phase, elevated creatine phosphokinase levels (as high as 3,000 IU/L) and hepatic transaminases (two to six times the upper limits of normal) have been noted. In the majority of patients, renal function has remained normal.

Initial diagnostic testing should include chest radiograph, pulse oximetry, blood cultures, sputum Gram's stain and culture, and testing for viral respiratory pathogens, notably influenza A and B and respiratory syncytial virus. Clinicians should save any available clinical specimens (respiratory, blood, and serum) for additional testing until a specific diagnosis is made. Clinicians should evaluate persons meeting the above description and, if indicated, admit them to the hospital. Close contacts and healthcare workers should seek medical care for symptoms of respiratory illness.

Chest radiographs might be normal during the febrile prodrome and throughout the course of illness. However, in a substantial proportion of patients, the respiratory phase is characterized by early focal interstitial infiltrates progressing to more generalized, patchy, interstitial infiltrates. Some chest radiographs from patients in the late stages of SARS also have shown areas of consolidation.

Serum antibody tests, including both enzyme immunoassay (EIA) and indirect immunofluorescence antibody (IFA) formats, have been developed. A positive test result means that both types of antibody tests were used and that results for both were positive. At this time, CDC is interpreting positive test results to indicate previous infection with this newly recognized human coronavirus. However, some people do not test positive until more than 21 days after onset of illness.

Reverse transcription-polymerase chain reaction (RT-PCR) testing is also available. This test can detect coronavirus RNA in clinical specimens, including serum, stool, and nasal secretions.

Viral isolation for the new coronavirus also has been done. In these studies, clinical specimens from SARS patients are co-cultured with well-characterized cell lines and then laboratorians look for evidence of coronavirus replication in these cultured cells.

Several laboratories have reported positive test results for human metapneumovirus in patients with SARS. There is not enough information to determine what role, if any, human metapneumovirus might have in causing SARS.

Management:

Treatment regimens have included several antibiotics to presumptively treat known bacterial agents of atypical pneumonia. In several locations, therapy also has included antiviral agents such as oseltamivir or ribavirin. Steroids have also been administered orally or intravenously to patients in combination with ribavirin and other antimicrobials. At present, the

most efficacious treatment regimen, if any, is unknown.

Limiting the spread of SARS:

Infection control precautions should be continued for SARS patients for 10 days after respiratory symptoms and fever are gone. SARS patients should limit interactions outside the home and should not go to work, school, out-of-home day care, or other public areas during the 10-day period.

During this 10-day period, all members of the household with a SARS patient should carefully follow recommendations for hand hygiene, such as frequent hand washing or the use of alcohol-based hand rubs

Each patient with SARS should cover his or her mouth and nose with a tissue before sneezing or coughing. If possible, a person recovering from SARS should wear a surgical mask during close contact with uninfected persons. If the patient is unable to wear a surgical mask, other people in the home should wear one when in close contact with the patient.

Disposable gloves should be considered for any contact with body fluids from a SARS patient. However, immediately after activities involving contact with body fluids, gloves should be removed and discarded, and hands should be washed. Gloves should not be washed or reused, and are not intended to replace proper hand hygiene

SARS patients should avoid sharing eating utensils, towels, and bedding with other members of the household, although these items can be used by others after routine cleaning, such as washing or laundering with soap and hot water.

Common household cleaners are sufficient for disinfecting toilets, sinks, and other surfaces touched by patients with SARS, but the cleaners must be used frequently.Other members of the household need not restrict their outside activities unless they develop symptoms of SARS, such as a fever or respiratory illness.

Suspected Case:

Respiratory illness of unknown etiology with onset since February 1, 2003, and the following criteria:

- Measured temperature > 100.5°F (>38° C) AND
- One or more clinical findings of respiratory illness (e.g. cough, shortness of breath, difficulty breathing, hypoxia, or radiographic findings of either pneumonia or acute respiratory distress syndrome) AND
- Travel within 10 days of onset of symptoms to an area with documented or suspected community transmission of SARS (see list below; excludes areas with secondary cases limited to healthcare workers or direct household contacts)

  OR

  Close contact* within 10 days of onset of symptoms with either a person with a respiratory illness who traveled to a SARS area or a person known to be a suspect SARS case.
- Close contact is defined as having cared for, having lived with, or having direct contact with respiratory secretions and/or body fluids of a patient known to be suspect SARS case.

  Areas with documented or suspected community transmission of SARS: Peoples' Republic of China (i.e., mainland China and Hong Kong Special Administrative Region); Hanoi, Vietnam; and Singapore

  Note: Suspect cases with either radiographic evidence of pneumonia or respiratory distress syndrome; or evidence of unexplained respiratory distress syndrome by autopsy are designated "probable" cases by the WHO case definition.

Source : Centre for disease control, Atlanta, USA.

PRACTITIONERS COLUMN

TIPS FOR PRACTISING PEDIATRICIAN

***Kamlesh R. Lala**
****Mrudula K. Lala**

Today doctors are practising under the constant pressure of the society which now a days see the doctor not as a GOD or messiah, but simply a professional and has expectations beyond our abilities to fulfill. Practising doctor always try to do away with professional hazards of allegation of unlawful activity and it's sequelae. Following are the tips for the practicing pediatrisian.

Personality of a doctor

- Doctor is expected to be gentle, soft spoken, well behaved and noble.
- Do not smoke or chew pan masala in front of patient
- Don't be overconfident. Never challenge your colleague. Never criticize.
- Do not examine the patient when you are sick, exhausted or under the influence of drug or alcohol.
- Develop empathy towards patients. Don't get emotionally attached.
- Never talk loose of your colleagues despite intense professional rivalry.
- Never try to challenge anybody.

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Before the arrival of a patient

- Our goal is to cure sometimes, relieve often but comfort always
- Do not prescribe without examining the patient. Discourage telephonic advice. Tackle diplomatically.

On arrival of a patient

- Receive the patient with a smile.
- See the patient as one of your relatives.
- Look at him as a "Patient" only without taking into consideration caste, religion, race, politics etc.
- Address the patient by his first name which he likes the most.

Letterhead

- Mention your qualifications and designation on the prescription.
- Qualification means recognized degree/ diploma as regulated by Indian Medical Degree Act 1916, as amended from time to time.
- Mentioning of scholarship, membership and awards should be avoided.
- Mention complete address, your registration number and telephone numbers along with timings.

Registration of the patient

- Always mention date and time of consultation. Mention the relation of informant to patient.
- Mention age, sex, weight of the patient.
- Enter address and contact number of the patient
- If referred, look at the referring note.

History taking

- Look carefully. Listen to the patient attentively. Ask questions intelligently.
- Ensure privacy and confidentiality even during history taking.
- Always face the patient. Maintain eye contact that is comfortable to the patient. Do not stare.
- Check for pregnancy, lactation or any other pediatric chronic disease.
- Take history of drugs being taken. Record history of drug allergy.
- Take family history.
- If the patient or relatives are erring on any account like history not giving a reliable, refusing investigations, refusing admission, make a note of it or seek written refusal preferably in local language.

Examination

- Ensure privacy.
- Always ensure the presence of a relative or female attendant before examining a female patient, even if she is your regular patient.
- Never neglect patient's complaints.
- Expose completely the part to be examined or you may miss something.
- Always put your hand on the part that the patient says is painful, last.
- Do a complete examination including ausculation.
- If after completing the examination, the patient or attendant feels that something has been left out or wants something to be reexamined, oblige him.
- Ask the patient to come back for review the next day, in case you have examined him hurriedly or if you are not sure.

Doctor patient relationship

- Try to establish healthy doctor-patient relationship.
- Professional courtesy, confidence and courage to tell the truth, coordination, communication, creative and imaginative thoughts; are all the bridges between doctor and patient.
- Problem arises only when there is lack of a proper interaction between doctor, patient and relatives.
- Try to understand the feelings of patients and try to convince them that you are doing / trying the best.
- Do not talk to any angry patient or relative about any other subject until you understand the reason for the same. Take necessary time and steps to calm him down. Be patient with patients. Patients are always impatient.

Investigations

- Investigation is not a substitute for your clinical judgement. They are only supportive.
- Refer to standard diagnostic centre or to a qualified doctor.
- Routinely advise X - rays in injury to bones and joints.
- Consider the affordability of the patient. Do only those investigations which are indicated.
- Remember to advise in writing the investigations required for periodic evaluation e.g. blood sugar estimation in diabetes mellitus, CBC in anti cancer drugs, LFT in hepatotoxic drugs and so on.
- Always read reports, interpret the results and make a note of it.

Conclusion

- Never label any condition functional unless exhaustive examination and investigations rule out any organic cause.
- Do not give high hopes, do not guarantee cure and be careful while informing the patient or the relatives about prognosis.
- Let the patient know the diagnosis and treatment of the condition he is suffering from.

Records

- Records should be genuine and not manipulated.
- Records are a must for medico legal, income tax and consumer protection purposes. A well kept record is your best friend and best defence in the court.
- Brief, incomplete and cryptic records are of no use in courts.
- Records should not be exhaustive, but should be brief yet informative and complementary to management.
- Records are based on facts and not on memory and expected findings. Maintain the record and not simply keep them.
- Medical records for inpatients are to be kept and maintained for three years from the date of commencement of treatment.
- Keep complete medical record of history, clinical findings, diagnosis, investigations and treatment etc.
- In complicated cases record precisely the history of illness and substantiate physical findings on your prescription.
- Mention "Diagnosis under review" or "under investigation" until diagnosis is finally settled.
- Non willingness of the patient for investigation and admission should be mentioned in local language.

Consent

- Always obtain a legally valid and informed consent before any surgical or invasive diagnostic procedure.
- Denial of consent should always be mentioned.
- Consent does not give blanket immunity to a doctor. It is not a protection against negligence.

Treatment

- Do not do anything beyond your level of competence i.e. qualification, training and experience.
- Always check and recheck injection and vaccines for name and expiry date. Also reconfirm the route of administration.
- Always use disposables or confirm sterilization.
- Avoid unnecessary injections, IV drugs and drips. "If I will not do it, somebody else would do it" is a wrong way to think.
- Justify indication of treatment and procedures.
- In case of any deviation from standard care, mention reasons.
- In an agitated child, restrain him properly with assistants to avoid needle being broken inside.
- In case a particular drug or equipment is not available, make a note.
- Try to avoid even a minor procedure under "local" anesthesia in a consulting room.

Inpatient

An inpatient's file should contain

- Case papers right from the day of admission with every personal detail. All examinations carried out and positive findings.

- If there are no positive findings, mention "No complaints. GC good".
- Investigations carried out and their reports.
- Date and time of daily check up and serial follow up in critical patient.
- Record daily vital parameters.

Prescription

General :

- Avoid writing ayurvedic formulations.
- Do not allow substitute from chemist.
- Remember major drug interactions and special situations like pregnancy and lactation.
- Write names of drugs clearly using capitals, to avoid confusion with similarly spelled drugs.
- Write in a sequential manner e.g. main drug first, then supportive and lastly vitamins.
- Use correct dose. Do not over prescribe (too many drugs, larger dose, for longer duration) or under prescribe.
- Mention mode, interval of administration and instructions in local language.
- Specifically mention review and follow up schedule.

Instructions:

- Explain likely side effects of drug and the actions to be taken if they occur.
- In chronic ailments, mention treatment to be taken immediately in case of emergency e.g. diazepam in seizures, paracetamol in fever, antispasmodics in renal colics and so on.
- Mention additional precautions e.g. food, rest, avoidance of certain drugs etc. if indicated.
- Advise accordingly if dose is to be tapered before stopping.

Remember:

- Explain the prognosis and mention it.
- Give alternate contact number in case of emergency and non availability.
- Don't forget to provide genetic counselling to couples and parents with known family history of children having genetic abnormalities.

Referring the patient

- Create, build and strengthen your relationship with practitioners of your area so that they may be of help in crisis.
- Prepare a list of specialists and super specialists whom you trust and have a good rapport.
- Always provide a referring note and if possible make a phone call. This is liked by the patient and shows your concern for him.
- Keep a record of this reference.
- If you are not sure about the diagnosis, do not hesitate to get the second opinion or to discuss the case with a friend
- Patients have the right for the second opinion. Let the patient choose another doctor if he wishes so.

Discharge

- Never refuse discharge against medical advise, as it is his right. Mention it and take his signature.
- Issue a discharge card with every detail of illness, investigation, treatment, procedures done etc. for future reference.
- Also mention treatment to be taken, follow up schedule, advice for diet and exercise.
- When asked for a written document, never hesitate to give them. But be careful to enter all appropriate details before handing over them.

Death of a patient

- Do not leave at the moment of death. Your presence and experience are most needed. Remember that the relatives have sustained a grievous loss.
- Keep cool, ignore the comments of others, and call for assistance if needed.
- It would and should appear human if you forego the fees for the incident that has triggered off the situation.

Payments

- When patient comes, doctor is 'GOD'

  When doctor treats him, it is his 'DUTY'.

  When bill comes, doctor is a 'DEMON'
- So be careful while giving a bill or if possible tell him rough estimate before starting treatment or giving costly vaccines.
- According to new rules by MCI, a doctor should display his fees and other charges.
- Never be rigid for charges as most of the troubles start with this only. A craze for money should not be there.
- Do not refuse the patient's right to examine and receive an explanation about your bill.

Certificates

General:

1. Issuing certificate is a tricky job.
2. Use proforma given by MCI. Write your registration number clearly.
3. Keep duplicate record. Instead of keeping carbon copy on a plain paper, keep both the pages same.
4. Always take signature or left thumb impression on certificate.
5. You can charge reasonable amount for the certificate.
6. Avoid false certificates diplomatically.

Sickness certificate:

1. Never give back dated certificates.
2. Never give it without seeing the patient.
3. Fitness certificate should be issued by a doctor who has issued illness certificate.
4. Never forecast fitness in advance.

Death certificate:

1. Do not issue it unless you yourself have verified it and the patient was under your care for recent illness.
2. State clearly the cause of death and if in doubt ask for police help.
3. It is to be issued free of charge.

Fees Receipts:

1. Never issue false receipts of fees received.
2. Should be printed, in duplicate and serially numbered as required by income tax department.
3. Take the signature of the patient on the duplicate.

CME

- Remember "Eyes cannot see what mind does not know".
- Regularly attend CME to update your knowledge and skill. There is no limit to knowledge. So even if you feel, you know, you learn and you will find something new every time.
- Keep with you and refer at times, the latest edition of the standard textbook of your branch.
- Always attend at least two updates and conferences every year.
- Subscribe at least to one update / journal.

Set up

- Should have efficient, competent and fast working manpower.
- Update knowledge and skill of your staff also.
- Update facilities and equipments according to prevailing current standards in your area.
- Do not purchase costly sophisticated equipments only for the sake of prestige. It may induce you to indulge in malpractice.

Time management

- Efforts should be there to have fixed consulting hours. Those having an overflow of outpatients, should keep appointment system.
- Discourage home visits as far as possible, except in emergency.
- Give fixed time slot for representatives during your consultation hours.
- Never encourage relatives and visitors during your busy consulting hours.
- Do not forget the importance of your physical fitness. Allot at least 20-30 minutes for yourself and your family in your appointment diary.
- Take a weekly off to meet social commitments and refreshment with your family.
- Take a vacation once or twice a year.

Litigation

- When healthy doctor-patient relationship can be created, evolved, nurtured and strengthened, no doctor has to fear about any litigation.
- Irritable nature, arrogance and high handed approach by doctor are his enemies.
- Remember that practice of truth is not only good as a principle but it is good as a policy.
- When you have the slightest doubt of litigation, complete all data meticulously and preserve them.
- Never fail to seek proper legal and medical advice before filing reply to the notice received from consumer court.
- Never entertain compromise as it may lead to blackmailing in future and a life time tension.
- Never give away any original to any authorities. You may give a xerox copy.

This is not an exhaustive account, but is meant for general information. It is needless to mention that each situation needs its own consideration. One will face different situation every time and so there cannot be the rule of thumb.

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QUESTIONS AND ANSWERS

Q.No. 1: Male / 7Yrs. H/O Puffiness and oedema abdominal wall 7 days. Oliguria. B.P 120/92. No headache/vomiting.Vitals Stable. Lab: Urine Alb +++ three/four days consecutive. 8-10 RBC. Granular cast. Blood Urea-104. S.Creatinine 1.4. S.Cholesterol 360. C3-Normal. Xray Chest Normal. USG Abd.Normal.

What are the D/D?

? MCNS (High Cholesterol)

? MPGN Presenting as NS.

? Nephrotic range of protienuria with Acute Glomerulonephritis. (High Creatinine High B.P.RBC and granular cast in urine.)

Please guide. Shall we

1. Wait As now S.Creatinine has gone down to

0.9.(Patient is on Amoxy+Lasix+Nifedipine)

2. Kidney Biopsy?

3. Start Steroid considering NS.

Dr. H.K.Takvani,
Children Hospital and Neonatal Care Centre,
Jamnagar, Gujarat.

A. No.1. This child is presenting with combined features of nephritic syndrome and nephrotic syndrome. Serum total protein and serum albumin values are not available. Lower levels will support the diagnosis of nephrotic syndrome. A combination of nephritic and nephrotic syndrome, hypertension, renal failure and age of more than 5 years indicate a very high possibility of non-minimal change disease. Renal biopsy followed by appropriate management depending on the histology would be the ideal approach. Alternatively a course of steroids may be given if parents are not willing for kidney biopsy even after adequate explanation about the need of it for diagnosis and management.

Dr. M.Vijayakumar,
Consultant Pediatric Nephrologist,
Kanchi Kamakoti CHILDS Trust Hospital,
Chennai 600 034.

Q. No.2 i) Rabies can be caused by bite of all animals except Rat. Is it true?

ii) Rabies rare to be transmitted by Rat. Harrison's TB of internal medicine.

Dr.Sanjeev Aggarwal
Chandigarh.

A. No.2. In the Red Book 2000 edition of the American Academy of Pediatrics Committee on Infectious Diseases under the heading zoonoses (Diseases transmitted by Animals) page no.776, Appendix vii Common animal sources for Rabies transmission are stated as Dogs, Cats, Ferrets, Bats, Skunks, Foxes & Wood Chucks and the mode of transmission is by "bites." Hence Rat Bites do not transmit rabies.

Dr.A.Parthasarathy,
Retd. Senior Clinical Professor of Pediatrics,
Madras Medical College,
Deputy Superintendent, Institute of Child Health & Hospital for Children.Chennai.

Q. No.3. Indrawing in respiratory distress. In case of respiratory distress, suprasternal, intercostal and subcostal indrawing is seen. Is it a real indrawing or a visual deception? My perception is that because of the underlying pathology, lung expansion is restricted, while the thoracic cage moves out normally causing the illusion that some portion of the thoracic cage is moving inwards. Why does the indrawing occur?

Dr.Yash Paul,
Consultant Pediatrician, Jaipur – 302 016.

A. No.3. Normal breathing is effortless. Breathlessness, dyspnoea, respiratory distress, all means increased work of breathing, characterized by sub-costal retractions, intercostal retractions, suprasternal hollowing and flaring of alae nasi. Flaring of alae nasi is a sign of increased airway resistance with breathing through the nose. 50% of the resistance of airflow occurs in the nose whereas the other 50% occurs in the large airways. With obstruction in the airways the infant can decrease total airway resistance by flaring the alae nasi and thus decreasing the resistance in the nose. Retractions is a sign of increased work of breathing. Normally tidal volume breathing generates a negative intrathoracic pressure of 4-5 cms of water. Retractions occur when the negative intrathoracic pressure is increased as in individuals with airway obstruction or poorly complaint lungs. Suprasternal hollowing are especially striking in extrathoracic airway obstruction, in which the large negative intrathoracic pressure that attempts to overcome the obstruction, results in collapse of extrathoracic airways. Intracostal retraction is a sign of increased lung stiffness or increased work of breathing due to airway obstruction. Subcostal retractions are always a sign of hyperinflation and a flattened diaphragm due to small airway obstruction. Normally when the dome shaped diaphragm contracts and moves into the abdomen, the lower edge of the ribcage to which the anterior edge of the diaphragm is attached, moves upward and outward. In the presence of hyperinflation, the diaphragm is depressed and when it contracts and moves further into the abdomen, it pulls the lower edge of the ribcage inwards resulting in subcostal retractions. Clinically, the presence of subcostal retraction means hyperinflation, when retraction is worsening, small airway obstruction is worsening; when retraction is decreasing in severity, the degree of air trapping is lessening. So indrawing in respiratory distress is a real indrawing and not a visual deception.

Dr.L.Subramanyam,
Consultant in Pediatric Pulmonology,
Kanchi Kamakoti CHILDS Trust Hospital,
Chennai 600 034.

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