

# The Child and Newborn

West Bengal Academy of Pediatrics, Oriental Apartments, Flat H1  
15C Canal Street, Kolkata 700014.

Phone: 033 2265 4072, Email: iapwb@rediffmail.com, Website: www.iapwb.org

E-version of this journal available at website



WBAP

ISSN 0975-0894

Vol 14, No 2, April - June 2010	CONTENTS
<b>EDITOR IN CHIEF</b> Dr Sumana Datta (Kanjilal)	<b>EDITORIAL</b> The Changing Scenario In Medical Education ..... 38 <i>Dilip Mukherjee</i>
<b>ASSOCIATE EDITORS</b> Dr Sanat Ghosh Dr Rakesh Mondal	<b>ORIGINAL ARTICLE</b> Epidemiological and Clinical Profile of Newborns with Community Acquired Neonatal Sepsis: A Hospital Based Study ..... 41 <i>Indrajit Mandal, Tarak Nath Ghosh, Atanu Roy, Aparna Khan, Nabendu Choudhury</i>
<b>CIRCULATION EDITOR</b> Dr Maitreyi Basu	<b>RECENT ADVANCES</b> An interesting Application of PCR in genetics Application of Multiplex Quantitative Fluorescence - Polymerase Chain Reaction in Prenatal Diagnosis ..... 48 <i>Manu Verma, Amar Verma</i>
<b>EDITORIAL BOARD</b> Dr Mridula Chatterjee Dr Kaberi Basu Dr Sucharita Datta Dr Kheya Ghosh Uttam Dr Sandip Samanta Dr Kalyan Brata Mondal Dr Madhumita Nandi (Banik) Dr Moloy Sinha Dr Tryambak Samanta	<b>OFFICE PRACTICE</b> Neonatal Seizures ..... 53 <i>Jayant K Ghosh</i>
<b>PAST EDITORS</b> Dr Umasankar Sarkar Dr Dilip Mukherjee Dr Late Tapan Kr Ghosh Dr Subroto Ckkraborty Dr Ranjana Chatterjee Dr Sutapa Ganguly	<b>SUBSPECIALITY SYMPOSIUM</b> Management of Kawasaki Disease ..... 60 <i>Rashna Dass</i>  Cardiovascular manifestation of HIV in pediatric population ..... 67 <i>Radha Binod Pal, Subhasish Bhattacharyya</i>
<b>EX-OFFICIO</b> Dr Amaresh De <b>President, WBAP</b>  Dr Nupur Ganguly <b>Secretary, WBAP</b>  <b>Special Correspondence</b> <b>Dr Sumana Datta (Kanjilal)</b> Editor in Chief, <i>The Child and Newborn</i> 16B, Prince Golam Mohammad Road, Kolkata - 700 026 WB, INDIA email: sumanadk@gmail.com email: iapwb@rediffmail.com	<b>PEDIATRIC TWEETS</b> <i>Sandip Sen</i> ..... 71
	<b>CASE REPORT</b> Unilateral Amastia ..... 74 <i>Bhaswati Ghoshal, Rita Chatterjee</i>  A child with Mixed Connective Tissue Disorder ..... 77 <i>Anjan Das, Rakesh Mondal, Madhumita Nandi</i>
	<b>CLINICAL IMAGE</b> Nephrotic Syndrome In Infancy In Identical Male Twins .. 80 <i>Sucharita Datta, Kaustabh Chaudhuri</i>

## The Changing Scenario In Medical Education

**Dilip Mukherjee**

*Prof. of Paediatrics and Ex. Dean*

*Ramakrishna Mission Seva Pratishthan, Vivekananda Institute of Medical Sciences, Kolkata*

Over the thirty years there has been considerable debate within the health science education literature model that best describes how expert clinicians generate diagnostic decisions.

Recent works suggest that clinical teachers should stress the importance of both forms of reasoning thereby enabling students to marshal reasoning processes in a flexible and context-specific manner. Specific implications are drawn from this overview for clinical teachers.

Analogous to the determining 'whodunit' while reading a mystery story the diagnostic challenge involves considering information gathered and determining most plausible explanation for the illustrated pattern. It entails careful observation, elicitation of history, accurate performance of physical manuvre, appreciation of data and relevant hypothesis and attempting to confirm or disconfirm it by diagnostic tests. Adding to the challenge is the fact that the psychological mechanisms underneath are not always available for introspection.

The medical educators have traditionally focused on the analytic model of clinics where a careful analysis of the relation between symptoms and sign and diagnoses are the hallmark of clinical expertise. A PG student must learn to gather information towards diagnosis of a case. Starting from history through general

examination and systemic examination he must learn to justify his observation at history which should be corroborated in subsequent examination of the various system in a systemic manner. Hence history that may suggest some possible reasons for a diagnosis should be further strengthened by inspection, palpation, percussion and auscultation. However too many details at this stage may baffle the student towards possible diagnosis and hence reconciliation of the whole story need to be done to give a plausible diagnosis.

The conceptualization and measurement of competence in patient care are critical to the design of medical education programme and outcome assessment. Two major components have emerged -'knowledge and clinical capability' and 'professionalism' which are measured by 'global assessment of medical knowledge, clinical judgment and data gathering skill' and 'global assessment of professional attitudes and rating of emphatic behaviour' respectively.

Much medical education from undergraduate programmes to continuing professional development is based on the idea of self directed learning. Two papers (by Dornan et al and Hoban et al) remind us that we should challenge the assumption underpinning SDL and explore its applicability to clinical medicine.

Dornan et al<sup>1</sup> in Manchester explored which is the use of a web-based learning management system in supporting student learning in the clinical environment in a large teaching hospital

---

**Corresponding Author:** Prof Dilip Mukherjee

**Email:** dilipmukherjee@rediffmail.com

and concluded that their 3rd year students were rarely fully autonomous and valued support and direction (organizational, affective and pedagogic) with which they became more motivated and apparently better able to identify and pursue their own learning needs than if left to their own devices. Previous findings that problem-based learning (PBL) does not automatically transfer to the clinical environment were also confirmed.

Hoban and colleagues<sup>2</sup> assessed the underlying factor structure of a commonly used instrument for measuring SDL, the self directed learning readiness scale (SDLRS) and concluded that SDLRS falls short of measuring characteristics that are claimed to be associated with SDL.

In a resource limited setting like India, we have no uniform examination system on completion of graduate, specialisation or superspecialisation courses and standard of teaching and examination vary widely throughout India. All medical professionals are certified but their competence depends on the local conditions and the standard of teaching and examination in a medical college therefore has an obvious bearing on the competence of the product. A ruling of supreme court of India a few years ago directed the medical council of India to institute immediate corrective measures to maintain standard of teaching in medical colleges across the country.

There should be further debate in this scenario as to consider the social role of a specialist and super specialist because the training of most medical professionals is highly subsidized by public funds. Healthcare facility here must be catered following a stepladder model where general public has a good access to competent health care providers for common diseases and idea of prevention and then if required can be referred to the specialists. But unfortunately the picture is not so. A rather unfortunate trend of management of common multisystemic diseases

by a number of super specialists increases the cost of health care. In USA it has been found the quality and outcome of patient care is no different in specialty hospital than general hospital.

The lack of nationwide standardized testing system for medical students and professionals is of particular concern. A phenomenal growth of private medical colleges in India is observed, with below standard staffs, training and research facility in many of them. Based on the recommendations of the Foundation for Advancement of International Medical Education and Research (FAIMER) the implementation of an uniform assessment system is really an urgent task. In Indian curriculum the current practice of testing only the factual knowledge instead of assessing ones attitude, responsibility and decision making skill seems to be outdated and unrelated to the contemporary needs.

World Federation for Medical Education (WFME) global standards<sup>3</sup> published in 2003 were developed as a template for regional, national and international standards to be used for recognition and accreditation of educational institutions. MEDINE<sup>4</sup> the thematic network on medical education in Europe, sponsored by the commission of the European Unions similarly has addressed activities for standard setting jointly with WFME. The division between the level of basic minimum standard and standard of quality development is fading out in the recommendations of the above authorities.

Post graduate medical education in UK is currently undergoing the most significant change with Modernising Medical Careers (MMC) is coming up rapidly. A reappraisal of senior house officer (SHO) with an effort to produce trained clinicians in shorter time has been taken up under MMC. Two year foundation programme representing the bridge between undergraduate training and entry to practice or specialty training is the key principle in it.

## REFERENCES

1. Dorman T, Hadfield J, Brown M, Boshuizeh H, Scherpbifr A. How can medical students learn in a self directed way in the clinical environment? Design based research. *Med Educ* 2005; 39: 256-64.
2. Hoban JD, Lawson SR, Mazmanian PE, Best AM, Seibel HR. The Self Directed Learning Readiness Scale : A factor analysis study. *Med Educ* 2005; 39: 370-379.
3. World Federation of Medical Education (WFME). Postgraduate Medical Education. WFME Global Standards for quality improvement. Copenhagen 2003. <http://www.wfmc.org>
4. MEDINE : The Thematic Network on Medical Education in Europe. Medine Secretariat. University of Bristol 2007. <http://www.bris.ac.uk/medine>

---

## 2010 Year Long Program of IAP West Bengal

### **July**

3rd July, 10  
19th July, 10

Monson CME, IAP Howrah District Branch  
ORS Day Celebration, NRS Medical College & Hospital

### **August**

4th August, 08

World Breastfeeding Week Celebration

### **September**

18 September, 10

CME on Pediatric Emergencies, GLT of IPGMER

### **November**

12, 13, 14 November, 10

PENCON 2010, Swabhumi

### **December**

4 & 5 December

WBAP State conference, Chinsura, Hooghly

## Epidemiological and Clinical Profile of Newborns with Community Acquired Neonatal Sepsis: A Hospital Based Study

Indrajit Mandal\*, Tarak Nath Ghosh\*\*, Atanu Roy\*\*\*, Aparna Khan\*\*\*\*, Nabendu Choudhury\*\*\*\*\*

\*RMO cum Clinical Tutor. Paediatrics, Chittaranjan Seva Sadan, Kolkata.

\*\* Associate Professor, Paediatrics, BMCH

\*\*\* RMO cum Clinical Tutor. Paediatrics, BMCH

\*\*\*\*Associate Professor, Dept. of Gynecology & Obstetrics, BMCH

\*\*\*\*\*Professor, Paediatrics, K.P.C.Medical College. Kolkata

### ABSTRACT

**Background:** Community Acquired Neonatal Sepsis (CANS) is the commonest cause of morbidity and mortality in developing countries like India. **Objective:** The purpose of the present study was to assess the various risk factors, causes, antibiotic sensitivity pattern and their outcome in CANS. **Setting:** Tertiary Care Hospital. **Study Design:** Prospective cross sectional study. **Materials and Methods:** Home delivered babies admitted with probable symptoms/signs of sepsis were screened. Those who met the prerequisite criteria of 'sepsis screen' were enrolled. Haematological parameters, sepsis screen pattern, blood culture results along with sensitivity pattern with outcomes were analyzed. **Results:** Of the 50 neonates enrolled, late onset sepsis (LOS) was found in 58% (n=29) of the cases. Poor feeding, lethargy, abdominal distension and hypothermia were the predominant symptoms. Only 11 babies had blood culture positivity, most common organism isolated was Klebsiella (n=3). Of the sepsis screen criteria, CRP was highly sensitive (84%). The antibiotic sensitivity pattern showed a changing trend of sensitivity from first line to second line antibiotics. The mortality rate was higher in LOS and more within the first 48 hours of life, though it was not statistically significant ( $p>0.05$ ). **Conclusion:** Early presumption, early recognition, early introduction of rational antibiotic therapy in correct doses and route along with supportive care can dramatically reduce not only the morbidity but also mortality of neonatal sepsis.

**KEY WORDS:** Community Acquired Neonatal Sepsis (CANS), Early onset sepsis (EOS), Late onset sepsis (LOS)

### INTRODUCTION

In developing countries, sepsis is the commonest cause of neonatal mortality accounting for 26 percent of the 4 million total neonatal deaths each year<sup>1</sup>. In India, nearly two-thirds of babies are born at home<sup>2</sup>, and few are taken for medical care, even if they are sick<sup>3,4,5</sup>. A community based study on the causes of neonatal death conducted by Society for Education, Action and Research in Community Health (SEARCH) at

Gadchiroli, Maharashtra has implicated sepsis as the leading cause of neonatal death contributing to 52 percent of all neonatal death<sup>6</sup>.

The etiology of neonatal sepsis from the community is not well understood. Perhaps the common organisms that are found in community acquired cases are the same as in hospital cases. In the WHO Young Infant Study in four developing countries (viz. Philippines, Papua New Guinea, Ethiopia and Gambia), the commonest pathogens identified in cases of culture positive Community Acquired Neonatal Sepsis (CANS) were *S.aureus* (23%), *Streptococcus*

**Corresponding Author:** Prof. Nabendu Chaudhuri

**Email:** atanuroy76@gmail.com

*pyogenes* (20%) and *E.coli* (18%)<sup>7</sup>.

CANS in neonates still continues to be an important problem in developing countries. Poor hygienic condition, dirty fomites, application of cow-dung on umbilical stump and customs of giving pre-lacteal feeds leads to colonization of vulnerable infants with pathogenic microbes. *E.coli* leads the list of the causative agents of non-nosocomial late onset sepsis followed by *S.aureus*<sup>8</sup>.

National Neonatology Forum (NNF) classifies neonatal sepsis, as either culture positive proven sepsis or probable sepsis. Probable sepsis includes babies with suggestive clinical features and two out of five sepsis screen factors positive. The sepsis screen factors are namely leucopenia, neutropenia, raised micro-ESR, raised band cells and raised CRP<sup>9</sup>. Blood culture is the gold standard diagnosis for neonatal sepsis, however less than half of the cases are often culture negative. Blood culture is also important for formulating rational drug therapy for sepsis in a community.

Bacterial flora that are predominant in the community and their antibiotic sensitivity patterns changes over time, and its periodic assessment is required for making rational protocols in treatment of these cases.

Our study has been considered with the objective to find out the causative organisms with their sensitivity pattern, to determine the precipitating factors responsible for development of septicaemia in the community and also to determine the relationship between the various precipitating factors and outcome of these cases.

## METHOD & MATERIAL

It was a hospital based cross sectional prospective study done over a period of July 2007 to June 2008. Home delivered babies who presented in our institute with clinical features of sepsis were included. The exclusion criteria those neonates who had received treatment in other healthcare system for more than 6 hours, before being referred.

The babies were evaluated by detailed antenatal history of the mothers which included assessment of risk factors. Simultaneously clinical examination for babies were done to detect any signs and symptoms of sepsis. Time of onset of these presentations helped to categorize them as early onset or late onset sepsis. Relevant investigations including sepsis screen and blood culture were performed to confirm the diagnosis. All were managed as per standard hospital protocol.

The study had necessary approval of Institutional Ethical Committee and proper consent was taken from parent/guardian. Statistical analysis was done by SPSS ver 10 with p value <0.05 taken as significant.

## RESULT AND ANALYSIS

Altogether 50 neonates were enlisted, most being males (n=30). Late onset sepsis (LOS) were more common amongst extra-mural babies than early onset sepsis (58% vs 42%). Table 1 shows types of sepsis & its outcome in home delivered (Extra-mural) babies.

**Table 1.** Showing types of sepsis & its outcome in home delivered (Extra-mural) babies

Type of sepsis	No. of cases	Percentage (%)	Outcome			
			Discharge		Death	
			(n)	(%)	(n)	(%)
Early onset sepsis(EOS)	21	42	15	71.4	06	28.6
Late onset sepsis(LOS)	29	58	17	58.6	12	41.4
Total	50	100	32	64	18	36

In the community, prototype is home delivery, and all the deliveries (100%) were conducted on the floor, either by trained or un-trained dais, 33 babies (66%) received T.Toxoid at birth, 35 babies (70%) received pre-lacteal feeding, 17 cases (34%) were given cord application (mercurochrome) and 16 babies (32%) were given bath at birth.

Poor feeding, lethargy were the commonest symptoms in extra-mural cases. Abdominal distension was also found in many of the cases (58%). Hypothermia was more common among home delivered babies (56%). Though most of the CNS infection are asymptomatic, convulsion is one of the symptoms of meningitis which is more in LOS (n=17). It had been noted that in this study convulsion was less common in extra-mural cases (28%).

Blood cultures were done in all suspected septic babies. The culture positivity rate was far less, and the incidence of neonatal septicemia confirmed by cultures was only 22%. In the present study *Klebsiella* was the major causative organism in home delivered (3 out of 11) septicemic babies followed by *S.aureus* (2 out of 11). Among 50 cases, major 'gram -ve' organisms was *Klebsiella* 8 (28%) followed by *E. coli* 5 (17%). The mortality rate among the culture positive cases of extra-mural babies was found to be more

(45.4%), and fatality rate was highest in *Coagulase negative Staphylococcus aureus* (CONS) (100%) and Candidial (100%) infection followed by *S.aureus* (50%) and *Klebsiella* (33%). Six types of organisms including one fungal (3.7% of all culture +ve cases) case were detected in extra-mural cases. Table 2 shows culture positive cases, organism and outcome of the home delivered (Extra-mural) babies.

Among hematological indices total leucocyte count (TLC) was not much helpful to diagnosis the neonatal sepsis. Only 4 babies were found to have TLC >20,000/cmm. Absolute neutrophil count (ANC) less than 1800/cmm was correlated in 9 cases. In the present study raised CRP was found in 84% of cases. It was found to be markedly raised in *E.coli* infection (64%). It was also moderately raised in screen-positive cases. In this study raised micro-ESR was seen in 42% home delivered cases. The I/T ratio was maintained only in 48% babies. Lumbar puncture was done in 10 patients. Most of them were either traumatic, dry or inconclusive.

Hemoglobin levels in different etiological types of sepsis show lowest value in *E.coli* infections (13.5gm%) and highest values seen in *Klebsiella* (16.4gm%) and *CONS*(16.9%) infections. Highest band cell count was found in

**Table 2.** Showing culture positive cases, organism and outcome of the home delivered (Extra-mural) babies

Organisms	No of cases	Sex	Outcome			
			Discharge		Death	
			(n)	(%)	(n)	(%)
<i>Klebsiella</i>	03	M=1, F=2	02	66.7	01	33.3
<i>S. aureus</i>	02	M=2, F=0	00	00	01, LAMA=1	50
<i>CONS*</i>	02	M=1, F=1	00	00	02	100
<i>E.coli</i>	02	M=1, F=1	02	100	00	00
<i>Pseudomonas</i>	01	M=1, F=0	01	100	00	00
<i>Candida</i>	01	M=1, F=0	00	00	01	100

\**Coagulase negative Staphylococcus aureus*.

*Pseudomonas* infection (42%) in extra-mural cases (though only one case of *Pseudomonas* was found). All *E.coli* infection in extra-mural cases had band cell count >20% of ANC. Table 3 shows hematological parameters in culture +ve and culture -ve screen +ve in home delivered (Extra-mural) septicemic babies.

The antibiotic sensitivity pattern in this study showed that *S.aureus* was 100% sensitive to Vancomycin. *Coagulase negative Staphylococcus* (CONS) was also 100% sensitive to Vancomycin. *Klebseilla* and *E.coli* were highly sensitive to Amikacin *Pseudomonas* was causative organism

for only one neonatal sepsis in extra-mural cases. It was highly sensitive to Gentamicin, Amikacin and Gatifloxacin. The statistical analysis showed that 'gram-ve' isolates were significantly multidrug resistant ( $p < 0.05$ ) than 'gram+ve' isolates. The combined sensitivity of all organisms to Ampicillin, Gentamicin and Cephalexin was poor.

The higher mortality that is noted in LOS (41.4%) in comparison to EOS (28.6%), however cannot be significantly correlated statistically ( $p$  value  $< 0.5$ ).

Eighteen cases (36%) died and 61% of which died within first 48 hrs of admission. Table 4

**Table 3.** Showing hematological parameters in culture +ve and culture -ve screen +ve in home delivered (Extra-mural) septicemic babies

Organisms	*Hb (gm%)	*TLC/cmm	*DLC (%)					Band cell (%)
			N	L	E	M	B	
	Mean±2SD	Mean±2SD	Mean±2SD					Mean±2SD
<i>Klebsiela</i>	16.43±1.37	12500±2000	73±5	24±4	2±1		0	20±8
<i>S. aureus</i>	16.15±0.65	12650±4150	77.5±7.5	20±5	2±1	3±2	0	21±5
CONS	16.9±0.9	10000±2500	65.5±9.5	30±8	3±2	1±1	0	18.5±3.5
<i>E. coli</i>	13.05±0.55	20300±1150	81±3	17±3	2±1	0	0	23±7
<i>Pseudomonas</i>	15.8±0	17800±0	58±0	38±0	4±0	0	0	26±0
<i>Candida</i>	16.8±0	10800±0	56±0	40±0	3±0	1±0	0	16±0
Culture -ve screen +ve cases	14.3±3.8	13500±9500	52±28	37±21	3±3	1.5±1.5	0	19±13

[\*Values are within 95% of confidence limit (mean ±2SD),  
SD = Standard Deviation, TLC = Total Leucocyte Count, DLC = Differential Leucocyte Count]

**Table 4.** Showing time interval between admission & death in home delivered (Extra-mural)

Time interval between admission & death	No. of death (n) (%)	Sex distribution	Type of septic death (n)
< 24 hrs	06 (33%)	M=3, F=3	EOS=0, LOS=6
24-48 hrs	05 (28%)	M=3, F=2	EOS =2, LOS =3
48-72hrs	03 (16.5%)	M=2, F=1	EOS =2, LOS =1
72hrs-96hrs	02 (11%)	M=2, F=0	EOS =1, LOS =1
96 -120hrs	01 (5%)	M=0, F=1	EOS =1, LOS =0
> 120 hrs	01 (5%)	M=1, F=0	EOS =1, LOS =0

shows time interval between admission & death in home delivered (Extra-mural).

Mortality rates among VLBW and babies weighing <2 kg were 57% and 50% respectively in contrast to 27.77% mortality among normal weight babies (wt =2.5kg). Babies with birth weight having <2 kg were high risk of acquiring sepsis. Table 5 shows admission as per body weight and its outcome in home delivered (Extra-mural) babies.

## DISCUSSION

In our study we had more cases of late-onset-sepsis. This is most likely due to delayed recognition, local injudicious antimicrobial therapy, poor communication, long journey and lastly financial constraints. This finding is consistent with the observation of other workers.

Male baby affection was more than female babies, which is consistent with the present literatures. The high predilection of male babies for neonatal sepsis may be due to the fact that X-chromosome is potentially more immune in compare to Y-chromosome.

The absence of '5' C during delivery, unhygienic cord application, dirty fomites, pre-lacteal feed and other unhygienic practice are the major contributory factors for development of sepsis. In addition to these factors, non-eugenic environment potentiated the occurrence of sepsis

in extramural babies who are by predilection are home delivered.

Poor feeding, lethargy were the commonest symptoms in extra-mural cases. Hypothermia was more common among home delivered babies (56%). The similar observation was noted by Bhakoo et al 1974<sup>10</sup>, Plaezek et al 1983<sup>11</sup>, Tallur et al 2000<sup>12</sup> and Basavaraz et al 2006<sup>13</sup>.

Only 22% of the cases were culture positive and it is corroborative with current literatures. Low incidence of culture positivity was probably because of early administration of irrational antibiotics. As per NNPD 1995 & 2000 and also earliar studies done by some workers, *Klebseila* is the most frequent cause of neonatal septicaemia, as we see in our study. *Staphylococci* were the predominant 'gm+ve' organisms with 8 (28%) *S.aureus* and 5(17%) *CONS*. Kumhar et al<sup>14</sup> have also reported that *Staphylococci* was the predominant 'gram +ve' pathogens. The above observation is also supported by the study of Bang et al<sup>6</sup>. It has been well documented that hemolysin is liberated from K1 antigen of *E.coli* which could be responsible for the low Hb% in the *E.coli* group. Markedly raised micro-ESR was found in *E.coli* group followed by *S.aureus* which is well correlated with study done by Thakre et al<sup>15</sup> and Lee et al<sup>16</sup>.

Routine LP as a part of work up of neonatal sepsis has been recommended because a significant proportion of cases of culture positive

**Table 5.** Showing admission as per body weight and its outcome in home delivered (Extra-mural) babies

Body weight of the babies (Kg)	No. of cases	Outcome			
		Discharge		Death	
		(n)	(%)	(n)	(%)
<1.5	05	01	20.0%	04	80.0%
=1.5 - <2	10	05	50	05	50
=2 - <2.5	18	13	66.66	05	33.33
=2.5	17	13	73.22	04	27.77
Total	50	32	64	18	36

septicemia are associated with meningitis. This policy has however been questioned more recently because the prevalence of meningitis is found to be much less (0-3.3%) in most studies.

The combined sensitivity of all organisms to Ampicillin, Gentamicin and Cephalexin was poor which is almost supported by the study of Usha Arora et al<sup>17</sup>. Gram -ve' isolates were most sensitive to amikacin. None of the 'gram+ve' isolates showed resistance against Vancomycin which also co-relates with earlier studies. Hence this drug can be used effectively if MRSA (methicillin resistant *Staphylococcus aureus*) is suspected.

The higher incidence of death in late onset sepsis was because of the fact that the neonates had suffered more due to inadequacy of proper referral system and mode of transport and deprivation of early rational antimicrobial therapy and supportive care.

More than half of the deaths have occurred within the first 48 hrs of admission. This was likely because of delayed admissions with ensuing complications such as hypothermia, hypoglycemia, dehydration, shock, aspiration following feeding and long journey, deprivation of eu-thermic environment, irrational therapy (mostly treated with I.M. and/ or oral junk antibiotics from the beginning) and devoid of supportive measures for long considerable periods.

We accept that delayed recognition of symptoms, injudicious/indigenous treatment, poor referral system & transport hazards all contribute to modify the interpretation of epidemiological and clinical profile of newborns with CANS in a hospital based study. So to eliminate this bias in the future we wish to undertake another study at the community level involving the peripheral health workers (ASHA, ANW, GPHN) and doctors of rural health service. Funds from IMNCI & NRHM could be utilized for

this purpose.

## CONCLUSION

Neonatal sepsis is the commonest cause of neonatal morbidity and mortality in our country. The pattern of predominant bacterial flora and their antibiotic sensitivity changes over time. The present study describes predominant causes of community acquired neonatal sepsis along with antibiotic sensitivity pattern. Risk factors associated with sepsis along with risk factor assessment by sepsis screen are also described. It can be concluded that early presumption, early recognition, early introduction of rational antibiotic therapy as per the current sensitivity pattern in community acquired sepsis, in correct doses and route along with supportive care can dramatically reduce not only the morbidity but also mortality.

## CONTRIBUTORS

IM, TNG, AR and AK managed the cases, collected data and prepared the draft. NC conceptualized the design of the study and approved the manuscript.

## REFERENCES

1. Lawn JE, Cousens S, Zupan J. Lancet Neonatal Survival Steering Team. 4 million neonatal deaths: When? Where? Why? *Lancet* 2005 Mar 5-11;365(9462): 891-900.
2. National Family Health Survey 11 (1998-1999). *International Institute of Population Sciences*. Mumbai. India. 2000.
3. Bang AT, Bang RA, Mornkar VP, Sontakke PG, Solaki JM. Pneumonia in neonates: can it be managed in the community? *Arch Dis Child* 1993; 68: 550-6.
4. Bhandari N, Bahl R, Bhatnagar V et al. Treating sick young infants in urban slum setting. *Lancet* 1996 ;347 :1774-5.
5. Bang AT, Bang RA, Baitude S, Deshmukh M, Reddy MH. Burden of morbidities and the unmet need for health care in rural neonates : a prospective observational study in Gadchiroli. India. *Indian Pediatr* 2001 : 38: 952-65.

6. Bang AT, Bang RA, Baitule S, Reddy MH, Deshmukh M. Effect of home- based neonatal care and management of sepsis on neonatal mortality: field trial in rural India. *Lancet* 1999 Dec 4;354 (9194):1955-1961.
7. WHO Young Infants Study Group. Bacterial etiology of serious infections of young infants in developing countries: results of multicenter study. *Pediatr Infect Dis J* 1999; 18(supplement):S17-S22.
8. Meeting to explore simplified antimicrobial regimens for the treatment of neonatal sepsis. WHO/FCH/CAH/04.1.
9. National Neonatology Forum: National Neonatal Perinatal Database Report 2002-03. Published NNPD nodal centre, All India Institute Medical Sciences, New Delhi.
10. Bhakoo ON, Agarwal KC, Narang A, Bhattacharya S. Prognosis and treatment of neonatal septicaemia, A clinicobacteriological study of 100 cases. *Ind Pediatr* 1974; 11: 519-26.
11. Placzek MM, Whitelaw A. Early and late neonatal septicaemia. *Arch Dis Child* 1983; 58: 728- 31.
12. Tallur SS, Kasturi AV, Shobha DN, Krishna BVS. Clinicobacteriological study of neonatal septicaemia in Hubli. *Ind J Pediatr* 2000; 67 (3):169-174.
13. Basavaraz M, Kerur B, Vishnu Bhat, Harish B.N, Habeebullah S, Uday Kumar C. Maternal genital bacteria and surface colonization in early neonatal sepsis. *Indian Journal of Pediatrics*; volume 73, January 2006:29-32.
14. Kumhar GD, Ramchandran VG, Gupta P. Bacteriological analysis of blood culture isolates from neonates in a tertiary care hospital in India. *J Health Popul. Nutr.* 2002; 20(4): 343-7.
15. Thakre R. Neonatal sepsis screen. *Pediatrics Today*; VIII (3) : 176.
16. Lee C. Haematological status of the neonate and young infant. In: *Wintrob's Clinical Haematology*, 10th ed, 1999, Lippincott Williams & Wilkins.
17. Arora U, Jaitwani J, Thaper K. A Clinico-bacteriological study of neonatal septicaemia in Amritsar. *Asian Journal of Paediatric Practice*. 2008; vol 11(4) :5-9.

---

### Dates and Place of IAP Clinical Meeting 2010

July 29	B R Singh Hospital
August 26	NRS Medical College
September 30	Medical College Kolkata
October 28	Apollo Gleneagles Hospital
November 25	IPGME&R and SSKM Hospital
December 30	R G Kar Medical College

## RECENT ADVANCES

### An interesting Application of PCR in genetics Application of Multiplex Quantitative Fluorescence -Polymerase Chain Reaction in Prenatal Diagnosis

Manu Verma\*, Amar Verma \*\*

\* B.tech (Biotechnology), MSc (Medical Genetics) Faculty of Medicine, University of Glasgow, UK  
\*\* Associate Professor, Department of Pediatrics & Neonatology, Rajendra Institute of Medical Sciences, Ranchi.

#### INTRODUCTION

"If I don't know my options, I don't have any"-  
(anonymous).

Prenatal diagnosis provides the options to pregnant women in case of chromosomal abnormalities in fetus or reassures them about the well being of the unborn child. But the recent surge in number of women going for prenatal diagnosis using conventional techniques has raised concerns in the health system setup about its economic implication as well as time and expertise involved in it (Nicolini et al, 2004). Karyotype analysis for chromosomal abnormalities is costly & the result takes around 2 weeks. So to provide better pregnancy management & reassurance for pregnant women, rapid aneuploidy detection [RAD] is used. Multiplex Quantitative fluorescence- Polymerase Chain Reaction [QF-PCR] is one of the latest approaches of RAD, based on the basic principle of PCR, which produces results in 1-2 days (Mann k et al, 2004). The working of the PCR is shown in Fig. 1.

Multiplex QF-PCR is a variation of PCR. It uses several primers specific to its target DNA in a single PCR reaction & fluorochrome is added to the primer so that the amplified product is detected by a DNA scanner. In prenatal diagnosis several short tandem repeats [STRs] present on chromosome 13, 18, 21, X & Y are used in QF-PCR

**Corresponding Author:** Dr Amar Verma

**Email:** draverma2003in@gmail.com

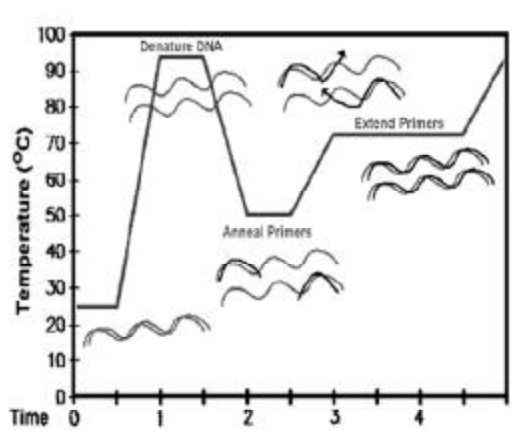


Fig. 1. Graphical Representation of working of the PCR used for exponential amplification of targeted DNA [single cycle] :

Step 1. Denaturation of the DNA to provide template for primer annealing & extension

Step 2. Cooling & annealing of primer to single stranded DNA for extension

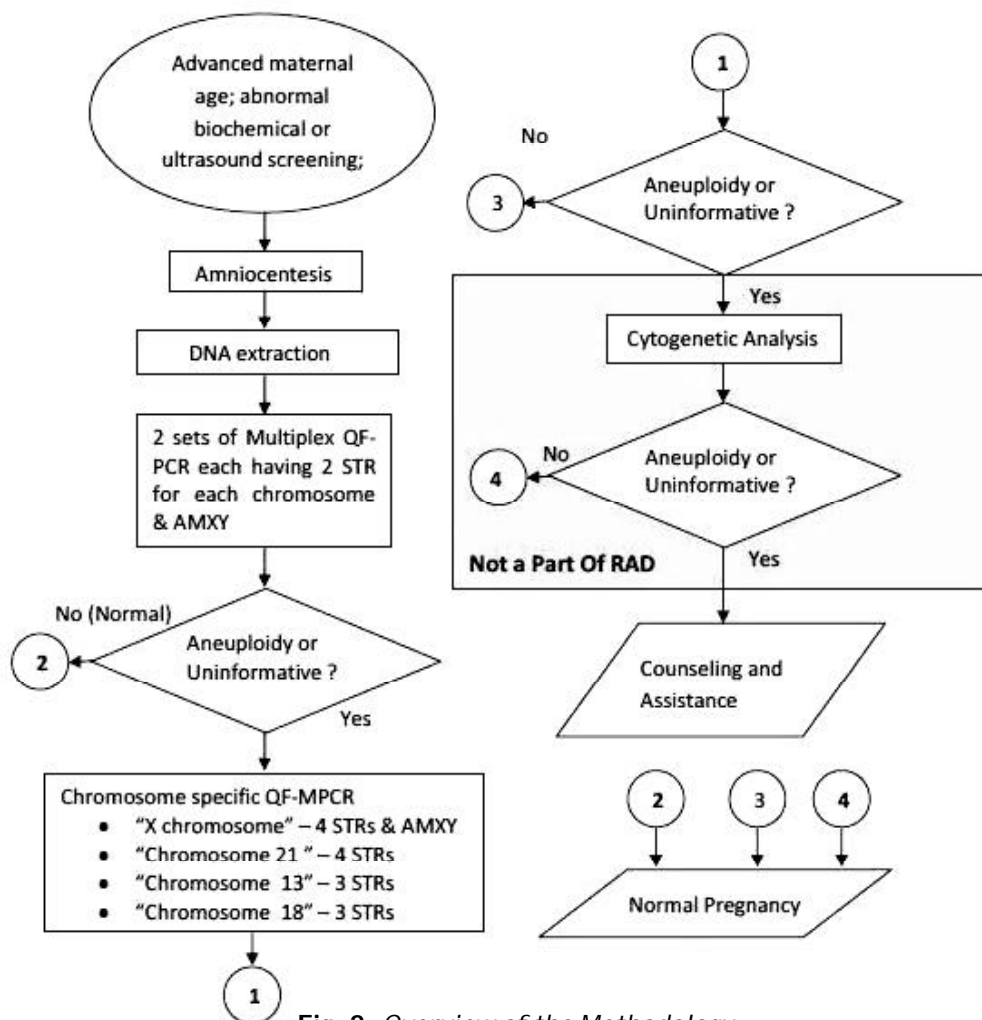
Step 3. Extension of the primer resulting in formation of new DNA strands.

Step 4. The steps 1-3 are repeated "n" times followed by Final extension step at ~ 74 °C for 5-15 minutes to ensure all single stranded DNA are extended (Brown T A (2006)) (Image [http://www.mun.ca/biology/scarr/PCR\\_sketch\\_3.gif](http://www.mun.ca/biology/scarr/PCR_sketch_3.gif), last accessed on 19th Oct, 09 )

analysis. Use of several STRs for each chromosome increases reliability of the test. Normal diallelic (heterozygous) individual will show peak pattern in 1:1 ratio, monoallelic (homozygous) will show single peak which may be uninformative in the absence of other markers, Abnormal triallelic trisomy will show 1:1:1 peak pattern or diallelic trisomy will show 1:2 or 2:1 ratio in peak pattern in DNA scanner (Shaffer & Bui 2007).

## METHODOLOGY

Advanced maternal age, abnormal biochemical or ultrasound screening forms the majority of factors due to which RAD is performed. Amniocentesis was carried out & amniotic fluid was used as a source of fetal DNA. The flowchart as shown in fig 2 was followed for RAD. The lists of all the STRs used for specific chromosome are listed in Table 1 (Cirigliano V et al, 2001).



**Fig. 2. Overview of the Methodology**  
 □ - Process, ◇ - Decision, ▱ - Feedback, ○ - Connector  
 Original Diagram compiled from information in (Cirigliano et al, 2001)

**Table 1.** The primer labeling, Size of PCR product & location of the markers used in the study. Table reproduced from (Cirigliano et al (2001)) Note: similar sized amplicons are labeled differently

Marker	Label	Amplicon size (bp)	Location
PCR X, Y			
AMXY	6-FAM	X 104, Y 109	Xp22.3/Yp11.2
X22	6-FAM	189-242	Xq/Yq (PAR2)
HPRT	6-FAM	268-296	Xq26.1
DXS6803	HEX	106-124	Xpter/qter
DXS6809	HEX	242-279	Xpter/qter
PCR 21			
D21S11*	6-FAM	214-242	21q21
D21S1412	6-FAM	384-414	21q22.2
D21S1411	HEX	266-319	21q22.3
D21S1435	HEX	163-187	21q21
PCR 18			
D18S535	TET	126-156	18q12.2
D18S386	TET	330-387	18q21.1
D18S51	6-FAM	271-331	18q21.33
PCR 13			
D13S631	HEX	192-218	13q31-32
D13S634	HEX	464-490	13q14.3
D13S258	TET	230-267	13q21

## RESULTS & SENSITIVITY

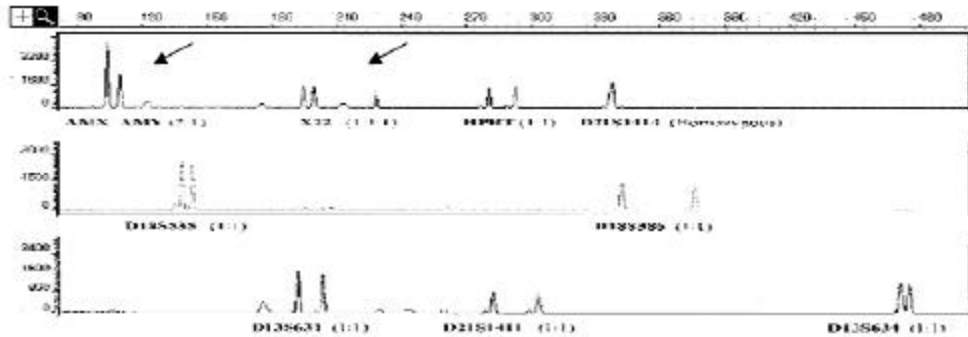
In the work undertaken by Cirigliano et al (2001) total 551 samples were tested for aneuploidy using Multiplex QF-PCR, out of which 488 showed distinctive heterozygous pattern for at least one STR after first 2 Multiplex QF-PCR. 43 samples were homozygous and thus uninformative, it was retested using chromosome specific STRs & Multiplex QF-PCR [actual aneuploidy samples were 20 and not included in his count]. The detection rate of Chromosome copy number after third QF-MPCR was 100% for chromosome X, Y & 21. In case of chromosome 18 it was 99.8% and 99.4% for chromosome 13. The 20 aneuploidy samples included trisomy 21 (n=7), trisomy 18 (n=6), trisomy 13 (n=3), 45 X (n=1) & 47, XXY (n=1). The number of peaks as well as peak ratio gave information about chromosome number. Electrophoretogram of the results and its explanation is given in fig 3.

## DISCUSSION

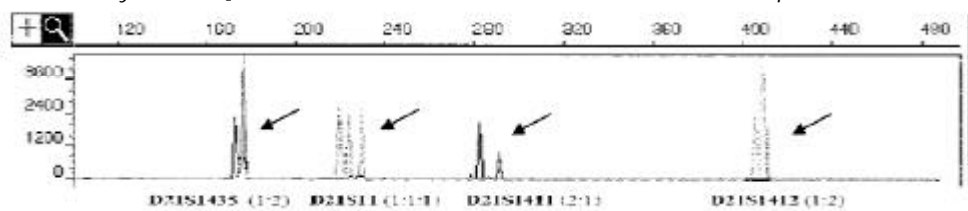
Most common RAD techniques make use of

Multiplex QF-PCR & fluorescence in situ hybridization (FISH). Although both of these methods involve fluorescence tagging of DNA, they are very different from each other. Table 2 below lists major differences between them.

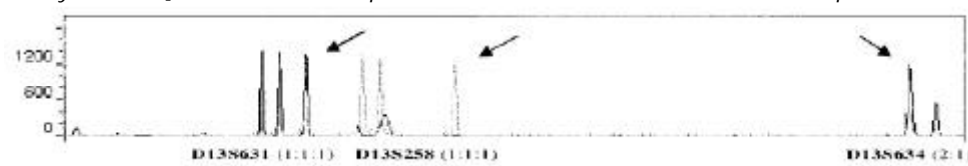
Multiplex QF-PCR is gaining popularity in European genetic laboratories for RAD because of its cheapness & ease of automation (Shaffer & Bui, 2007). However the abnormalities detected by RAD comprise only 70-80% of Karyotype abnormalities and even though it covers almost 99% of the disorder in low risk pregnancies, certain uncommon disorders or structural abnormalities cannot be detected (Hult ´en et al, 2003). So by offering RAD as a preliminary screening test to all and followed by karyotyping in relevant cases would enable proper resource allocation without compromising much on "Healthy mother & Healthy baby" paradigm. Nevertheless fetal karyotyping should always be considered as "gold standard of prenatal diagnosis" for high risk pregnancies because of the amount of



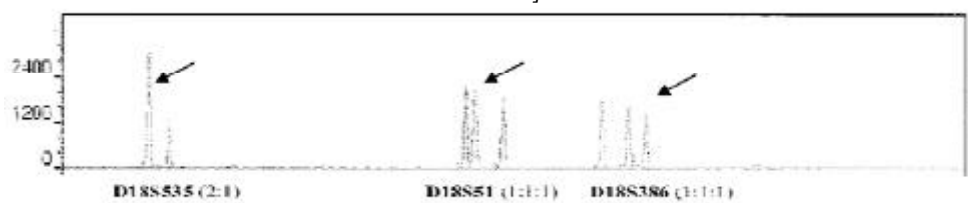
A) Klinefelter syndrome [Peak ratio of AMXY marker & Trisomic triallelic pattern of X22 marker]



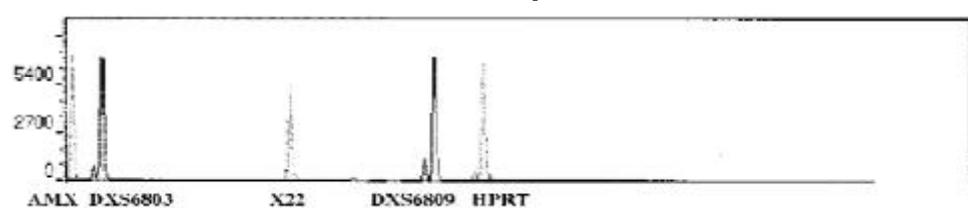
(B) Down syndrome [Trisomic diallelic pattern of D21S1435 & Trisomic triallelic pattern of D21S11]



(C) Patau syndrome [Trisomic diallelic pattern of D13S631, D13S258 & Trisomic triallelic pattern of D13S634]



(D) Edward syndrome [Trisomic diallelic pattern of D18S535 & Trisomic triallelic pattern of D18S51, D18S386]



(E) Turner syndrome [assumption that the probability all the markers showing only one peak "x" specific product and absence of "y" specific AMXY is due to X monosomy rather than homozygosity]

**Fig. 3.** Electrophoretogram & interpretation of result of the disorders. (A) shows the results of First round of Multiplex QF-PCR with 2 STRs per chromosome; (B)-(E) shows the results of 2nd round multiplex QF-PCR with chromosome specific STRs; Reproduced from Cirigliano V et al, 2001)

**Table 2.** Comparison between FISH & Multiplex QF-PCR Original Table is based on information in (Hult en et al, 2003)

Parameters for comparison	FISH	Multiplex QF-PCR
Working	Fluorescently labeled chromosome specific DNA sequences are hybridized with Chromosome preparations & visualized under microscope	It involves PCR amplification of chromosome specific STRs & quantitative analysis by fluorescent tagging of primer
Sample & labor required	Requires 1.0-1.5 ml of amniotic fluid & is labor intensive	Requires 0.5-1.0 ml of amniotic fluid, less labor intensive & more favorable to automation
Handling maternal cell contamination	Contamination is undetectable for female fetus but can be detected for male fetus	Readily detected in form of characteristic pattern with extra allele or skewed ratio between peaks for specific chromosome but diagnosis can still be achieved by comparison with maternal blood profile
Handling & ease of automation	Relatively take more time per sample & difficulty in automation	Relatively takes less time per sample & can be easily automated

information obtained from it (Nicolini et al, 2004). More recent approaches in prenatal diagnosis involve non-invasive combined ultrasound & biochemical test, but is mainly done for Down syndrome (Stenhouse et al, 2004). However non-invasive prenatal diagnosis holds a lot of promise for future.

#### REFERENCES

- Brown T A (2006), *Gene cloning and DNA analysis*, chapter 9, 4th edition, Blackwell science Ltd, Oxford, UK, 179-193.
- Cirigliano V, Ejarque M, Canadas M, Lloveras E, Plaja A, Perej M, Fuster C & Egozcue J (2001), Clinical application of multiplex quantitative polymerase chain reaction for rapid prenatal detection of common chromosome aneuploidies, *Molecular human reproduction*, 7(10), Pg 1001-1006.
- Hult en M A, Dhanjal S & Pertl B (2003), Rapid and simple prenatal diagnosis of common chromosome disorders: advantages and disadvantages of the molecular methods FISH and QF-PCR, *Reproduction*, 126, 279-297.
- Mann k, Donaghue C, Fox S P, Docherty Z & Ogilvie C M (2004), Strategies for the rapid prenatal diagnosis of chromosome aneuploidy, *European Journal of Human Genetics*, 12, 907-915.
- Nicolini U, Lalatta F, Natacci F, Curcio C & Bui T (2004), The introduction of QF-PCR in prenatal diagnosis of fetal aneuploidies: time for reconsideration, *Human Reproduction Update*, 10(6), 541-548.
- Shaffer L G & Bui T H, (2007), Molecular Cytogenetic and Rapid Aneuploidy : Detection Methods in Prenatal Diagnosis, *American Journal of Medical Genetics Part C (Seminars in Medical Genetics)* 145C, 87-98.
- Stenhouse E J, Crossley J A, Aitken D A, Cameron A D & Connor J M, (2004), First-trimester combined ultrasound and biochemical screening for Down syndrome in routine clinical practice, *Prenatal Diagnosis*, 24,774-780.

## Neonatal Seizures

Jayant K Ghosh

Assistant Professor, Department of Pediatrics, North Bengal Medical College  
Shushrutnagar, Dist: Darjeeling, West Bengal

### INTRODUCTION

Seizures are the most distinctive manifestation of neurologic dysfunction in newborn infants. Incidence of neonatal seizures varied from 3 in 1,000 full-term neonates to 60 in 1,000 pre-term neonates as documented in different studies. The National Neonatal-Perinatal Database (NNPD) of India that collected information from 18 centers across country in the year 2002-03 had reported an incidence of 1.0%.<sup>1</sup> However, regardless of their precise incidence, it is clear that seizures are more common in the newborn period than at any other time in life, and that the tendency towards recurrent seizures and status epilepticus is far greater in this period.

### Decreased seizure threshold in the newborn:<sup>2</sup>

- i) Transient overdevelopment of the excitatory system compared to inhibitory system: e.g. in the immature brain there is transient over expression in the density of excitatory amino acid (glutamate) receptors and a relative paucity of glutamate reuptake transporters.
- ii) Inhibitory GABA ion channels are relatively under expressed in immature brain.
- iii) In certain areas of the developing brain immature GABA may be depolarizing (i.e. excitatory) rather than hyperpolarizing (inhibitory).

### Peculiar clinical characteristics of neonatal seizures:

- i) The relatively underdeveloped organization of the cortex and under-myelination of axons likely underlies the disorganized convulsive activity and lack of orderly seizure propagation in newborn. For the same reasons, primary generalized seizures are rare in the newborn.
- ii) In accordance with the caudal-to-rostral gradient of brain development, the brain stem functions are relatively developed in advance. This fact may underlie the prevalence of behaviors such as sucking and chewing oromotor automatism, excessive drooling, oculomotor activity, and respiratory irregularities seen in subtle seizures.

### Clinical subtypes:<sup>3,4</sup>

- i) **Subtle Seizures:** Most common subtype, comprising about 50-60% of neonatal seizures.
  - a) *Ocular phenomenon:* Tonic eye deviation, roving nystagmoid eye movements, and sudden eye opening.
  - b) *Oro-bucco-lingual movements:* Chewing, sucking, lip-smacking, or excessive drooling of saliva.
  - c) *Limb movements:* Pedaling, boxing, rowing, or swimming movements.
  - d) *Autonomic phenomenon:* Sudden changes in skin color and capillary size, initial tachycardia followed by bradycardia and apnea.Most subtle seizures are have other seizure types as well. As most subtle seizures are

---

**Corresponding Author:** Dr Jayant K Ghosh

**Email:** drjayantkg@yahoo.co.uk

not associated with EEG seizures, poor response to conventional anticonvulsants, many consider them as nonepileptic brainstem release phenomena.

ii) **Clonic seizures:** Repetitive biphasic movements with a fast contraction phase and a slower relaxation phase. Could be unifocal, multifocal, or generalized. Most common cause of unifocal clonic seizure is neonatal stroke. Each sequential seizure may appear different from the previous seizure both clinically as well as EEG features.

iii) **Tonic seizures:** Sustained period of muscle contraction without repetitive features. May be focal or generalized. Generalized tonic seizure closely resembles decorticate or decerebrate posture. Tonic seizures are most common in premature infants with diffuse neurologic dysfunction or major intraventricular hemorrhage. EEG shows multifocal or generalized voltage depression. Prognosis is very poor.

iv) **Myoclonic seizures:** They are distinguished from clonic seizures by their lightning fast contractions and non-rhythmic character. Even when repetitive they tend to be irregular and erratic in nature. Sometimes Myoclonic seizures can be elicited by stimulus or suppressed by restraints. The electroclinical association is variable. EEG may show burst-suppression pattern. Myoclonic seizures are generally associated with diffuse and serious brain dysfunction and have poor long-term outcome.

**Jitteriness:** Seizure-mimic, stimulus sensitive, can be abolished by passive restraint or repositioning of the infant and they are not associated with any autonomic changes. Further, they have equal amplitude and faster equiphase rhythm as compared to slower, fast-and-slow component of clonic seizures. Most of the authors consider it as release reflex. However, others

consider it as true epileptic origin which can't pick up by conventional EEG.

**Apnea** may be a rare manifestation of neonatal seizure. Apnea due to seizure may have tachycardia initially and bradycardia is a late manifestation of it where as in true apnea bradycardia is an early manifestation.

### ETIOLOGY<sup>3</sup>

Etiology	Incidence (%)
1. Cerebral hypoxia-ischemia	–
a. Global( e.g. Perinatal asphyxia)	40
b. Focal infarction ( arterial or venous)	15
2. Intracranial hemorrhage	15
3. CNS infection	5
4. Metabolic disease	–
a. Transient	5
b. Inborn errors of metabolism	1
5. Cerebral dysgenesis	5
6. Neonatal epileptic syndromes	1
7. Neonatal abstinence syndrome	1
8. Unknown	10

### APPROACH

- Seizure history:** Complete description of the seizure, associated eye movements, restraints of episodes by passive flexion, autonomic phenomena and whether the infant was conscious at the time of seizure should be obtained from the attendant. Seizures occurring on day 0-3 may be related to perinatal asphyxia, intracranial hemorrhage, metabolic and developmental defects. Seizures occurring beyond 72 hours of life could be due to sepsis, meningitis, metabolic causes and developmental defects.
- Antenatal history:** History suggestive of intrauterine infections, maternal diabetes and addiction should be elicited.

3. **Perinatal history:** Perinatal asphyxia is the most common cause of neonatal seizure and a detailed history including history of fetal distress, decreased fetal movements, instrumental delivery, need for resuscitation in the labor room/O.T., low Apgar scores, any investigations suggestive of asphyxia such as ABG should be obtained.
4. **Feeding History:** Lethargy, poor activity, drowsiness, and vomiting after feeding may be suggestive of inborn errors of metabolism. Late onset hypocalcemia should be considered in the presence of top feeding with cow's milk.
5. **Family History:** History of consanguinity, family history of seizures or mental retardation, previous fetal/neonatal deaths would be suggestive of inborn errors of metabolism (IEM). History of seizures in parents or in sibs in the neonatal period may be suggestive of benign familial neonatal seizures.

#### EXAMINATION

Vitals must be checked first and they should be stabilized without any delay. Gestational age, birth weight and weight for gestational age should be taken which may give clue to the cause of seizure. As seizure in a term baby may be due to subarachnoid hemorrhage whereas that in a LGA baby could be due to hypoglycemia. A neonate should be examined for any gross malformation or dysgenesis. Presence of a bulging fontanel is suggestive of meningitis or intracranial bleed. A detailed neurologic assessment including level of consciousness, tone, and presence of chorioretinitis should be done.

#### INVESTIGATIONS

1. **Mandatory investigations: (Should be done in all neonates with seizure)**  
Blood sugar, Hematocrit, Serum Electrolytes (Na, Ca, Mg), CSF, Cranial USG, EEG and serum bilirubin if jaundice is present. **CSF study has**

- to be done in all cases of seizures** as seizures may be the first sign of meningitis. It should not be omitted even if another etiology such as hypoglycemia is present, because meningitis can often co-exist. CSF study may be temporarily postponed if severe cardio-respiratory compromise or any other contraindication is present but one should try it as soon as these conditions have improved. An ABG may be performed if IEM is a strong suspicion. One should carry out all of the above investigations even if one or more investigations are positive, as multiple etiologies can co-exist.
2. **Specific investigations:** should be considered in cases who don't respond to combination drugs (e.g. phenobarbitone and phenytoin) or in neonates with specific features. These include neuroimaging (CT scan and MRI), TORCH screening and IEM screening.
    - a) **Neuroimaging:** USG should be done in all cases with seizures and is an excellent tool for detection of IVH and parenchymal hemorrhage but not very good in detecting subarachnoid hemorrhage (SAH) or subdural hemorrhage (SDH). CT scan should be done if the etiology is unknown after USG. CT scan can detect SAH and developmental malformations. MRI is indicated only if other investigations are unremarkable and seizures are persisting after the conventional anticonvulsant drugs. It can detect cerebral dysgenesis, lissencephaly and other neuronal migration disorders.
    - b) **TORCH** screening should be considered in the presence of severe IUGR, hepatosplenomegaly, thrombocytopenia and chorioretinitis.
    - c) **IEM** screening includes blood and urine ketones, urine reducing substances, blood ammonia, anion gap, urine and plasma aminoacidogram, serum and CSF lactate/pyruvate ratio.

3. **EEG:**<sup>2,5,6</sup> It has got both diagnostic as well as prognostic role in seizures. Ictal EEG may be useful in diagnosing suspected cases of seizures and also for diagnosis in hypotonic neonates. Unlike epilepsy in older children or in adults where EEG abnormality may persist for a long period of time, in neonatal seizures the EEG becomes rapidly normal once the ictal phase is over. Ictal EEG should be done as soon as possible. However, EEG facility in a neonate with active seizure is possible only when EEG facility is there in the neonatal unit itself and of course, there should be one trained personnel who can interpret the neonatal EEG. Except for a few advanced neonatal centers in India this ictal EEG is not always possible. However, once the baby is stable EEG may be done at the end of first week. This EEG has got prognostic value. If this EEG is abnormal then the baby has poor long-term prognosis. A background abnormality in both term and pre-term indicates a high risk of neurologic sequelae. These background changes include burst-suppression pattern, low voltage invariant pattern and electro-cerebral inactivity. EEG should be done for at least 1 hour.

#### TREATMENT<sup>2,5</sup>

1. **Initial medical management:** The first step is to nurse the baby in thermoneutral environment and ensure airway, breathing and circulation. If baby is apnoeic provide PPV and resuscitate the baby initially. O<sub>2</sub> should be started, secure IV access and blood should be collected for investigations. A brief relevant history should be done and quick clinical examination should be performed and all these should be completed within 2-5 minutes.
2. **Correct Hypoglycemia:** If glucoStix shows hypoglycemia or if glucoStix is not available then give 10% dextrose 2 ml/kg and if seizures are controlled then it should be followed by a continuous infusion of 6-8 mg/kg/min and managed as per hypoglycemia protocol.
3. **Correct Hypocalcemia:** If hypoglycemia has been excluded and seizures are persisting then give I.V. 10% calcium gluconate 1:2 dilution with 5% dextrose very slowly under cardiac monitoring. If seizures are controlled then continue calcium gluconate IV, 8 hourly or as infusion for at least 48 hours after serum calcium level becomes normal.
4. **Correct hypomagnesaemia:** If seizures persist even after calcium correction, inj. 50% MgSO<sub>4</sub> 0.2ml/kg single dose should be given. Some studies have suggested further that calcium administration leads to increased renal excretion of magnesium. Hence all infants treated for hypocalcemia should also receive magnesium.
5. **Phenobarbitone:** Loading dose is 20 mg/kg IV slowly (not faster than 1mg/kg/min). If seizures persist after completion of this loading dose, a repeat dose of 10 mg/kg IV slowly can be given and may be repeated till a total dose of 40 mg/kg. After this, chances of apnea and respiratory depression occur and hence it is better not to go beyond this dose. The maintenance dose is 5 mg/kg/d in 1-2 divided doses, started 12 hours after the loading dose.
6. **Phenytoin:** It is indicated when the maximum dose of phenobarbitone (40 mg/kg) fails to resolve seizures, or earlier if toxicity of phenobarbitone appears. The loading dose is 20 mg/kg after 1:2 dilution with normal saline slow IV at a rate not faster than 1 mg/kg/min. Phenytoin shouldn't be diluted in any dextrose containing fluid. Very fast infusion of phenytoin can lead to bradycardia, hypotension or other cardiac arrhythmias. A repeat dose 10 mg/kg may be given in refractory seizures. Phenytoin shouldn't be given by I.M. route as it may lead to tissue necrosis. However, fosphenytoin, a prodrug

of phenytoin, doesn't cause the same degree of hypotension or bradycardia, water soluble and can be given by I.M. route. It is dosed in phenytoin equivalents (1.5 mg/kg of fosphenytoin is equivalent to 1 mg/kg of phenytoin). It is available in India.

7. **Benzodiazepines:** If seizures are not controlled by phenytoin, then benzodiazepines should be added. However, benzodiazepines have been recommended even before phenytoin in many international protocols. A) Diazepam is avoided because of its short duration of action, narrow therapeutic index and because of the presence of sodium benzoate as preservative which can lead to dissociation of albumin-bilirubin complex and thus increase the risk of kernicterus in jaundiced infants. Dose of diazepam is 0.1 to 0.3 mg/kg IV may be repeated 1-2 times. B) Lorazepam is preferred due to its fast onset and long duration of action and less side effects. Dose: 0.05 to 0.1 mg/kg IV over 2-5 minutes may be repeated. C) Midazolam: Short acting and should be given very cautiously under cardio-respiratory monitoring as it may lead to respiratory depression, apnea and bradycardia. Dose: 0.1 to 0.2 mg/kg IV bolus followed by 0.1 to 0.4 mg/kg/hr.
8. **Pyridoxine:** Patients not responding still should receive inj. Pyridoxine. IV administration is the preferred route but IV preparation is not available in India. Hence, IM route may have to be used instead (e.g. inj. Neurobion contains 50 mg/ml and hence 1 ml each can be given IM into either the gluteal region or into the anterolateral aspect of thigh. Hypotension and apnea can occur. Patients should be diagnosed as pyridoxine dependent seizures and should receive pyridoxine at a maintenance dose of 10 to 100 mg/day for lifelong.
9. **Folinic acid:** Infants failing to respond to adequate doses of anticonvulsants and

pyridoxine warrant a trial of Folinic acid. The starting dose of enteral Folinic acid is 2.5 mg twice daily and may be increased up to 8 mg/kg/day.

#### **REFRACTORY SEIZURES<sup>5</sup>**

According to Volpe<sup>4</sup>, the expected response to anticonvulsants is 40% after the initial 20 mg/kg loading dose of phenobarbitone, 70% to a total of 40 mg/kg of phenobarbitone, 85% to loading dose of phenytoin (20 mg/kg), and 95 to nearly 100% to Lorazepam. After the trial of pyridoxine and Folinic acid all other seizures must have responded. However, in exceptional cases when seizures are refractory to the above mentioned protocol the second line of anti-convulsants may be tried.

1. **Lidocaine:** It has been used in Europe as an effective adjunctive anticonvulsant for neonatal seizures, usually after the failure of phenobarbitone and phenytoin. Start with 4 to 6 mg/kg/hr IV on first day. Once seizures are controlled, reduce by 1 mg/kg/hr on each subsequent day. In spite of its potential cardiac toxicity, the only adverse effect described in the reports is recurrence of seizures during the weaning period.
2. **Paraldehyde:** 0.1 -0.2 ml/kg/dose deep IM or 0.3 ml/kg/dose mixed with coconut oil 3:1 dilution per rectal may be given. Additional doses may be used after 30 minutes and then every 4-6 hourly. Adverse effects include pulmonary hemorrhage, pulmonary edema, hypotension and hepatic toxicity.
3. **Sodium valproate:** It can be used for maintenance therapy in neonates. IV preparation is available and the dose is 20-25 mg/kg/d followed by 5-10 mg/kg every 12 hours.
4. **Vigabatrin** (50 mg/kg/day) and **Topiramate** (3 mg/kg/d) may be used in refractory infantile spasms.
5. **Exchange transfusion:** It is indicated in life threatening metabolic disorders, accidental injection of anesthetic drugs, transplacental

transfer of maternal drugs and bilirubin encephalopathy.

seizures are uncontrolled with this or if toxicity appears then only add a second anticonvulsant drug or change to another one. The choice may vary from phenytoin, carbamazepine or valproic acid.

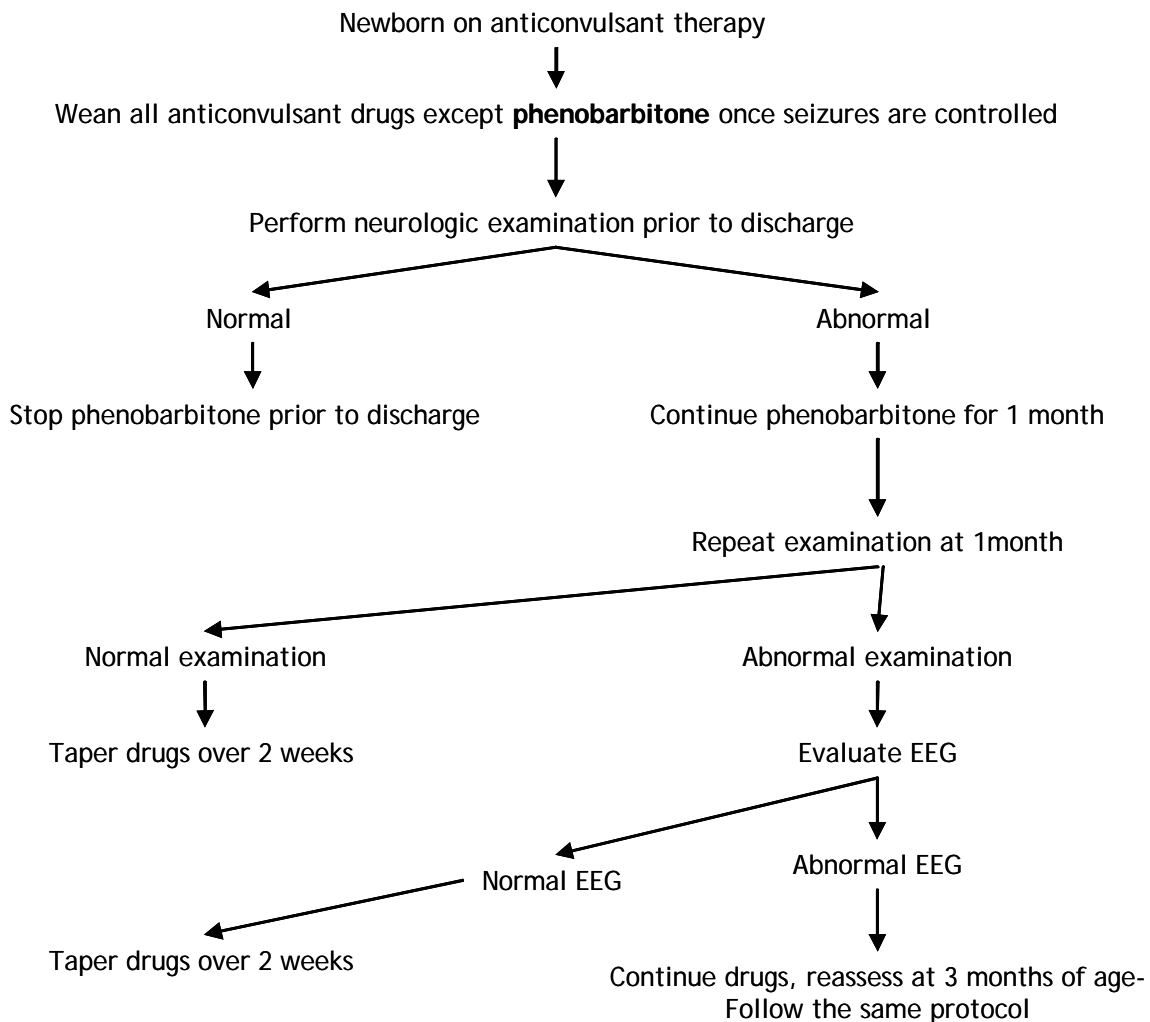
**Maintenance anti convulsants therapy**

Monotherapy is the most appropriate strategy as maintenance therapy to control seizures. All sincere efforts should be made to stop all anticonvulsant drugs and try to wean the baby to only phenobarbitone at a dose of 3-5 mg/kg/day. If

**When to discontinue anticonvulsant therapy?**

This part is highly individualized and there are many guidelines. The one which is practical and followed in many national institutes is the

*Flow diagram showing weaning and duration of anticonvulsant therapy<sup>4,5</sup>*



*Intractable seizures may need lifelong therapy, consider switching over to or adding other drugs if not controlled*

adaptation of Volpe protocol<sup>4</sup>. Try to discontinue all medications prior to discharge if the baby is clinically normal and seizure free, irrespective of etiology and EEG findings. However, in cases of cerebral dysgenesis or major CNS anatomical defects it's not wise enough to stop anticonvulsant drugs. If neurological examination is persistently abnormal at discharge, anticonvulsant drugs should be continued and the baby is reassessed at 1 month. If the baby is normal on examination and seizure free at 1 month, phenobarbitone is weaned over next 2 weeks and stopped. If the neurological assessment is abnormal, an EEG should be performed. If the EEG is not overtly paroxysmal, anticonvulsant drugs are tapered and stopped over next 2 weeks. If EEG is overtly abnormal then continue

anticonvulsant drugs and the infant is reassessed in the same manner at 3 months and then 3 monthly till 1 year of age.

***Prognosis according to etiology:***<sup>2</sup>

Etiology	Normal outcome (%)
HIE	50
Meningitis	50
Hypoglycemia	50
Subarachnoid hemorrhage	90
Early onset hypocalcemia	50
Late onset hypocalcemia	100
Dysgenesis	0
IVH	10
Unknown	75

**REFERENCES**

1. National Neonatal Perinatal Database. Report for the year 2002-03. National neonatology Forum, India.
2. Plessis AJ du. Neonatal seizures. In Manual of Neonatal Care. Cloherty JP, Eichenwald EC & Stark AR eds, Lippincott Williams & Wilkins, Philadelphia, Sixth edition 2008; pp 483-498.
3. Tekgul H, Gauvreau K, Soul JS et al. The current etiologic profile and neurodevelopmental outcome of seizures in term newborn infants. Pediatrics 2006; 117(4): 1270-1280.
4. Neonatal seizures. Neurology of the newborn. Volpe JJ, ed. 4th ed. Philadelphia: WB Saunders, 2001: 178-216.
5. Sankar MJ, Agarwal R, Aggarwal R, Deorari A, Paul VK. Seizures in the newborn. Indian J Pediatr 2008; 75 (2): 149-155.
6. Laroia N. Controversies in diagnosis and management of neonatal seizures. Indian Pediatr 2000; 37: 367-68.

## **Management of Kawasaki Disease**

**Rashna Dass**

*Associate Professor and I/C  
Department of Pediatric Disciplines,  
North Eastern Indira Gandhi Regional Institute of Health and Medical Sciences (NEIGRIHMS), Shillong*

---

### **ABSTRACT**

*Kawasaki disease is associated with the serious complication of development of coronary artery aneurysms and therefore management of the disease is an important issue. The mainstay of acute phase treatment remains intravenous immunoglobulin (IVIG) along with acetylsalicylic acid. However, the high cost of IVIG has prompted many other therapies being used increasingly in these patients. Long term management assumes importance in view of the fact that cardiac morbidity is very high with long term consequences. Interventional cardiac procedures and long term anti-lipids and anti-platelet agents have an important role to play.*

**KEY WORDS:** *Kawasaki disease, treatment, acute, long-term*

---

### **INTRODUCTION**

Kawasaki disease (KD) is an acute self-limited vasculitis of unknown aetiology occurring predominantly in infants and young children. It was first described in Japan by Tomisaku Kawasaki<sup>1</sup>. Though a self-limiting disease, the most dangerous complication that arises is the development of the coronary aneurysms in about 15 to 25% of untreated children and these may lead to myocardial infarction, sudden death, or ischemic heart disease<sup>2,3</sup>. Early diagnosis and management therefore assumes importance in this condition. IVIG has remained the mainstay of therapy along with aspirin. However alternative therapies are being increasingly used nowadays especially in resistant cases. Moreover various researchers and clinicians have also tried alternative therapies in view of the high cost of IVIG. The management of KD, discussed here,

will include the diagnosis as well as the treatment of the acute phase, difficult cases and the long term follow up.

### **DIAGNOSIS OF KD**

The diagnosis of KD is mostly clinical. The diagnostic criteria for KD have recently been modified to be more inclusive as shown in Table<sup>1</sup><sup>4</sup>.

### **LABORATORY TESTS**

The laboratory tests are used mostly to supplement the clinical diagnosis, identify cases with risks for failure with the initial treatment or to detect complications. There is however no pathognomonic laboratory tests for the diagnosis of KD. The hemogram reveals leukocytosis and in 50% of cases, the total white blood cell (WBC) count is >15,000/cumm. Leukopenia is rare. The anemia is normocytic normochromic in nature<sup>3</sup>. Severe hemolytic anemia is extremely rare and may be seen as a complication of IVIG therapy<sup>5</sup>. There is a universal elevation of the acute phase

---

**Corresponding Author:** *Dr Rashna Dass*

**E-mail:** *rashnadass@gmail.com*

**Table 1.** *New diagnostic criteria of KD<sup>4</sup>*

	<b>Criteria</b>
A	Fever for at least five days ( <b>mandatory criterion</b> ) plus
B	Four of the following five features: a) Changes in peripheral extremities or perineal area b) Polymorphous exanthema c) Bilateral conjunctival injection d) Changes of lips and oral cavity: injection of oral and pharyngeal mucosa e) Cervical lymphadenopathy
*	<b><i>In the presence of coronary artery involvement (detected on echocardiography) and fever, fewer than four of the remaining five criteria are sufficient</i></b>

reactants such as the erythrocyte sedimentation rate and C-reactive protein and they return to normal by 6-10 weeks of the illness. Platelet counts are usually normal in the first week of the illness, starts rising by the second week, peaks in the third week and normalizes by the fourth week of the illness. The platelet count ranges from >5,00,000 to 10,00,000 /cumm with a mean of 7,00,000/cumm. Thrombocytopenia is rare in the first week and if present indicates disseminated intravascular coagulation<sup>6</sup>. The joint fluid in those with arthritis will typically reveal purulent fluid with a WBC count of 1,25,000 to 3,00,000/cumm, a normal glucose level, and negative gram stain and culture<sup>7</sup>. Plasma lipids are markedly elevated in the acute phase but with low plasma cholesterol, high density lipoprotein (HDL) and apolipoprotein AI<sup>6</sup>. The liver enzymes are elevated moderately in less than 40% of the cases, about 10% of the cases have mild hyperbilirubinemia and approximately 67% have elevated plasma gammaglutamyl transpeptidase<sup>6</sup>. Hypoalbuminemia is common and associated with more severe and prolonged acute disease. The coagulation parameters may show an elevated prothrombin time, disseminated intravascular coagulation and D-dimer positivity. Sterile pyuria is seen in approximately 33% of the cases. About 50% of the cases show evidence of aseptic meningitis with the cerebrospinal fluid showing mostly mononuclear cells but normal glucose and

proteins. Troponin I is usually raised in acute KD but has no role in the routine management of KD<sup>6</sup>.

The changes in the electrocardiogram (ECG) are mostly secondary to myocarditis, pericarditis or myocardial infarction and may reveal arrhythmias, prolonged PR interval, non-specific ST-T wave changes and abnormal Q waves suggestive of myocarditis. Echocardiography is revealing and show specific changes in the acute, sub-acute and chronic phases of the illness<sup>6</sup>. Findings in the acute phase consist mainly of perivascular brightness of the coronary arteries, ectasia, lack of the normal tapering of the coronary arteries, decreased left ventricular contractility, mild aortic or mitral regurgitation (AR/MR) and pericardial effusions. In the sub-acute and chronic phases there is more severe involvement of the coronary artery musculature revealing frank coronary artery dilatation, aneurysm formation, stenosis, thrombosis in coronary arteries, calcification in coronary arterial walls (ring calcification), myocardial dysfunction and severe AR/MR.

#### **TREATMENT OF KD**

The treatment of KD consists of three phases: acute, convalescent and chronic or long term.

#### **Treatment of Acute KD**

The standard therapy of KD remains a single

dose of IVIG at 2g/kg given as an infusion over a few hours. Along with this, high dose aspirin at the dose of 80-100 mg/kg/day is given in three to four divided doses. In those with KD shock syndrome one would require to use inotropes such as dopamine, dobutamine or milrinone. IVIG produces a generalized anti-inflammatory activity and acts by the following possible mechanisms: Inhibition of the tumor necrosis factor  $\alpha$  (TNF $\alpha$ ) induced factor kappa-B activation, blockade of Fc $\gamma$  receptor expression on the membranes of monocytes/macrophages, direct anti-inflammatory effects on endothelial cell activation, neutralization of bacterial superantigens and augmentation of T-cell suppressor activity<sup>6</sup>. IVIG reduces the chances of development of coronary artery aneurysms (CAA) from 20-25% to 1-2%, causes prompt resolution of fever and also improves myocardial function in KD patients having myocarditis<sup>8,9</sup>. The reason for using a single high dose of IVIG is attributed to the findings that lower peak levels of IgG are associated with worse outcomes<sup>10</sup> and the greatest efficacy of treatment has been demonstrated with a higher dose of IVIG<sup>11</sup>.

#### **Can the dose of IVIG be reduced or titrated?**

The question of a dose reduction or titration of IVIG arose out of concerns for the high cost and affordability of IVIG in resource constrained settings, especially in developing nations or in nations where there were no means of governmental supply of IVIG. Moreover attempts at stratification of KD cases to high or low risk have been tried both clinically as well as by the use of laboratory parameters. Thus an ability to stratify KD cases can help to decide in reducing the initial dose of IVIG. Many authors have suggested that in the high risk cases, a high dose of IVIG at 2gm/kg can be used, whereas in low risk cases a lower dose at 1gm/kg can be used. Higher doses can also be used for those with huge cervical adenopathy and absence of conjunctival

injection. Others have suggested a step by step administration of IVIG starting with 1 gm/kg and then followed by a second dose of 1 gm/kg depending on the response. In a recent study involving 274 KD patients it was seen on retrospective analysis that a large proportion of patients (n=220) received a single dose of 1 gm/kg of IVIG versus 54 patients who received more than one dose of IVIG. On long term follow up it was found that the group who received a single dose of 1gm/kg of IVIG had coronary artery lesions (CAL) developing in 23.2% of cases in the acute phase and 6.4% in the convalescent phase versus 48.1% and 20.4% (p<0.05) respectively in the group which received more than one dose of IVIG. The authors concluded that this significant difference was probably because the group receiving more than one dose of IVIG were in higher risk stratification<sup>12</sup>. More and more authors believe that the dose of IVIG depends on the risk category of the patient.

#### **Risk Stratification in KD**

Various authors have described significant points to classify KD patients into high or low risk groups. KD patients are said to fall in the high risk group if they fulfil certain clinical criteria as enumerated in Table 2<sup>6,13,14</sup>.

#### **Treatment of KD in the convalescent phase**

The high dose aspirin is continued till 14 days even after the fever subsides followed by 3-5 mg/kg of Aspirin till 6-8 weeks or till there is resolution of the CALs.

#### **Treatment of difficult KD**

A small proportion (10-20%) of patients would not respond to the usual therapy and would require additional treatment. Failure of treatment or non-response is said to occur when there is persistent fever >38°C or recurrence of fever after the first 36 hours of the initial IVIG treatment. Such patients usually fall in the high

risk groups. The treatment options consist of a repeat dose of IVIG at 2gm/kg. Usually most patients would respond to the second dose. If fever still persists then a third dose of IVIG, pulse methylprednisolone at 30mg/kg/dose given as an infusion for three days. Infliximab, cyclophosphamide, methotrexate and plasma exchange therapy have all been tried with good response. However these are all anecdotal reports and no controlled studies are available as yet<sup>6</sup>. Many authors have also questioned in recent times whether steroids can be used as a first line along with IVIG. The current evidence shows that steroids with IVIG reduce the rate of re-treatment but do not decrease the incidence of coronary aneurysms or adverse events. Therefore the evidence is still not clear on this and more prospective studies would be required before recommendations in this regard can be made<sup>15</sup>.

#### Long term treatment of KD

Long term treatment would focus on prevention

of thrombosis in those patients with CALs. Anti-thrombotic therapy in KD is related to the severity of coronary artery involvement (Table 3).

#### Coronary artery aneurysms (CAA) in KD

CAA form the most serious complication of KD. The various factors responsible for development of CAA are a family history of KD, age less than 1 year, male sex, fever for > 14 days with double spikes, hemoglobin < 10 gm/dl, WBC count > 30,000/ cumm, platelets < 3 lakhs/ cumm, ESR > 101 mm, sodium < 135 meq/L, and serum albumin < 3gm/dl, atypical or incomplete KD and delayed administration of IVIG. A small proportion of cases may develop coronary artery stenosis.

#### Advanced evaluation of CAA<sup>6</sup>

Besides echocardiography, magnetic resonance imaging (MRI) and MR angiography (MRA) have been found to have good accuracy in detection of CAA and are especially useful for the

**Table 2.** Clinical findings to classify KD patients as high risk

Clinical findings	Values in question
Large cervical adenopathy	-
High S Bilirubin, SGOT & SGPT	-
Higher polymorphs in blood	>12,000/cumm
Lower platelet counts	<3.5 lakhs
Lower hematocrit	<35%
High ESR	>100 mm in one hour
Low albumin levels	<3.5 gm/dl
High CRP	3+
Young age	=12 month
Male sex	-
KD shock syndrome	Requiring inotropes

**Table 3.** Anti-thrombotic therapy in KD

Degree of coronary artery involvement	Anti-thrombotic treatment
Mild coronary involvement	Low dose aspirin
Mild to moderate coronary involvement	Aspirin with dipyridamole
Coronary aneurysm in rapid expansion	Heparin + Aspirin
Giant aneurysm	Warfarin + Aspirin

detection of peripheral artery aneurysms. Cardiac stress testing is useful to detect reversible ischemia. The various modalities available are nuclear perfusion scan with exercise, exercise echocardiography, myocardial contrast echocardiography using small air bubbles and stress echocardiography with dobutamine or dopamine in those children who cannot exercise such as young infants. Cardiac catheterization with angiography remains the gold standard for evaluation of CAA. It is usually recommended after 6 months of the illness when the acute inflammation is passive, or earlier, if indicated. Since the procedure is associated with its own risks, it is to be done only in complex CAA. Along with the coronary angiography, both abdominal and subclavian angiography are to be done to detect peripheral aneurysms most commonly seen in the subclavian, brachial, axillary, abdominal and renal arteries.

#### **Treatment of CAA**

The treatment of CAA includes the use of drugs to prevent thrombosis as discussed before in Table 3. Along with this, other modalities may be required for definitive therapy such as surgical correction, balloon angioplasty, stent placement, rotational ablation and fibrinolysis in established thrombus. The indications of definitive surgery include recurrent myocardial infarction, severe occlusion of the main trunk of the left main coronary artery, severe occlusion of >1 major coronary artery, severe occlusion of the left anterior descending artery and if the collaterals are in jeopardy<sup>6</sup>. Long term follow up and treatment of patients with CAA is important as studies have shown that giant aneurysms (>8 mm) do not regress at all whereas in those with moderate aneurysms ( $\geq 4$  mm to < 8 mm), more than 50% of the cases show no change in 2 years and at the end of 3 years 30% of the cases show no change. As far as small aneurysms (<4mm) are concerned, most regress in 2 years but 4% of

cases have persistent aneurysms at the end of 5 years<sup>16</sup>.

#### **Long term follow up in KD**

Long term follow up in KD is important as studies have found by the use of intravascular ultrasound (IVUS) that patients of KD with CALs have premature coronary atherosclerosis, stenosis of coronary arteries, left ventricular dysfunction, ventricular tachycardia, sudden death due to rupture of CAA and persistent lipid abnormalities. In view of these findings the long term follow up of the KD patient is important and should be done as depicted in Table 4.

#### **Use of statins in KD with Coronary artery abnormalities**

IVUS and histopathologic studies suggest that there is extensive fibro-intimal changes which take place in KD patients even if there is regression of the CALs. There is extensive infiltration of lymphocytes and plasma cells in the coronary artery walls which continue to occur over many years. Along with this there is increased systemic endothelial dysfunction and lipid abnormalities in KD patients. Statins improve the endothelial dysfunction, inhibit inflammation, stabilize the atherosclerotic plaques, moderate procoagulant activity and platelet function and also increase nitric oxide function which in turn promotes re-endothelialization. So overall statins are beneficial in KD. Studies have shown statins to be safe at a dose of 10 mg/day in children<sup>18</sup>.

#### **CONCLUSION**

In spite of more than 40 years of the first description of KD by Dr Tomisaku Kawasaki and subsequent experiences from various parts of the world, KD still remains an enigma. The diagnostic criteria have changed little over the years. Attempts are now on to have more inclusive criteria for the diagnosis and management of the disease. Considering the risk of development of

**Table 4. Long term follow up of KD<sup>17</sup>**

<b>Risk level</b>	<b>Drugs</b>	<b>Physical activity</b>	<b>Follow up non- Invasive tests invasive tests</b>	
I: No coronary inv. at any stage	None beyond 6-8 weeks	No restriction beyond 6-8 weeks	None after 1 year	None
II: Transient coronary ectasia - disappear during 6-8 weeks (convalescence)	Same	Same	Every 3-5 years	None
III: Small to medium solitary aneurysm	Aspirin: 3-5 mg/kg/day	Age <10 yr: No limitation >10 yr-directed yearly stress test ± : No Physical Training	Yearly Echo Stress testing	Angiography if stress Echo positive
IV: One / more giant aneurysm or multiple small to medium aneurysm without obstruction	Long term aspirin ± Warfarin OR LMWH	Discourage recreation sports	6 monthly Echo Yearly stress test	Angiography if stress positive
V: Coronary artery obstruction	Aspirin ± Warfarin Anti-ischaemics	Recreational sports to be avoided	6 monthly Echo and stress test	Angiography if stress test changes in symptomatics

[LMWH = Low molecular weight heparin]

the CALs, one should treat KD whenever KD is suspected or thought of. Treatment should be early. The drug of choice still remains IVIG at a dose of 2 gm/kg along with high dose aspirin as per current recommendations preferably within the first 10 days. However, even if patients come after 10 days, IVIG must be given to reduce the intense inflammation in the coronary arteries. There is no recommendation as yet of the maximum time beyond which IVIG should not be given. A certain group of patients with high risk factors may not respond to the initial dose of IVIG. In such patients repeat doses of IVIG (if affording) or other alternatives may be tried. Risk stratification at diagnosis may help to identify the recalcitrant cases. More studies are required for the use of steroids as a first line agent or for a step wise use of low dose IVIG. Extensive

evaluation is required for those patients who develop CALs. In established CALs, management consists of prevention of thrombosis, use of statins, treatment of thrombus and occasionally surgical or interventional therapy. Long term follow up is important because coronary artery abnormalities can progress and lead to development of early and accelerated atherosclerosis even after lesions have regressed on echocardiography. The biggest study from India has shown that response to therapy with IVIG is usually prompt and repeat courses of IVIG are not required<sup>19</sup>.

#### REFERENCES

1. Kawasaki T. Acute febrile mucocutaneous syndrome with lymphoid involvement with specific desquamation of the fingers and toes in children (in Japanese). *Arerugi* 1967; 16: 178.

2. Kato H, Sugimura T, Akagi T, Sato N, Hashino K, Maeno Y *et al*. Long term consequences of Kawasaki disease. A 10- to 21 year follow-up study of 594 patients. *Circulation* 1996; 94: 1379-1385.
3. Dajani AS, Taubert KA, Gerber MA, Shulman ST, Ferrieri P, Freed M *et al*. Diagnosis and therapy of Kawasaki disease in children. *Circulation* 1993; 87: 1776-1780.
4. S Ozen, N Ruperto, M J Dillon, A Bagga, K Barron, J C Davin, T Kawasaki, C Lindsley, R E Petty, A M Prieur, A Ravelli, P Woo. EULAR/PReS endorsed consensus criteria\* for the classification of childhood vasculitides. *Ann Rheum Dis* 2006; 65: 936-941.
5. Shulman ST. Hemolysis in Kawasaki disease. *Transfusion* 1991; 31: 572.
6. Newburger JW, Takahashi M, Gerber MA, Gewitz MH, Tani LY, Burns JC *et al*. Diagnosis, treatment and long term management of Kawasaki disease. *Circulation* 2004; 110: 2747-2771.
7. Hicks RV, Melish ME. Kawasaki syndrome. *Pediatr Clin North Am* 1986; 33: 1151-1175.
8. Singh S, Kawasaki T. Kawasaki disease- An Indian perspective. *Indian Pediatrics* 2009; 46: 563-571.
9. Rowley AH, Shulman ST. Kawasaki disease. *Clin Microbiol Revs* 1998; 11(3): 405-14.
10. Durongpisitkul K, GururajVJ, Park JM, Martin CF. The prevention of coronary artery aneurysm in Kawasaki disease: a metanalysis on the efficacy of aspirin and immunoglobulin treatment. *Pediatrics* 1995; 96(6): 1057-61.
11. Terai M, Shulman ST. Prevalence of coronary artery abnormalities in Kawasaki disease is highly dependent on gamma globulin dose but independent of salicylate dose. *J Pediatr* 1997; 131(6): 888-93.
12. Yeo JS, Choi JW. Effectiveness of medium-dose intravenous immunoglobulin (1 g/kg) in the treatment of Kawasaki disease. *Korean Circ J* 2010; 40: 81-85.
13. Cha S, Yoon M, Ahn Y, Han M, Yoon KL. Risk factors for failure of initial intravenous immunoglobulin treatment in Kawasaki disease. *J Korean Med Sci* 2008; 23: 718-722.
14. Kanegaya JT, Wilder SM, Molkara D, Frazer JR, Pancheri J, Tremoulet AH *et al*. Recognition of a Kawasaki disease shock syndrome. *Pediatrics*. 2009; 123 (5): e783-e789.
15. Attappan G, Gale S, Ponniah T. Corticosteroid therapy for primary treatment of Kawasaki disease - weight of evidence: a meta-analysis and systematic review of the literature. *Cardiovasc J Afr* 2009; 20: 233-236.
16. Akagi T, Rose V, Benson LN, Newman A, Freedom RM. Outcome of coronary artery aneurysms after Kawasaki disease. *J Paed* 1992; 121 (5Pt.1): 689-94.
17. Freeman AF, Shulman ST. Summary of the American heart association guidelines. *Am Family Physician* 2006; 74(7): 1141-1148.
18. Huang Sm, Weng KP, Chang JS, Lee WY, Huang SH, Hsieh KS. Effects of statin therapy in children complicated with coronary arterial abnormality late after Kawasaki disease- a pilot study. *Circ J* 2008; 72: 1583-1587.
19. Singh S, Bansal A, Gupta A, Manojkumar R, Mittal BR. Kawasaki disease - A decade of experience from North India. *Int Heart J* 2005; 46: 679-689.

## **Cardiovascular manifestations of HIV in pediatric population**

**Radha Binod Pal\*, Subhasish Bhattacharyya\*\***

*\*Junior Resident, Deptt of Pediatrics, Medical College & Hospital, Kolkata*

*\*\* Associate Professor, Deptt of Pediatrics, Medical College & Hospital, Kolkata.*

*Nodal Medical Officer, Regional Pediatric ART Centre, Medical College & Hospital, Kolkata.*

### **INTRODUCTION**

The link between HIV infection and heart disease was established early in the history of the AIDS pandemic<sup>1</sup>. The incidence of cardiovascular disease reported amongst HIV infected children ranges from 72% to over 90%<sup>2,3</sup>. HIV virus involves multiple organ systems. The heart is one of the major organs to be targeted by the direct effects of HIV infection and by secondary opportunistic infections caused as a result of the acquired immunodeficiency.

The pathogenesis is multifactorial including direct toxic effects, viruses, autoimmunity, nutritional deficiencies and drugs. The common cardiovascular manifestations include cardiomyopathy, myocarditis, pericarditis, cardiac arrhythmias and chronic congestive heart failure.

Lipodystrophy, caused by antiretroviral therapy is common and may be a risk factor in ischemic heart disease.

Subclinical cardiac abnormalities in HIV infected children are common, persistent and often progressive<sup>4</sup>.

### **PATHOGENESIS**

The exact mechanism by which HIV induces cardiac disease is not completely clear although there are a lot of hypotheses. Some of the possible mechanisms are direct toxic effects of the HIV virus on cardiac myocytes, other co-existing

cardiac opportunistic infections, autoimmunity, drug related cardiotoxicity and nutritional deficiencies.

### **Probable mechanisms involved in pathogenesis of HIV induced cardiac disease**

- A) Intracellular HIV in cardiac myocytes causes myocarditis and cardiomyopathy. This is caused by direct toxic effect of the virus. The myocardial dendritic cells may play an important role in the mechanism of entry of the virus into the myocytes.
- B) Cardiotropic opportunistic viral infection - coxsackie group B virus, Epstein-Barr virus, cytomegalo virus etc.
- C) Autoimmune processes involving major histocompatibility complex class I molecules, anti alpha-myosin autoantibodies and cytokines such as tumor necrosis factor  $\alpha$  (TNF- $\alpha$ ) and inducible nitric oxide synthase (iNOS).
- D) Nutritional deficiencies - selenium, carnitine and thiamine.
- E) Cardiotoxic drug use - antiretrovirals, interferon alpha, doxorubicin, other antiviral and antifungal drugs.

### **CLINICAL MANIFESTATIONS OF HIV INDUCED HEART DISEASE**

HIV is known to affect, directly or indirectly, every structural aspect of the heart including the pericardium, myocardium, endocardium and the coronary vessels. HIV associated cardiomyopathy

---

**Corresponding Author:** Dr Radha Binod Pal

**Email:** rbinod100@gmail.com

is in clinical stage 4 disease in revised WHO clinical staging of HIV/ AIDS for infants and children.

### **Pericardial disease**

Involvement of pericardium is common in HIV infected patients and could result in pericardial effusion, pericarditis, cardiac tamponade or constrictive pericarditis. In HIV infected children, pericardial effusions occur almost exclusively in those with AIDS. Causes of pericardial effusion in AIDS patients include infection with *Staphylococcus aureus*, *Mycobacterium tuberculosis*, *Streptococcus pneumoniae*, *Cryptococcus neoformans* as well as other microorganisms. Adenocarcinoma, Kaposi's sarcoma and lymphoma may also rarely cause pericardial effusion in HIV infected patients<sup>5-9</sup>. However, in the majority of cases, a specific cause of the effusion cannot be identified.

Several theories exist to explain the pathogenesis of these idiopathic effusions. They include "capillary leak syndrome", cytokines such as interleukin-2 and tumor necrosis factor which are elevated in end-stage AIDS and the direct effect of the HIV virus itself.

AIDS patients with pericardial effusion tend to have a lower CD4 count than those without pericardial effusion and those with pericardial effusion also tend to have a shortened survival (36 percent mean 6 month survival vs 93 percent) independent of albumin levels and CD4 counts<sup>10</sup>.

### **Myocardial and valvular disease**

HIV associated myocardial and valvular disease is manifested as dilated cardiomyopathy, left ventricular hypertrophy, myocarditis, ischemic heart disease, cardiac arrhythmias, second degree heart block and neoplastic invasion from lymphoma or Kaposi's sarcoma. Right ventricular involvement can also stem from HIV related pulmonary disease.

### **Cardiomyopathy**

Dilated cardiomyopathy in AIDS patients is

strongly associated with depressed CD4 cell count. Patients are known to have significant left ventricular dysfunction. Compared to ischemic or idiopathic cardiomyopathy, HIV related cardiomyopathy has an extremely poor prognosis. It is shown that monthly IV infusion of immune globulin improves left ventricular function in HIV infected patients thought to be immunologically mediated<sup>11</sup>.

### **Myocarditis**

Myocarditis is a common cause of left ventricular dysfunction. It could be caused by the cytotoxic action of the HIV virus itself or by accompanying opportunistic infections such as cytomegalovirus, coxsackie virus, Adenovirus, *Candida albicans*, *Cryptococcus neoformans* or *Toxoplasma gondii*.

### **Ischemic heart disease & hypertension**

A possible reason for accelerated coronary artery disease in HIV-infected patients is stimulation of local monocyte-macrophages by the virus. A wide range of inflammatory vascular diseases (e.g. polyarteritis nodosa, Henoch-Schönlein purpura, drug-induced hypersensitivity vasculitis) occur in HIV-infected individuals<sup>12</sup>. Vascular inflammation appears multifactorial and may result from HIV-induced immunological abnormalities and exposure to xenoantigens such as HIV-1 itself, other infectious agents and drugs<sup>12</sup>.

Coronary artery disease is observed with increasing frequency among HIV patients receiving therapy with protease inhibitors (PI) in the ambit of Highly Active Anti Retroviral Therapy (HAART) regimens<sup>13</sup>. Despite the clinical benefits of PI therapy, complications such as lipodystrophy, insulin resistance, and high levels of low-density lipoprotein cholesterol and triglyceride develop in patients treated with these regimens<sup>13</sup>.

HIV patients are at higher risk of becoming hypertensive than the general population, and hypertension develops at a younger age<sup>14</sup>.

Predisposing factors include vasculitis in small, medium, and large vessels in the form of leukocytoclastic vasculitis, atherosclerosis secondary to HAART regimens, and aneurysms of the large vessels such as the carotid and femoral arteries and the abdominal aorta, with impairment of flow to the renal arteries<sup>14</sup>.

### **Pulmonary hypertension and right ventricular dysfunction**

Pulmonary hypertension is also being recognized as a serious complication of HIV infection. It could occur both in the early and late stages of HIV infection and is not related to the degree of immuno-suppression.

Patients present with progressive shortness of breath, effort intolerance, exertional dyspnea, pedal edema, non productive cough, fatigue, syncope or chest pain. Examination reveals increased intensity of P2, with P2 being louder than A2, right sided S3 and S4 gallop, murmurs of tricuspid and pulmonary regurgitation, increased jugular venous pressure and peripheral edema. Diagnosis is made after ruling out all other secondary causes.

Chest X-ray generally reveals enlarged central pulmonary arteries and clear lung fields, but could be entirely normal in early stages of the disease. Electrocardiogram is usually significant with right axis deviation and right ventricular hypertrophy with tall P waves in leads II, III and aVF, tall R waves in V1 and abnormal S waves in V5 and V6. Complete or incomplete right bundle branch block may also be present. Transthoracic echocardiography usually reveals systolic flattening of the interventricular septum, enlarged right atrium and ventricle and a reduction in both left ventricular systolic and diastolic dimensions. The gold standard test for diagnosis of pulmonary hypertension however is cardiac catheterization.

Treatment of pulmonary hypertension is not different in HIV patients and is as unsatisfactory

as in non HIV infected patients. Vasodilators such as calcium channel blockers are the mainstay of therapy. Other medications that could be used are orally active prostacyclin, beraprost sodium, carvedilol and anticoagulants. Pulmonary hypertension tends to be more aggressive in HIV patients than in those without HIV. The median survival of HIV infected patients diagnosed with pulmonary hypertension is only about 1.3 years<sup>15</sup>.

### **Lipodystrophy**

Lipodystrophy caused by antiretroviral therapy is a syndrome characterized by peripheral fat loss from face, limbs and buttocks, and central fat accumulation in abdomen, breasts and over the dorso-cervical spine. Metabolic features associated with the syndrome include hypertriglyceridemia, hypercholesterolemia, insulin resistance and type 2 diabetes mellitus. It is thought to be highly prevalent in HIV infected patients receiving antiretroviral therapy, especially those receiving stavudine & protease inhibitors. Though incidence of lipodystrophy in children is less than adults infected with HIV, use of HAART increases risk of coronary heart diseases in pediatric population. As children are more vulnerable than adults to cumulative metabolic side effects, monitoring fasting lipids and body composition is suggested in order to add diet and life style suggestions.

### **CONTRIBUTORS**

RBP acts as manuscript writer & SB revised the manuscript. The manuscript is finally approved by both authors.

### **REFERENCES**

1. Autran B *et al.* AIDS in a Haitian woman with cardiac Kaposi's sarcoma and Whipple's disease. *Lancet* 1983. 1: p767.
2. Luginbuhl LM, Orav EJ, McIntosh K, Lipshultz SE. Cardiac morbidity and related mortality in

- children with HIV infection. *JAMA* 1993;269:2869-2875.
3. Lipshultz SE, Easley KA, Orav EJ, et al. Cardiovascular status of infants and children of women infected with HIV-1 (P2C2 HIV): a cohort study. *Lancet*. 2002;360:368-373
  4. Ram Yogev, Chadwick EG. Acquired Immunodeficiency Syndrome (Human Immunodeficiency Virus). In: Kliegman RM, Behrman RE, Jenson HB, Stanton B, eds. *Nelson Textbook of Pediatrics*. 18th ed. Vol. I, Saunders, Philadelphia, 2007, p.1427-1443.
  5. Flum, D.R., J.T. McGinn, D.H. Tyras: The role of the "pericardial window" in AIDS. *Chest* 107, 1995,1522-1525.
  6. Decker C, C.U. Tuazon: Staphylococcus aureus pericarditis in HIV infected patients. *Chest* 105,1994, p. 615-616.
  7. Karve M, Murali MR, Shah HM, Phelps KR: Rapid evolution of cardiac tamponade due to bacterial pericarditis in two patients with HIV-1 infection. *Chest* 101,1992, p.1461-1463.
  8. Sunderam G, Maniatis RJ, Oleske J, Kapila R, Reichman LB : Tuberculosis as a manifestation of the acquired immunodeficiency syndrome. *JAMA*, 1986, 256, 362-366.
  9. Zuger A, Louie E, Holzman RS, Simberkoff MS, Rahal JJ: Cryptococcal disease in patients with the acquired immunodeficiency syndrome: diagnostic features and outcome of treatment. *Ann Intern Med* 1986, 104, p234-240
  10. Heidenreich P, Eisenberg M, Kee L, Somelofski CA, Hollander H, Schiller NB, Cheitlin MB : Pericardial Effusions in AIDS: Incidence and Survival, *Circulation* 1995, 92 (11) 3229-3234.
  11. Park MK. Cardiovascular Infections. *Pediatric Cardiology for Practitioners*, 5th ed., Elsevier, Noida, 2008, p380.
  12. Gherardi R, Belec L, Mhiri C, et al. The spectrum of vasculitis in human immunodeficiency virus-infected patients. A clinicopathologic evaluation. *Arthritis Rheum* 1993; 36:1164 -74.
  13. Rerkpattanapipat P, Wongpraparut N, Jacobs LE, Kotler MN. Cardiac manifestations of acquired immunodeficiency syndrome. *Arch Intern Med* 2000;160: 602-8.
  14. Aoun S, Ramos E. Hypertension in the HIV-infected patient. *Curr Hypertens Rep* 2000; 2: 478 -81.
  15. Pellicelli P, Palmieri F, Cicalini S, Fabrizio NP : Pathogenesis of HIV-related Pulmonary Hypertension, HIV Associated Cardiovascular Disease. *Ann NY Acad Sci* 946, 2001,82-94.

## PEDIATRIC TWEETS

### **Elective high frequency oscillatory(HFOV) vs conventional ventilation in preterm infants-the controversy refuses to die.**

In this study published in the Lancet, data from 3229 participants from ten randomised controlled trials, showed that the relative risk of death, broncho-pulmonary dysplasia at 36 wks post menstrual age, and severe adverse neurological event were no different in infants ventilated with HFOV compared to conventional ventilation.

The study does not support the selection of preterm infants for HFOV on the basis of gestational age, birth weight or exposure to antenatal steroids. They suggest that HFOV seems equally effective in comparison to conventional ventilation in preterm infants.

*Cools P, Ashie LM, Offringa M and PreVILIG collaboration. Elective HFOV vs conventional ventilation in preterm infants: a systematic review and meta analysis of individual patient data. The Lancet. Vol 375, Issue 9731, pp. 2082-2091, 12 June 2010.*

### **FDA issues new contraindications for rotavirus vaccines while allowing its use despite finding new viral contaminants.**

Although Porcine Circovirus-1(PCV-1) has been found in Rotarix and PCV-1 and PCV-2 DNA has been found in Rotateq, but it has been shown to be present throughout product development and is not infective to humans(see [www.fda.gov](http://www.fda.gov)).

A new contraindication is infants with severe combined immunodeficiency (SCID) as they are shown to have rotavirus vaccine-associated diarrhoea and prolonged viral shedding.

A new interim Vaccine Information Statement is available at [www.cdc.gov/vaccines/pubs/vis/downloads/vis-rotavirus.pdf](http://www.cdc.gov/vaccines/pubs/vis/downloads/vis-rotavirus.pdf).

*Willoughby RE, FDA gives OK to use rotavirus vaccines, adds contraindications. AAP News, 2010 DOI:aapnews.20100526-1*

### **New Percentile Charts :A study giving reference ranges for Oxygen saturation levels immediately after birth in normal premature and term babies.**

In a study of 468 infants ,61650 SpO2 data points were recorded in the first 10 minutes after birth in infants who received no medical interventions including supplemental oxygen after birth. 3rd-97th percentiles were given for each of the 10 min. in separate charts for term >37 wks, preterms 32-36 wks, and extremely preterm infants <32 wks. Interestingly it took a median of 7.9 min to reach an SpO2 value of >90%.

*Dawson JA, Defining the Reference Range for Oxygen Saturation for Infants After Birth. Paediatrics Vol.125 No. 6 June 2010 pp e1340-e1347.*

### **Is ADHD a valid diagnosis in adults?**

The unfortunate answer is Yes. The authors of this article use the Washington University criteria for the National Institute for Health and Clinical Excellence (NICE) study as the DSM IV criteria are for children only.

Follow up studies of children with ADHD showed that 65% of them have ADHD as adults (15% with full diagnosis and a further 50% in partial remission). They suggest that common problems like forgetting car keys, unemployment and criminal convictions can be traced to ADHD.

Critics say that this provides drug companies an "expanding and lucrative market" for stimulant and related drugs as in contrast to children, stimulants are prescribed as 1st line drugs for adult ADHD

*Asherson P, Adamou M, Bolea B. Is ADHD a valid diagnosis in adults? BMJ, 2010;340:c547 published on 3 Apr 2010.*

### **The continuing problem of Staph infections.**

In this study, 64813 patients were enrolled from 25 children's hospitals in US from 1999-2008. Here it was found that the incidence of MRSA increased 10 fold during the period of study whereas the incidence of MSSA remained the same. Clindamycin emerged as the most commonly prescribed antibiotic for staph infections in hospitalised children. In India, we are yet to set up a database to monitor the incidence and the antibiotic susceptibility of this common pediatric infection.

*Herigon JC et al. Antibiotic management of staph. aureus infections in US children's Hospitals, 1999-2008. Paediatrics Vol. 125, No 6, June 2010 pp e1294 -e1300.*

### **Pertussis vaccine induced encephalopathy and**

### **Dravet's syndrome-Effect of vaccination on onset and outcome.**

Pertussis vaccination has been alleged to cause an encephalopathy that involves seizures and subsequent intellectual disability. Previous studies showed that 11 of 14 patients with so called vaccine encephalopathy had Dravet's syndrome, a disorder associated with mutations of sodium channel gene SCN1A. This study showed that vaccination might trigger an earlier onset of Dravet's syndrome in children, but found that vaccination should not be withheld from children with SCN1A mutations, because there is no evidence that vaccination affects outcome.

*McIntosh AM, McMahon J, Dibbens LM et al . Effect of vaccination on onset and outcome of Dravet's syndrome: a retrospective study. The Lancet Neurology Vol 9, Issue 6, pg 592-598, June 2010.*

**Compiled by  
Sandip Sen**

*Associate Professor, Pediatrics, CNMCH, Kolkata  
Email: drsandipsen@yahoo.com*

# The 22nd National Conference of Pediatric Nephrology

**Dates:** 12th November (Friday) 2010: Workshop on Renal Imaging (limited seats)  
13th and 14th November (Sat & Sun) 2010: Conference  
**Venue:** Swabhumi, Kolkata, India

## Registration fees (Rs):

Last date	30/04/10		31/08/10		thereafter	
	Conference	Workshop	Conference	Workshop	Conference	Workshop
IAP/ISPN members	1500	500	2000	500	2500	500
Postgraduates	1200	300	1700	300	2200	300

DD/Cheques in favour of "PENCON 2010" payable at Kolkata. Please add Rs 50/- for outstation cheques.

**Conference Secretariat:** WBAP Office, "Oriental Apartment", 15C Canal Street, Flat H1, Kolkata 700014.  
Phone: 033 22654072, email: pencon2010@gmail.com

**Enquiries:** Dr Jayati Sengupta 9831171123 or Dr Mousumi Nandi 9432674488

**Abstract Submission** last date 15/8/10, for details contact Dr SK Patnaik 9903618684

## HIGHLIGHTS OF SCIENTIFIC PROGRAM

### Workshop

Application of different imaging modalities in pediatric nephrology (USS, Doppler, MCU, IVU, Radio-isotopes, CT and MRI)

### Chronic Kidney Disease

Nutrition and Growth  
Anemia  
Bone Disease  
Retarding Progression  
Complications of dialysis  
Optimising Dialysis  
Long term outcome of dialysis and transplantation

### Panels

Common Renal diseases: ask the experts  
Nephrotic Syndrome

### Guest Lectures

The Hypertension Epidemic  
Immunisations in renal disease  
Renoprotective strategies in critical care

### Updates

UTI / VUR  
Tubulopathies  
HUS

### New Immunomodulatory medications

In Nontransplant renal disease  
In Renal Transplantation  
In Indian Transplant protocols

### Case based discussion

Hydronephrosis  
Incontinence  
Hematuria

## INTERNATIONAL FACULTY

Dr Lesley Rees (London, UK)

Dr Dieter Haffner (Rostock, Germany)

Dr David Milsford (Birmingham, UK)

Dr Melanie Hiorns (London, UK)

## NATIONAL FACULTY

Dr AS Vasudeva (Delhi), Dr Arvind Bagga (Delhi), Dr BR Nammalwar (Chennai), Dr Indira Agarwal (Vellore), Dr Kishore Phadke (Bangalore), Dr Kumud Mehta (Mumbai), Dr M Vijaykumar (Chennai), Dr Madhuri Kanitkar (Pune), Dr Mehul Shah (Hyderabad), Dr Pankaj Hari (Delhi), Dr RN Srivastava (Delhi), Dr Sanjeev Gulati (Delhi), Dr Uma Ali (Mumbai), Dr Vinay Aggarwal (Delhi), and others.

**Hosts:** INDIAN SOCIETY OF PEDIATRIC NEPHROLOGY & WESTBENGAL ACADEMY OF PEDIATRICS

**Chairpersons:** Dr Amitava Pahari and Dr Sushmita Banerjee **Organising Secretary:** Dr Jayati Sengupta

**Treasurer:** Dr Mousumi Nandi **Scientific Secretary:** Dr SK Patnaik **Publications Secretary:** Dr Sanat Ghosh

## CASE REPORT

### Unilateral Amastia

**Bhaswati Ghoshal\*, Rita Chatterjee\*\***

\* Assistant Professor, Department of Pediatric Medicine, Calcutta National Medical College & Hospital, Kolkata, \*\* Associate Professor, Department of Pediatric Medicine, Medical College, Kolkata

---

#### ABSTRACT

Isolated unilateral complete absence of breast tissue with nipple and areola on one side is a rare entity. An otherwise normal female infant presented with unilateral absence of breast, nipple, areola and bilateral preauricular sinus. No other associated congenital anomaly was found.

**KEY WORDS:** Amastia

---

#### INTRODUCTION

Isolated unilateral amastia is sporadic and exact incidence is not known. It occurs as a result of arrested growth of mammary ridge at early weeks of intrauterine development. Bilateral preauricular sinus with unilateral amastia is not reported in literature.

#### CASE REPORT

A six weeks old female infant attended to Pediatric O.P.D. with complete absence of breast on right side. The infant was delivered at home at term by a primi mother. The perinatal period was uncomplicated. Birth weight was not recorded. There was history of first degree consanguinity among parents. There was no family history of similar illness. Infant was exclusively breastfed. On clinical examination, body weight was 3.5 kg and head circumference was 36 cm. The areola, nipple, breast tissue were not palpable on right side. (Fig-1) There was no asymmetry of chest wall. Rib cage appeared normal clinically. External genitalia was normal. There was bilateral



**Fig. 1 . Infant with right sided amastia**

---

**Corresponding Author:** Dr Bhaswati Ghoshal

**E-mail:** bhaswatighoshalmailme@yahoo.com

preauricular sinus. There was no history of discharge from preauricular sinus. No external ear deformity was noticed.

On investigation, hemogram was within normal limits. Chest X ray did not reveal any abnormality of rib cage. USG abdomen was normal. Auditory brainstem evoked response did not reveal any abnormality.

## DISCUSSION

The breast is a highly modified sudoriferous gland that develops as an ingrowth of ectoderm. The supporting vascularised connective tissue is derived solely from mesenchyme. At the 5th or 6th week of foetal development two ventral bands of thickened ectoderm (mammary ridge or milk lines.) are evident in the embryo. In the majority of the class mammalia, paired glands develop along this ridge and extend from the base of the fore limb (future axilla) to the region of hind limb (inguinal area). This ridge is not prominent in the human embryo and disappear shortly thereafter, except for a small portion that may persist in the pectoral region<sup>1</sup>.

Amastia occurs as a result of arrested growth of mammary ridge around 6 weeks of fetal development<sup>1</sup>. Typically, bilateral amastia is not associated with other anomalies<sup>1</sup>. By contrast, unilateral variety may be associated with absence of pectoralis major and minor muscles, costal cartilage and rib defects, hypoplasia of subcutaneous tissues of chest wall and of ipsilateral hand (Poland syndrome)<sup>2</sup>. The additional defects reported sporadically include hemivertebrae, renal anomalies, dextrocardia and Sprengel deformity, absent phalanges or digits and hypoplasia of forearm, wrist and hand<sup>3,4,5</sup>. The incidence of Poland Syndrome is 1 in 20,000 live births with about 10% of patients with syndactyly demonstrating features of the syndrome<sup>4</sup>. The present case does not have the muscle and rib abnormalities of Poland Syndrome. More than, 75% of the defects associated with

this syndrome are present on the right side<sup>6</sup>.

In his 1841 autopsy note, Poland referred to the hypoplastic appearance of the thoracic vessels supplying the intercostal spaces<sup>7</sup>. Others have postulated that the underlying cause of this disorder is a congenital vascular mal-development in which arterial vasospasm or vessels malformation could result in hypoxia to one side of the fetus as the limb bud develops adjacent to the chest wall. Bouvet et al described stenosis of the left subclavian artery in a child with Poland Syndrome affecting the left side<sup>8</sup>. Intrauterine insults resulting in the formation of thrombi or thrombotic emboli within the placenta have also been suggested as cause of Poland Syndrome<sup>5</sup>. Vasospasm induced by various drugs has also been postulated as a possible mechanism of inducing adverse effects in developing fetus<sup>9</sup>. Exact etiology of isolated amastia is not known. The localized disruption of vascular supply may be the cause.

Kumar V et al from Banaras Hindu University reported an unusual association of esophageal atresia and tracheoesophageal fistula and left amastia with high variety of anorectal malformation, hypospadias and absent left pectoral muscle with weak shoulder girdle<sup>10</sup>. The esophageal and anorectal anomalies are absent in our case.

The index case has bilateral preauricular sinus. Preauricular sinuses are of congenital origin arising from faulty developmental closure of the hillocks of first and second branchial arches that form the auricle. No other congenital anomaly or branchial arch remnants were found in this case.

Management of amastia poses a challenging plastic surgical dilemma. Management is done after puberty by both implant and autologous reconstructive technique. Aracho A et al in their review imported cases of unilateral amastia treated with single monopodicle transverse rectus abdominis muscle flap<sup>11</sup>. Goutam A K et al reported congenital breast deformity

reconstruction using perforator flap<sup>12</sup>. Internal mammary vessels were recipient vessels of choice. Deep inferior epigastric or superficial inferior epigastric artery flaps were used.

Rarity of unilateral amastia with bilateral preauricular sinus as a congenital anomaly is the reason of presenting this paper.

#### CONTRIBUTORS

SRC diagnosed the case and revised the manuscript and will act as the guarantor of the paper. BG was involved in the literature review and preparation of the manuscript.

#### REFERENCES

1. Bland KI, Romrell LJ. Congenital and acquired disturbances of breast development and growth. In Bland KI, Copeland EM, eds. *The Breast: Comprehensive Management of Benign and Malignant Diseases*, 3rd ed, WB Saunders; Philadelphia, 1991; 187-188.
2. Bland KI, Vezeridis PM, Copeland EM. Breast. In Schwartz SI, Shires GT, Spencer CF, Daly JM, Fischer JE, Galloway AC eds. *Principles Of Surgery*, 17th edition, McGrawhill ; New York, 1999; 533-534.
3. Mace JW, Kaplan JW, Schanberger JE, Gorlin RW. Poland's Syndrome report of 7 cases and review of the literature. *Clin Pediatr* 1972; 11: 98-102.
4. Jones KL. Poland Sequence. In Jones KL eds. *Smith's Recognizable Patterns of Human Malformation*, 6th ed, WB Saunders; Philadelphia, 2009; 340.
5. Darian VB, Argenta LC, Pasyk KA. Familial Poland's Syndrome. *Ann Plast Surg* 1989 ; 23 : 531-537.
6. Lord MJ, Lauemzano KR, Hurtman RW. Poland Syndrome. *Clin Pediatr (Phila)* 1990 ; 29 : 606-609.
7. Poland A. Deficiency of the pectoral muscles. *Guys Hosp Rep* 1841; 6: 191-93.
8. Bouvet JP, Leveque D, Bemetieres F, Gross JJ. Vascular origin of Poland Syndrome? *Eur J Pediatr* 1978; 128: 17-26.
9. David TJ. Nature and etiology of the Poland anomaly. *N Engl J Med* 1972; 287: 487-89.
10. Kumar V, Apte AV, Gangopadhyay AN, Singh S. Tracheoesophageal fistula and amastia with other anomalies: an unusual association. *Pediatr Surg Int* 2004; 20:378-379.
11. Araco A, Gravante G, Araco F, Gentile P, Castri F, Delogu D, Filingery V, Cervelli V. Breast asymmetries: a brief review of our experience. *Aesthetic Plast Surg* 2006 ; 30: 309-319.
12. Goutam AK, Allen RJ , LoTempio MM, Mountcastle TS, Levine JL, Allen RJ, Chiu ES. Congenital breast deformity reconstruction using perforator flaps. *Ann Plast Surg* 2007; 58: 353-358.

## CASE REPORT

### A child with Mixed Connective Tissue Disorder

Anjan Das\*, Rakesh Mondal\*\*, Madhumita Nandi\*\*\*

\*MD (PGT), \*\*Associate Professor, \*\*\*Assistant Professor  
Department of Pediatrics; IPGME&R and SSKM Hospital, Kolkata. India

---

#### ABSTRACT

Mixed connective tissue disorder is an overlap syndrome having common features of two or more major rheumatic disorders. An 8-year old female child presented with arthritis of knee joints and small joints of both hands with sclerodermatous thickening of skin with raised ESR, C-reactive protein, positive Rh-factor, anti-nuclear antibody and Anti UI-snRNP with negative anti-Scl 70 antibody. She responded well to oral naproxen, prednisolone and methotrexate.

**KEY WORDS:** MCTD; Overlap Syndromes

---

#### INTRODUCTION

Overlap Syndromes have common features of two or more major rheumatic disorders, e.g., systemic lupus erythematosus (SLE), juvenile dermatomyositis (JDM), juvenile idiopathic arthritis (JIA), scleroderma and vasculopathy<sup>1</sup>. Two distinct overlap syndromes in children are mixed connective tissue disorder (MCTD) and Sjogren syndrome<sup>1</sup>. Described first in 1972 by Sharp & his colleagues, MCTD is the least common connective tissue disorder in children, occupying 0.1 to 0.3% of Pediatric Rheumatology Database<sup>2</sup>. Here we describe such a case.

#### CASE REPORT

Salma Khatun, an 8-year old muslim female child from Basirhat, North 24- Parganas, West Bengal, presented to the Pediatric Rheumatology Clinic of SSKM & IPGME&R, Kolkata with painful swelling and restricted mobility of all major peripheral joints for the last one year. She had

high grade intermittent fever for the first 6 months of her illness which was not present during the last 6 months. She also had a peculiar generalized thickening and tightening of her skin for the last 3 months. She had past history of recurrent pyoderma, but no other major illness. She was the 5th child of a non-consanguineous marriage, from a lower middle class social background. There was no family history of any musculoskeletal or skin disease. The perinatal history was unremarkable, developmental milestones were within normal limits and immunization status was up-to-date.

On clinical examination, she had mild degree of pallor, her body weight was 15 kg, calculated height was 120 cm, US:LS ratio almost 1:1, vitals stable and within normal limits. Both of her knee joints and all small joints of both hands were swollen but non-tender with restricted joint mobility. There was typical sclerodermatous bilaterally symmetrical skin thickening and flexion contractures of both knees joints, both wrist joints, all metacarpophalangeal and interphalangeal joints. The fingers were spindle-

---

**Corresponding Author:** Dr Rakesh Mondal

**Email:** rkm1971@indiatimes.com



**Fig. 1.** A child of MCTD with features of arthritis of multiple joints with sclerodermatous skin

shaped with shiny skin over knuckles. Mobility of all the peripheral and to some extent the axial joints were restricted. There was no skin rash, alopecia or visceromegaly, and examination of other systems revealed no gross abnormality.

The baseline investigations showed mild elevation of leukocyte count (15,700/cmm) with polymorph dominance (P-77, L-19, M-1, E-3), a raised ESR (62mm, 1st hr) and CRP (18.2mg/dl), reactive Rheumatoid factor as well as Antinuclear factor. The renal and liver function tests were within normal ranges except modest rise of serum globulin and alanine amino transferase (AST) values (U-29mg/dl, CR-0.4mg/dl, TSB-0.8mg/dl, PR-8.4gm/dl, ALB-3.2gm/dl, GLB-5.2gm/dl, ALP-266 IU, AST-117 IU, ALT-51 IU). The chest skiagram was normal and Mantoux test was negative. Although clinically asymptomatic, her pulmonary function tests suggested very severe restrictive pattern (FVC-26%, FEV1-25%, FEV1/FVC-100%, PEF-44%, FEF25-75-63%).

Examination of eyes on slit lamp biomicroscopy revealed no abnormality, GI examination and echocardiography was normal. But since scleroderma alone could not account for such an extent of joint involvement, the possibility of an overlap was considered. Bilateral knee joint sonogram showed evidence of synovitis and effusion. Serum CPK values were grossly elevated (1342 IU/L) suggesting myopathy. Anti-Scl 70 IgG was not detected but Anti-U1 snRNP was strongly positive. Now, a diagnosis of Mixed Connective Tissue Disorder (MCTD- an Overlap Syndrome) was made.

The child was put on oral naproxane, glucocorticoids and methotrexate along with other supportive measures like iron, folate, multivitamin supplements and ranitidine. The subsequent improvement, both clinically and physically was dramatic. The girl was discharged after two weeks of indoor treatment and then reviewed at OPD periodically. Follow up at 6 months showed remarkable improvement. There was no pain, fever, joint tenderness and the flexion contractures were released greatly allowing much more joint mobility. The child now can sit with knees flexed, can squat, kneel down, clench fist, flex elbow and wrist joints easily which she previously could not do. She gained 3 kg of body weight; her erect height was measured as 132cm (due to relaxed contractures) and she has been continuing her studies in 3rd standard.

#### DISCUSSION

The median age at onset of overlap syndrome is 11 years (range 4-16); females are three times more commonly affected than males. Our case was a 8 yr old female child. HLA class II specificity associated is HLA DR4 and DR2. They have a region of homology of seven amino acids in highly polymorphic antigen binding sites of HLA DR B1 gene<sup>3</sup>.

These are linked to antibody to Uridine-rich small nuclear ribonucleoprotein (U1snRNP). T-cell

clones are directed against 70 kD polypeptide of U1snRNP and of principally of CD4+, Th1 type<sup>3</sup>. T-cell reactivity induces high B-cell immune response to incite pathogenesis<sup>3</sup>. At the onset, ANA is very high. ANA in MCTD has a speckled pattern on Hep2 cell substrate. Hallmark of the disease is increased levels of anti-U1RNP<sup>4</sup>. Anti dsDNA is found positive in only 20% cases<sup>4</sup>. There is widespread intimal proliferation and medial hypertrophy of vessel walls. The skin histopathology resembles systemic sclerosis with less fibrosis. Nail-fold capillary abnormalities are similar to scleroderma. Renal glomerular basement membrane abnormality or vascular sclerosis may be present, but less common and less severe. Pulmonary hypertension is the commonest serious complication. Lung disease is very often initially asymptomatic and manifests later. Polyarthritides and Raynaud phenomenon are the usual early presentations. Flexion contractures are quite common<sup>4</sup>. Hepatomegaly or splenomegaly may be found in 25% of cases<sup>4</sup>.

Diagnosis of MCTD is based on Sharp's criteria<sup>5</sup>. Presence of at least 4 major and positive anti U1RNP + anti-ENA in 1:4000 make it a definite diagnosis whereas presence of 3 major or 2 major and 2 minor criteria + anti U1RNP + anti-ENA in 1:1000 make it probable one. Diagnosis of a possible MCTD is made in presence of 3 major criteria alone or 2 major criteria + anti U1RNP and anti-ENA in 1:100 or 1 major and 3 minor criteria + anti U1RNP and anti-ENA in 1:100.

There is no specific treatment. Management is directed towards predominant problems. Many children respond well to NSAIDs (Nonsteroidal anti-inflammatory agents), HCQ (Hydroxychloroquine), glucocorticoids or a combination of these<sup>4</sup>. Severe myositis, renal or visceral disease often requires high dose steroids or cytotoxic drugs, especially in severe PAH. Methotrexate is a good disease modifier. Autologous HSCT attempted for refractory life-threatening diseases<sup>4</sup>. Our case responded well to naproxen,

glucocorticoids and oral methotrexate.

Outcome is variable and unpredictable<sup>4</sup>. Morbidity or mortality is mostly associated with PAH or restrictive lung disease. Renal failure and severe thrombocytopenia resistant to conventional therapy are other causes of mortality. Anti-ENA titers decrease with prolonged remission. Favorable outcome has been documented in 62% patients with early diagnosis and management with 17% in remission off therapy without residual functional disability<sup>6</sup>.

#### CONTRIBUTORS

AD, RKM and MN were involved in the management of the patient and preparation of the manuscript.

#### REFERENCES

1. Sharp GC, Irvin WS, Tan EM, *et al*: Mixed connective tissue disease: an apparently distinct rheumatic syndrome associated with a specific antibody to an extractable nuclear antigen. *Am J Med* 1972; 52; 148-159.
2. Bowyer S, Roettcher P, and the members of the Pediatric Rheumatology Database Research Group: Pediatric Rheumatology clinic populations in the United States: results of a three year study. *J Rheumatology* 1996; 23; 1968-1974.
3. Kaneoka H, Hsu K, Takeda Y *et al*: Molecular genetic analysis of HLA-DR and HLA-DQ genes among anti-U1-70kD autoantibody positive connective tissue disease patients. *Arthritis Rheum* 1992; 35; 83-94.
4. Cassidy JT, Petty RE; *Overlap Syndromes*; In Cassidy JT, Petty RE eds. "*Text book of pediatric rheumatology*"; Fourth edition, Philadelphia, W.B Saunders company 2001; 544-552.
5. Sharp GC: Diagnostic criteria for classification of MCTD. In Kasukawa R, Sharp GC: *Mixed connective tissue disease and Anti-Nuclear Antibodies*. Amsterdam, The Netherlands, Excerpta Medica 1987; pp 23-32.
6. Burdt MA, Hoffman RW, Deutscher SL, *et al*: long-term outcome in mixed connective tissue disease: longitudinal clinical and serologic findings. *Arthritis Rheum* 1999; 42; 899-909.

**Nephrotic Syndrome In Infancy In Identical Male Twins****Sucharita Datta\* , Kaustabh Chaudhuri\*\****\*Associate Professor, \*\* RMO cum Clinical Tutor**Department of Pediatric Medicine**NRS Medical College and Hospital, Kolkata*

Two siblings, 14-month old identical male twins, born of a Muslim consanguineous marriage presented with generalized edema, ascites and oliguria since 11 months of age. Both the siblings, had simultaneous development of periorbital and pedal edema with progression of anasarca in form of ascites over the ensuing 2 months associated with oliguria. On admission, hypertension (>95th percentile for the age and sex) was found in both siblings. Investigation suggest normal blood counts, hypoalbuminemia and raised serum cholesterol (570 mg/dl and 487 mg/dl respectively) were found in both children. Urinalysis revealed proteinuria (+++) in both with no evidence of hematuria. Pus cells was found significant (8 to 10 /hpf) in one while it was normal with other. Simultaneously urine culture report suggest E.coli urinary tract infection in first while other one was normal.

Tests for HBsAg and Anti HCV were non-reactive. USG of KUB showed increased echogenicity with loss of corticomedullary differentiation in one, while both kidneys were enlarged and swollen with increased cortical echogenicity in the other twin.

The clinical picture and laboratory parameters were consistent with the diagnosis of nephrotic syndrome. However the onset of symptoms at

11 months of age, presence of hypertension and the loss of corticomedullary differentiation with increased cortical echogenicity on USG made minimal change disease less likely and stressed the need for a renal biopsy.

Both the twins were started on steroids and transfused with fresh frozen plasma (FFP) and renal biopsy was planned. The first twin was started on Nitrofurantoin therapy as per urine culture sensitivity report. But as the twins were released against medical advice by the parents, renal biopsy was not possible.

The first differential diagnosis to consider was "congenital nephrotic syndrome". Parental consanguinity and occurrence of similar disease in identical twins (assumed on the basis of same sex, identical appearance and common blood group, i.e. B +ve) prompted us to consider this condition, as a hereditary disease.

Other causes of congenital nephrotic syndrome include the 'STARCH' complex, which presents in the neonatal period.

In congenital nephrotic syndrome diffuse mesangial sclerosis characterized by progressive sclerosis of the glomerular mesangium and rapid loss of renal function with end-stage renal disease may occur. It may also be a part of Denys-Drash syndrome, a condition characterized by Wilms tumor and male pseudohermaphroditism due to a mutation in the Wilms tumor gene (WT1) on chromosome 11.

---

**Corresponding Author:** Dr Sucharita Datta  
**E-mail:** suchisarkar2004@yahoo.co.in



**Fig. 1 .** *The identical twins with nephrotic syndrome*