The Child and newborn

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Tufpro

Bacillus clausii spores 2 billion/5 ml suspension

The Tough Probiotic

Ready to Drink Formulation

Announcement

WB PEDICON 2023

42 WB State PEDICON

Organised by West Bengal Academy of Pediatrics

CII Suresh Neotia Hall, 9,10 December 2023

	Up to 31st August	Up to 31 October	From 1st November And spot
Delegate	2500	3000	4000
Postgraduate	1000	1500	2500

Star Speakers
Prof. Arun Bansal
Prof. Piyush Gupta

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Bela Bhattacherjee 9830866712,
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Workshop on 8th December, Registration Rs.1000/-
(Conference Registration is mandatory)

WORKSHOP

Basic Ventilation	UTI, Nephro Imaging, Antenatal Hydronephrosis		
AED and EEG	POCUS	PICU and NICU Procedures	ALLERGY
CPAP and Surfactant	ADOLESCENT Health in Clinical Practice	Basic Cardiac Intensive Care	

Request

Members are generously requested to provide News, Views, Reviews, Case Reports, Articles to our esteemed journal.

Contact :

Dr Kaustav Nayek

Editor-in-Chief, The Child and Newborn

"Oriental Apartments" Flat H1, 15C, Canal Street, Kolkata 700 014,
Email : kaustav25@yahoo.co.in

In Memories

Dr Kajal Kr Ghosh
(1955-2023)

The Child and Newborn

West Bengal Academy of Pediatrics, Oriental Apartments, Flat H1
15C, Canal Street, Kolkata 700 014
Phone : 033 2265 4072, Email : wbap2013@gmail.com, Website : www.wbap.in
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Dr Kaustav Nayek
Editor-in-Chief, The Child and Newborn
"Oriental Apartments" Flat H1
15C, Canal Street, Kolkata 700 014
Email : kaustav25@yahoo.co.in

President's Address

My fellow Academicians,

I am honoured to address you today on behalf of WBAP, recognizing the crucial role that you play in shaping the child health issues and academic (Paediatric) landscape of our state.As paediatricians, researchers, educators, and thinkers, your dedication and pursuit of knowledge have a profound impact on our society, especially paediatric population of our state. For the last few months, you are doing tremendous work on IAP President's Action Plans, webinars and CMEs. Recently we had two successful national conferences, Vaccicon and Asthmacon, Nationalmidterm CME on adolescent health in association with central AHA and WBAP and Durgapur Pedicon. Many subspeciality chapters' state conferences and Zonal conference successfully held in association with WBAP.ALS, BLS and CPR arealso going on throughout the states in association of WBAP. Our dream projectSandhya Pathshala and Workshop on EEG, Neuro imaging, Denguewere well attended and well appreciated.Clinical meetings are in full swing. This year we are having regular physical and digital clinical meet alternately in a month involving both peripheral colleges and colleges in and around the Kolkata.

We also celebrated World Obesity day, Autism awareness day, National BLS and CPR day, ORS day, complementary feeding and world breast feeding week throughout the state. Inthe spirit of collaboration, I encourage you all to engage with us, to bridge the gap between theory and practice. Your insights have the potential to shape policies that address pressing societal issues of the children, child abuse and neglects, vaccinations, nutrition and promote sustainable development.As we move forward, let us remain steadfast in our commitment to improve health, education and safety of our children. Together, we can build a brighter future of our children for our nation and the world at large. I am eager to witness the remarkable contributions that you will continue to make, and I extend my deepest gratitude for your unwavering dedication to the mankind.

Please do contribute articles, research work and case report for forthcoming Child and Newborn Issues.

Thank you, and may your endeavours continue to inspire and support us all.

JAI IAP

JAI HIND

Prof. Kalpana Datta
President, WBAP 2023

Editorial

It gives me immense pleasure to pen this from the desk of the editor. Yes the third issue of Child and Newborn is out and that too in time. It was our big dream from the office bearers of West Bengal Academy of Pediatrics to revive this Journal and work towards indexing it. When I was given the job of the Editor in Chief , initially I was very apprehensive. But I was confident. I had huge faith in my fellow pediatricians. Togather we are working towards improving this journal in all aspects. I am also very proud of our young brigade. They have contributed a lot . Togather we will be able to index this journal in near future surely. We have been successful in working out the mechanism so that the journal reaches you in time. I hope all of you have received it. Please let me know if any of you are yet it receive it. This will help us to identify loop holes and make the system more perfect.

I request you to please give your valuable feedback. Constructive criticism is essential for improvement of our journal. Keep sending your articles. Inform your fellow pediatricians who are yet not members of IAP about our journal. Also request them to be mbers of IAP to make our family larger. I must congratulate WBAP. We have been successful in uplifting academics in different ways. New events like SANDHYA PATHSHALA is very popular for post graduate students. ASTHMACON was hugely successful. Different district branches are organizing Academic events. For the very first time the Executive Body meeting for the month of August was held in Siliguri. Also a very successful Uttoracon was organized by IAP Silguri branch.

Hope you all enjoy the third issue of CHILD AND NEW BORN

Dr Kaustav Nayek
Editor-in-Chief,
The Child and Newborn

Understanding The Genetic Background of Congenital Neuromuscular Disorders

Rupesh Thapa*, Anupam Basu,**
**Dept of Zoology, The University of Burdwan.*
***Associate Director, National Institute of Biomedical Genomics (NIBMG), Kalyani*

Abstract:

Around the world-wide millions of peoples suffering from the rare diseases and congenital neuromuscular spectrum of diseases are the one of the most diversified and complicated spectrums of disorder. More than 20 different kinds of myopathies and muscular dystrophies have been identified. Most of them have the effect on skeletal, cardiac, and respiratory muscles and leads to severe and complicated life crisis. At the diagnosis point of view these spectra of diseases cannot be diagnosed only based on physical, biochemical, muscle biopsy, repetitive nerve stimulation test, imaging technique and simple PCR based method due to the overlapping observing symptoms and genotypic heterogeneity. Next generation sequencing based technologies such as whole exome, whole genome, mitochondrial genome sequencing can be helpful and reliable for proper diagnosis and treatment. Sharing of knowledge between researchers and clinician will play a remarkable huge role in discovering the genes and gene panel for these huge spectra disease in future and ultimately helps in better prognosis and treatment improvement of patients.

Introduction:

In terms of rare disease approximately 350 million people across worldwide suffered and more than 70 million individuals from India suffered from different kinds of rare diseases. These diseases areindividually rare, but in aggregate they affect 4%–8% of the population [1,2]. Morethan 3800 rare diseases are listed by Orphanetofwhich~80% are genetic or have genetic subtypes. Paediatric medicine department from any hospital or health care system mainly served as the hub for different types of rare diseases and deliver a huge challenge to patients and their families and to the health care systems [3]. The exact data about the suffering from rare diseases is lacking in India probably due to the lack of proper information. As per Indian Rare Disease Registry, congenital neuromuscular spectrum of diseases (NMDs) represents the one of the most frequent types of rare diseases in India. Congenital NMDs are the vast categories of rare diseases[4,5]. Several types of NMDs are presented along with their genetic perspectives.

Duchene Muscular Dystrophy:

Duchene muscular dystrophy (DMD), a very rare X-linked recessive muscle degenerative disease has been found due to the mutation in DMD gene which is more prevalent nature in male that is 1 in 3600 to 6000 live male births [6,7]. In India the prevalence is 1.6 in 100000 population [8]. Multiplex polymerase chain reaction (mPCR) and multiplex ligation-dependent probe amplification (MLPA) are the two most common diagnostic methods for DMD and still used in India [9,10]. MLPA is more effective than mPCRwith higher detection rate. NGS is a newer and more rapid diagnostic method that is being developed and solved more than 90-95% of cases.

GNE Myopathy:

GNE myopathy is a rare progressive skeletal muscle degenerative disorder due to mutations in GNE gene that encode the bifunctional enzyme UDP-N-acetylglucosamine (GlcNAc) 2-epimerase/N-acetylmannosamine (ManNAc) kinase. The world-wide prevalence of GNE myopathy is 1 to 9 in 1,00,000 population [11]. The majority of GNE myopathy-associated mutations are missense mutations, which result in the production of an enzyme that is not fully functional. About 70% of GNE myopathy patients have compound heterozygous mutations and besides the missense mutations, a few indels, intronic variants, rearrangements, and

Correspondance : Anupam Basu, Dept of Zoology, The University of Burdwan. *Email ab3@nibmg.ac.in, abasu@zoo.buruniv.ac.in*

copy number variations with recombination hotspots have also been reported in GNE myopathy patients [12,13]. Recent studies from India showed that c.2179G>A; p. Val727Met was concerned as the major pathogenic variant along with c.1853T>C; p. Ile618Thr in India [14].

Congenital Myasthenic Syndrome:

Congenital myasthenic syndrome (CMS) is a neuromuscular junctional disease where the safety margin of neuromuscular transmission is compromised leads to the weakness and fatigue of both voluntary and involuntary muscles [15]. CMS is one of the best examples of typical genotypic and phenotypic heterogeneity where not less than 30 genes are involved [15,16] (Table1). In Great Britain approximately 9.2 people per 1million population have been affected with CMS, where as in Brazil 0.18 people affected per 1 million population [17,18]. In India the epidemiological sex ratio of myasthenic syndrome is M: F being 2.70:1 [19]. The inheritance pattern of CMS can be either AR or autosomal dominant (AD) manner [20].

Pompe Disease:

Pompe disease is an autosomal recessive inherited metabolic lysosomal storage disorder where neuromuscular system especially skeletal and cardiac muscles are severely involved and effected. Acid a-glucosidase, encoded by GAA gene helps in glycogen metabolism. But the biallelic loss of function of GAA gene responsible for the dumping of glycogen in lysosome of almost all kinds of cell especially in skeletal and cardiac muscle which ultimately causes cell destruction and impairment of muscle function [21]. Infantile onset of Pompe disease (IOPD) where the acid a-glucosidase enzyme is almost completely lost (<1%) and IOPD is much more severe and life threatening than the Late onset of Pompe disease (LOPD) [22]. Prevalence is not equal in different populations such as African American showed 1 in 14000, United States showed 1 in 40000, European population showed 1 in 100000 for IOPD and 1 in 60000 for LOPD [23].

Limb Girdle Muscular Dystrophy:

Limb girdle muscular dystrophy (LGMD) is another type of neuro muscular [24,25]. All forms of LGMDs are autosomal in inheritance and classified as autosomal dominant type or LGMD1 and autosomal recessive type or LGMD2 (Table 2&3) [26]. But LGMD2 is more prevalent (1 in 15000) than LGMD1

Table 1: Genotypic heterogeneity of CMS with responsible genes [15,16].

Types of CMS	Responsible Genes
Pre-synaptic CMS	SLC5A7, CHAT, SLC18A3, SANP25, VAMP1, SYT2, RPH3A
Synaptic basal laminal associated CMS	COLQ, LAMB2, LAMA5, COL13A1
Post-synaptic CMS	CHRNA1, CHRNB1, CHRNG, CHRND, CHRNE, DOK7, MUSK, LRP4, AGRN, RAPSN
CMS associated with defective glycosylation	GFPT1, DPAGT1, ALG2, ALG14, GMPPB
Other CMS	SCN4A, PREPL, PLEC1, MTM1

Table2: Autosomal dominant (AD) forms of LGMDs and responsible genes [26].

Inheritance Pattern	Types of LGMD	Responsible Gene
Autosomal Dominant (AD)	LGMD1A	TTID
	LGMD1B	LMNA
	LGMD1C	CAV3
	LGMD1D	DNAJB6
	LGMD1E	DES
	LGMD1F	TNPO3
	LGMD1G	HNRNPDL

Table3: Autosomal recessive (AR) forms of LGMDs and responsible genes [26].

Inheritance Pattern	Types of LGMD	Responsible Gene	Types of LGMD	Responsible Gene
Autosomal Recessive (AR)	LGMD2A	CAPN3	LGMD2M	FKTN
	LGMD2B	DYSF	LGMD2N	POMT2
	LGMD2C	SGCG	LGMD2O	POMGnT1
	LGMD2D	SGCA	LGMD2P	DAG1
	LGMD2E	SGCB	LGMD2Q	PLEC1
	LGMD2F	SGCD	LGMD2R	DES
	LGMD2G	TCAP	LGMD2S	TRAPPC11
	LGMD2H	TRIM32	LGMD2T	GMPPB
	LGMD2I	FKRP	LGMD2U	ISPD
	LGMD2J	TTN	LGMD2V	GAA
	LGMD2K	POMT1	LGMD2W	LIMS2
	LGMD2L	ANO5	LGMD2X	BVES

[24]. However according to Orphanet data base the world-wide prevalence is 1-9 in 100000 population [11]. A study from India showed LGMD2 represented as more prevalent than LGMD1 [27].

Hereditary Spastic Paraplegia:

Hereditary spastic paraplegia (HSP) is a highly heterogenous neurodegenerative diseases effecting the corticospinal and dorsal spinal cord and leads to the impairment of gait and muscle stiffness. HSP represent a prevalence of 0.1- 9.6 people per 100000 population around the globe [28]. According to the Indian rare disease registry till now 60 thousand people recorded as to be affected with HSP [8]. Interestingly more than different genes are involved with almost all kinds of inheritance pattern (AR, AD, X-linked recessive, and mitochondrial) responsible for heterogeneity and complexity [29,30]. The genetic loci are designated as SPG (for Spastic paraplegia) and are numbered sequentially as SPG1, SPG2, SPG3. As per Online Mendelian Inheritance in Man (OMIM) data bases, more than 100 genetic loci are reported.

Hypertrophic Cardiomyopathy:

Hypertrophic Cardiomyopathy (HCM) is one of the most common cardio vascular disorder with the prevalence of 1 in 500 in general population across the globe [31]. In that case India also represent a large number of HCM cases (approx. 2.4 million) [32]. Genetic heterogeneity plus incomplete penetrance and expression variability make the HCM more complicated and challenging to understand [33]. The most causal genes responsible for this disorders are MYH7 and myosin binding protein C (MYBPC3). Other genes are TNNT2, TNNI3, and TPM1, ACTC1 (cardiac a-actin), MYL2 (myosin light chain 2), MYL3 (myosin light chain 3), and CSRP3 (Cysteine and Glycine Rich Protein 3) responsiblefor HCM,[34,35].

Discussion:

A major challenge in neuromuscular spectrum of disorder is that the proper diagnosis and then the proper management. But the presence of huge genotypic heterogeneity and overlapping symptoms make difficulties to identify the actual disease manifestation. Proper diagnosis before starting the treatment may be harmful for patients [36,16]. Mitochondrial diseases can affect both muscle and nerve, and can mimic the clinical presentation of other neuromuscular disorders. So, there are clinical guidelines and protocols that should be used to distinguish between mitochondrial diseases and other neuromuscular disorders [37]. However, during the era of sanger sequencing it was very much difficult period to diagnosis the neuromuscular spectrum of disease. Also, physical, biochemical, muscle biopsy, imaging techniques like MRI, and repetitive nerve stimulation tests etc. are not only the reliable methods to diagnose correctly the NMDs. After availability of NGS, the proper diagnosis become relatively easy and reliable. But as a developing country the patients and their families in India could not bear the cost of WES or WGS always. So the target sequencing of desire gene panelsspectrum might be the cost effectiveness for routine diagnosis

[38]. However, there are some challenges that need to be addressed, such as confidentiality of patient data and lack of funding for research. But all genetic, clinical, pathological, and functional data should be available into public mutation databases and the sharing of data among professionals are important steps in improving knowledge of NMDs and their diagnosis and management.

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A Case of Malaria with Atypical Presentation

Swastika Ghosh*, Subhasish Bhattacharyya, Ira Das***, Mousumi Das******
**2nd Year Postgraduate, **Professor, ***Assistant Professor, ****RMO*
Department of Pediatrics, CSS College of Obstetrics, Gynaecology & Child Health

Introduction

Malaria in the neonateand early infancy may be acquired by transfusion of infected blood products, perinatal transmission from mother & in endemic areas by mosquito bite. The predominant clinical features are fever, anemia & splenomegaly. These clinical features are seen in more than 80% of cases [1]. Sometimes presentation may be atypical. Here we report a case that present atypically.

Case Report

A 1 month 20 days old female child presented with complaints of feeding difficulty & vomiting for 1 day.

Baby was born to a primi mother through normal vaginal delivery at 32 wks of gestation with birth weight of 1.1 kg. Baby was admitted in SNCU for Respiratory Distress Syndrome for 20 days. Mother had a history of fever with rash in 1st trimester of pregnancy.

On examination, the baby was lethargic, significantly pale. Systemic examination reveals hepatoslenomegaly. Liver was palpable 3 cm below costal margin & firm in consistency. Spleen was palpable 4 cm below costal margin soft to firm in consistency. There was no free fluid in abdomen.

Laboratory evaluation showed anemia (Hb- 9.1 gm %), normal WBC count (12000/cu mm) with lymphocytic predominance (Polymorhs20%, Lymphocytes 75%), thrombocytopenia (Platelet-50,000/cu mm). Other relevant results include elevated CRP (42.7 mg/L) & CSF examination showed 5 cells (50% polymorphs & 50% lymphocytes), CSF protein- 138 mg/dl & sugar-43 mg/dl (CBG-83 mg/dl). CSF was suggestive of meningitis. A diagnosis of late onset sepsis (Meningitis) was done and initially antibiotics were started empirically. Blood culture was sent which showed growth of Staphylococcus haemolyticus & was sensitive to Linezolid. Antibiotic was modified (Inj. Linezolid was started and planned for 21 days). Baby was improved clinically & was able to accept oral feeding well.

But there was progressive anemia requiring repeated blood transfusion (5 transfusions in 14 days), persistent thrombocytopenia & hepatosplenomegaly. Haemoglobin electrophoresis & other differentials of hemolytic anemia were sent and appeared normal.

TORCH profile was sent as there was history of fever with rash in 1st trimester of pregnancy & report showed raised titre of CMV IgM. Urine for CMV DNA PCR showed 70,000 copies. CMV related investigations showed no evidence of chorioretinitis & hearing loss. Neuroimaging (USG & MRI Brain) did not show any abnormality (Intracranial calcification or ventriculomegaly). So, Ganciclovir was not started.

In view or repeated blood transfusions for progressive pallor, persistent thrombocytopenia & hepatosplenomegaly the baby was sent for hematological opinion and repeat peripheral smear showed multiple trophozoites of Plasmodium vivax.

The diagnosis P. vivax malaria was done & started with syrup Chloroquine (10 mg/kg B.W followed by 10mg/kg B.W 0n 2nd day & 5 mg/kg/B.W on 3rd day). The repeat blood smear at the end of the treatment showed no parasite.

The baby was discharged with normal Haemoglobin-11.1 gm%, normal Platelet count- 2,94,000/cu mm & normal inflammatory marker. The child was kept

Correspondance : Subhasish Bhattacharyya, *Professor, Department of Pediatrics, CSS College of Obstetrics, Gynaecology & Child Health. Email :dr_subhasish@hotmail.com*

on follow up showed normal growth & development, Liver & Spleen size gradually decreased & there was no recurrence of anemia or thrombocytopenia.

The history of mother was reviewed. There was no history of malaria or any fever in late pregnancy. So, Congenital Malaria is unlikely. No history of blood transfusion prior to the presentation. So, transfusion related malaria is also unlikely.

Discussion

Malaria in pregnancy and newborn causes significant burden of disease and estimated to cause more than 300,000 fetal and infant deaths [2] worldwide annually. In spite of this serious health problem very few epidemiological studies have been conducted to investigate the disease burden, approach to diagnosis, management and prevention of malaria in neonates.

Malaria in the neonatal period may be acquired by transfusion of infected blood products to neonate, perinatal transmission from mother and in endemic areas by mosquito bite. Congenital malaria is defined as malaria acquired from the mother prenatally or perinatally.

Congenital malaria results from transplacental transmission of malaria parasite from mother to the baby in utero or during delivery. Maternal history of fever or malaria during late pregnancy is often available. Signs and symptoms typically occur between 10 and 30 days of age. Its diagnosis is based upon detection of asexual forms of malaria parasites on a blood smear of a newborn or later if there is no possibility of infection through infective mosquito bites. So, it is very difficult to differentiate between two in endemic region.

Malaria usually present as a triad of fever, anemia & hepatosplenomegaly. But newborn does not have sufficient muscle mass to produce shakes of chill. In addition, huge amount of antimalarial antibody binds to merozoites, restrict free movement of parasite and invasion of babies red blood cells. Moreover, high fetal hemoglobin [3] [4] and low PABA (Para aminobenzoic acid) [5] in breast fed babies prevents parasite multiplication inside RBC. All these factors can cause atypical presentation in neonates and infants.

In our case the diagnosis of malaria was initially missed due to unusual presentation (no fever). Anemia & organomegaly was thought to be due to Congenital CMV infection. Initially parasite was not detected in peripheral smear (thin smear) may be due to low parasite densities.

Newborn with malaria can present with common neonatal complaints like persistence of physiological jaundice, exaggerated physiological anemia of infancy and other non specific features mimicking sepsis or other congenital infections. More often we did not consider malaria as differential in such situations. Mostly diagnosis is done retrospectively while examining the smear for blood count. So, whenever a neonate present with unexplained anemia, thrombocytopenia & organomegaly malaria should be always kept as differential diagnosis in endemic region.

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SMR Assessment and its Clinical Issues

Sukanta Chatterjee
Ex Professor & Head of Pediatrics, Medical College , kolkata
International Member of Society for Adolescent Medicine (USA)

Sexual Maturity Rating (SMR) refers to a quantitative scale of anatomic changes an adolescent undergoes in visible sexual characteristics eg. genital organ and pubic hair in boys , breast development and pubic hair changes in girls . Originally described by JM.Tanner in 1960s is still recognized as an important tool to measure physical maturation of a child towards an adult.(1) . The details of SMR stages 1 – V for boys and girls in each item mentioned above is available in literature for clinical use (2). Besides physical changes a series of psychological changes also occur in adolescents towards fulfilling the developmental task to become an adult as described by Erik Erikson (3). WHO defines adolescent between 10-19 years of age as most of the changes of puberty are complete by this age. Depending upon the degree of changes the period is further divided into early (10-13yrs), mid (14-16yrs) and late (17-19yrs) adolescence (4).

The onset and progress of normal pubertal growth in an individual may vary widely with chronological age in different family and social settings. On the other hand it is closely related to SMR stage of the individual. Therefore an adolescent's maturation will be better assessed by sexual maturity rating stages or 'SMR age' than 'chronological age'. Besides sexual organ growth the height spurt, weight gain, adolescent BMI changes (increase in boys , decrease in girls) , hematocrit changes (39% at SMR 1 , 43% when SMR V in boys) and ECG changes are more closely related to SMR age (5 , 8) . Normal developmental task of an adolescent are achieved at a wide range of chronological age but it is more related to SMR stages of the individual e.g. the body image and physical activity (6). Boys with behavior problems had significantly advanced Tanner SMR stages than comparison group (7). Children at higher SMR stages than their peers were more likely to experiment with smoking (9). Eating Disorders like 'bulimia' were more common in early maturing (SMR) girls and in off-time (early or late) maturing boys (10). Depression amongst girls are higher with early maturing pubertal status (11). Headache , musculoskeletal pain were seen more commonly in off-time pubertal developer (early or late) than that of on-time ones (12) .Early maturing (SMR) girls reported more interest than on-time / later maturing ones in seeing sexual contents in movies , magazines (13) .Early developing boys (SMR) had more aggressiveness / unruliness , more girl friends and other sexually active behavior (14) .

Therefore the need of determining the SMR stage of an adolescent and its comparison with chronological age is of great clinical importance to understand the etiology and to plan management of both physical and developmental issues in them. Examination of SMR is always embarrassing to an adolescent due to undressing. Getting consent for the examination is difficult and the process itself might reduce friendliness of the clinician or the clinic. To overcome this negative impact on this very important clinical examination, self assessment of SMR staging was tried by many workers like

'breast cancer screening' self-examination (15) . The reliability of self assessment of SMR were compared to clinical examination by many authors (16- 24) .The reliability is more in pubic hair staging in self examination than in breast / penis staging .This was attributed to existing high or low body image perceptions in the adolescents (25) . It could also be due to less absolute criteria of differentiation between

Correspondance : Sukanta Chatterjee International Member of Society for Adolescent Medicine (USA). Email- sukantachatterjee@hotmail.com

SMR stage II / III or IV / V in breast or penis staging unlike pubic hair staging where every stage has its absolute criteria in Tanner Scale. The examination should be done after getting the consent of the adolescent and preferably not in front of the parents as recommended for pelvic examination (26).

Process of Clinical Examination: In our clinic setting we found adolescents more comfortable in absence of parents. Best way we obtained consent for SMR examination was by proposing that we want to examine whether you are growing at per in your sexual maturity. The adolescents who prefer self examination were explained about Tanner staging by demonstrating photographs. Many of them subsequently could be convinced to consent for clinical examination. However considering the issues of reliability of self examination it is recommended that clinical examination is preferred but could be deferred and replaced by self examination till the consent is obtained. The self examination could be a part of annual screening. It's usually not done on the first visit unless they came with genital organ as a presenting problem.

Per cent of agreement for self-assessment and physician assessment of SMR recording at Adolescent Health Clinic, Medical College Kolkata are shown in table form:

Per cent agreement on pubic hair by physician and adolescent in boys and girls (n = 69)

SMR Stage	% agreement
I	75% (n = 8)
II	55.5% (n = 9)
III	55% (n = 20)
IV	52.4% (n = 21)
V	70.3% (n = 11)

Key message: Relation of SMR staging and symptoms / signs of adolescent growth and psychological development should be worked out as a routine. It will explore the cause and effect relation on many occasions and could avoid unnecessary investigations and interventions. On the other hand it can guide for early useful intervention. Examination may be embarrassing but useful and clinicians have to look for and create opportunities for it to get consent

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Efficacy of Montelukast In Comparison To Inhaled Corticosteroid In 1-6 Years Old Children With Mild Persistent Asthma

Pinki Barui*,Sanajit Ghosh*,Mihir SarkarProf. Kalpana Datta****
JR,Professor*
Dept.of.Pediatric Medicine, Medical College Kolkata

Background

Asthma is a common chronic obstructive pulmonary disorder that usually becomes the major reason of disability,economic burden and poor quality of life.Inhaled corticosteroids have always been a popular choice of treatment to manage asthma both in adults and children. Nevertheless,studies have also shown ICS are potentially harmful for children in long run. According to former studies,Montelukast can be prescribed as an alternative therapy of low dose ICS since it was found to provide similar antagonizing effects like ICS on clinical indicator of asthma especially in intermittent or mild persistent asthma.

Objective

To find out the efficacy of Montelukast in comparison with inhaled corticosteroid as first line therapy of mild persistent asthma in 1-6 yr of children on the basis of level of control as per GINA guidelines

Material and Method

This is a prospective double arm open level comparative randomised parallel group interventional study among patients attended asthma clinic and opd with diagnosed mild persistent asthma from march 2020 to aug 2021.

Results

In our study out of 60 patients with mild persistent asthma.mean age of the study population is 42.35(12.97) months .Mean age of first symptoms 28.4+/-11.40 months.among the 60 patients 68% have family history of asthma.the level of control after 1 month among all patients,6(10%) well controlled,38(63%) partially controlled and 16(26%) uncontrolled.in ICS group 1(3%) well controlled,22(68%) partially controlled,and 9(28%) uncontrolled.in the Montelukast group5(17%) well controlled,16(57%) partially controlled and 7 (25%) uncontrolled.

Conclusions

The study demonstrates that oral Montelukast and ICS both are effective against asthmatic symptoms in children less than 6 years of age.However ,Montelukast has been reported as a more satisfactory regimen in terms of soothing the symptoms like nasal congestion specially in mild persistent asthma.

Correspondance : Pinki Barui. Dept.of.PediatricMedicine,Medical College Kolkata Junior resident Email- baruipinkitahar@gmail.com

A Case of Atypical Presentation of Tuberculosis:

***Jyotirmoy Ghosh, **Subhasish Bhattacharyya**
**2nd Year Postgraduate, **Professor*
Department of Pediatrics, CSS College of Obstetrics, Gynaecology & Child Health

Abstract:

Tuberculosis is a bacterial disease caused by Mycobacterium tuberculosis, and when the disease affects the central nervous system it is called as neruotuberculosis. Patient with a tuberculoma typically present with pulmonary involvement of tuberculosis. The risk factors for tuberculosis includes bacillary load, proximity to infectious case, immunosuppressive state , malnutrition ,young age. Although rare, but it is possible for a patient to present with CNS tuberculosis without pulmonary involvement and risk factors.

Case Report

A 6 yr old male child presented to us with fever for 7 days continous in nature, not relieved but medication and was associated with body ache, with vomiting non projectile in nature, in this course the baby had progressive somnolence with increased unresponsiveness The boy was examined : GCS:7/15 ,Pupil: Right sided non reactive to light ,left sided sluggishly reactive to light bradycardia, shallow respiration, hypovolemic ,thread pulse ,no radio radial or radio femoral delay, blood pressure more than 95th%, with Vesicular breath sounds with crepts.

On neurological examination, Boy was not responding to vocal commands or any stimulus GCS-7/15 ,No signs of meningeal irritation was elicited at that time. Cranial nerve examination was not possible, except 2nd nerve pupillary reflex was absent with B/L pupil fixed and non reactive to light, Fundoscopy showed grade 3 papilledema.

Motor system examination showed Power in upper and lower limb grade 0 ,tone spastic type in lower limb and upper limb. Deep tendon reflex was exaggerated upper and lower limb reflex with positive Babnski sign indicates, UMN type of lesion.

Investigations showed normal LFT,RFT, Leucocytosis with polymorphic predominance. Due to raised ICT lumber puncture was not performed. HIV serology was negative and scrub typhus, dengue, chikungunya was excluded. Mantoux test was negative and CBNAAT for gastric aspirate was also negative. Chest x-ray was normal . Patient was on prolonged ventilation needed tracheostomy, with each passing week the patient detoriated neurologically. Subsequently patient developed euvolemic hyponatremia along with a dischargeof pus from tracheotomy sites and central venous sites, with was not responding to any antibiotic therapy .

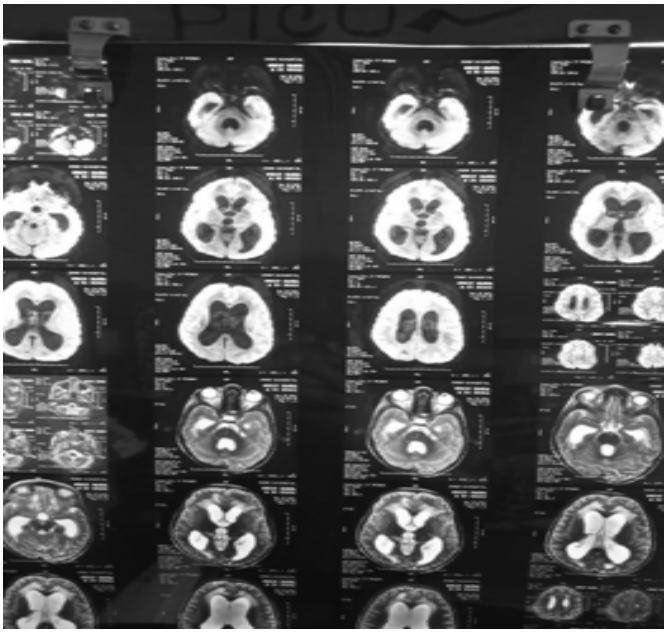
Subsequently MRI brain was done which showed communicating hydrocephalus with basal exudates and ring enhancing lesion . Antitubercular drug and corticosteroid was started . The boy showed marked improvement neurologically and hemodynamically within one week of starting of treatment and discharged home with antituberculer medications.

Discussion

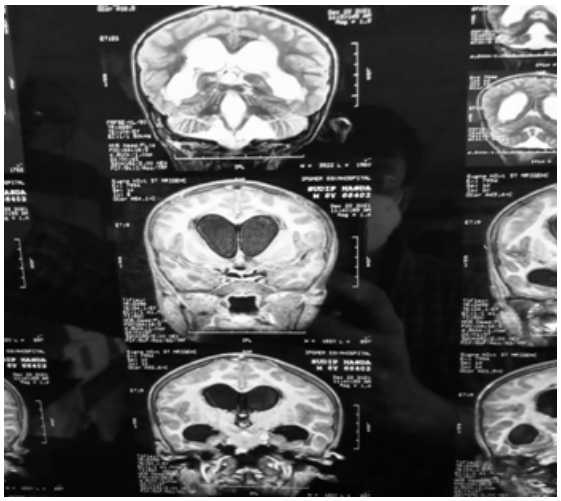
Tuberculous meningitis is the most serious and commonest form of neurotuberculosis in developing countries .It carries high mortality and morbidity despite having adequate chemotherapeutic drugs. The disease has peak occurance at 9month till 9yr age. Poor response to therapy or death occurs due to failure to initiate or delayed initation of anti tubercular drugs with proper regime. Diagnosis is based on clinical features, CSF findings and imaging. Clinically the neurotuberculosis patients

Correspondance : Subhasish Bhattacharyya, *Professor, Department of Pediatrics, CSS College of Obstetrics, Gynaecology & Child Health. Email :dr_subhasish@hotmail.com*

present with no to few signs of meningitis in stage 1 then procceds to signs of meningitis with cranial nerve palsies` with drowniness in stage 2 and stupor and come in stage 3. Atypical presentation with pus from tracheostomy site and from central venous site may occur, which respond to anti tubercular drugs. Neurotuberculosis often presents as UMN type lesion . Even if mantoux test and CBNAAT is negative in neurotuberculosis. If lumber puncture cant be done , CNS imaging can diagnose CNS tuberculosis that responds to Anti tubercular drugs and corticosteroids.



MRI brain of our patient



New Treatment Option for Thalassemia

Upasana Bhattacharyya*, Anupam Basu,**
**Dept of Zoology, The University of Burdwan.*
***Associate Director, National Institute of Biomedical Genomics (NIBMG), Kalyani*

Abstract

A new age of novel drug based therapeutic management, apart from transfusion therapy and iron chelation therapy aiming to improve anemia and as a result, overall quality of life is coming up in thalassemia. Among the new options, Luspatercept has shown initial success with significantly improved Hb levels or transfusion demand. Many other new and/or repurposed drugs are in the research phases. Accordingly, EHMT 1/ 2 inhibitors, PDE9 inhibitors, and Mitapivat, a pyruvate kinase activator, mTOR inhibitors, oral ferroportin inhibitors, etc. have already shown some success in clinical or preclinical studies. Moreover, recent studies have shown that thalidomide can increase the life span of RBCs and can be used for thalassemia treatment.

Introduction

ß-Thalassemia is a monogenic hereditary autosomal recessive disease caused by reduced or absence of ß-globin synthesis caused due to mutation in the beta globin gene. It is characterised by ineffective erythropoiesis. In this condition, maturation of erythroid cells is delayed and also hindered by apoptosis 1,2,3,4. This leads to a reduced number of mature RBCs in circulation, anemia and extramedullary erythropoiesis. Until now, there was no effective oral medication improving anemia in ß-thalassemia patients. Regular blood transfusions being the only current management strategy, which has many unwanted side effects like, iron overload, transmission of pathogens like HIV, HCV. It is the need of the hour to have some other treatment options. Bone marrow transplantation is also a potential cure but the success rates, cost and risks make it a less used management measure. Thus, several compounds are in different stages of newer drug development.

Drugs currently in use

Hydroxyurea:

Hydroxyurea (HU) is a cytotoxic agent that is proven to induce fetalhemoglobin (HbF) production. Study has shown previously that elevated ?-globin expression is strongly correlated with donation of NO-radical by hydroxyurea which acts via the sGC/cGMP pathway 5. Hydroxyurea as a NO donor directly causes the stimulation of intracellular sGC for the production of cGMP from guanosine-5'-triphosphate. cGMP stimulates cGMP-dependent protein kinase (PKG) in erythroid cells and increases fetalhemoglobin synthesis 6. Though there is a lack of approval and clinical evidence for ß-thalassemia (Foong et al., 2016), hydroxyurea is used and is beneficial in some beta thalassemia patients7,8. However, many patients don't respond to hydroxyurea and some responders lose their sensitivity to the treatment after repeated HU administrations, thus newer interventions are necessary.

Thalidomide

Thalidomide has been shown to cause the reduction of the transfusion volume in thalassemia. Thalidomide helps in promoting erythropoiesis via induction of GATA1 and STAT5 transcription factors. Derivatives of thalidomide like lenalinomide, as well as pomalidomide cause bone marrow function preservation, erythropoiesis augmentation and also cause reversal of ?-globin repression through reprogramming of transcription.

Correspondance : Anupam Basu, Dept of Zoology, The University of Burdwan. *Email ab3@nibmg.ac.in, abasu@zoo.buruniv.ac.in*

Lenalidomide, and pomalidomide was found to delay erythroid cell differentiation and maturation, promoting immature erythroblast proliferation, and causing transcriptional regulation of hemoglobin, and inducing HbF in healthy subjects and sickle cell anemia patient derived CD34+ cells9. Thalidomide increased RBC lifespan and alleviated hemolysis as exemplified by the decrease in LDH, IBIL and TIBIL after treatment 10,11,12.

Thalidomide benefits beta thalassemia by the regulation of hematopoietic stem and progenitor cell stages, differentiation stage, globin protein synthesis, and also RBC lifespan.

Luspatercept

Luspatercept, a recombinant fusion protein, was developed by Acceleron Pharma. Currently Luspatercept is marketed as Reblozyl. It is an activin receptor ligand trap. It binds to ligands of TGF (transforming growth factor beta) superfamily. In ß-thalassemia patients and patients with myelodysplastic syndrome, it has been shown to downregulate the TGF-ß pathway, which as a result inhibits the Smad2/3 signalling and reduces anemia13. Luspatercept has been approved by the FDA to treat transfusion dependent thalassemia patients at the starting dose of 1 mg/kg every 3 weeks. In TDT patients (n=31), when compared to the 12 weeks before baseline, 81% patients were observed to achieve a diminished transfusion of =20% over 12 weeks on study14.

Drugs: pre-clinical and clinical studies

mTOR inhibitor:

mTOR inhibitor like Rapamycin, is a lipophilic drug candidate which causes strong HbF induction both in vivo and in vitro15,16,17,18. It is also used in some cases for sickle-cell disease (SCD). In mouse model of thalassemia, Rapamycin (sirolimus) treatment19was correlated with reduced accumulation of a-globin as well as reduced ineffective erythropoiesis, and increased RBC lifespan. Rapamycin might increase the hematopoietic stem cells via mTOR pathway regulation20. Currently, Sirolimus (Rapamycin) is in clinical trials for beta thalassemia treatment (NCT03877809 and NCT04247750).

Phosphodiesterase 9 inhibitor:

IMR-687 (tovinontrine) is a selective phosphodiesterase-9 (PDE9) inhibitor that elevates intracellular cGMP. The cGMP-dependent pathway is needed for HbF production. As phosphodiesterase (PDE) 9 causes selective degradation of cGMP in erythroid cells, the use of PDE9 inhibitors can increase cGMP levels and reactivate HbF21. Administration of IMR-687 in Hbb th1/th1 mice (Beta thalassemia model) for 30 days improved disease progression markers, like, significantly increased Hb and RBCs and decreased reticulocytes and also improved differentiation of splenic erythroblasts. Moreover, IMR-687 was well tolerated in vivo. IMR-687 can be useful in beta-thalassemia treatment by improving RBC maturation and ineffective erythropoiesis22. Currently, a phase 2 study for evaluating the safety and tolerability of IMR-687 in TDT and NTDT adult thalassemic patients is going on (NCT04411082).

EHMT1/2 Inhibitor:

UNC0638 is an EHMT1 and EHMT2 histone methyltransferase inhibitor, which causes the induction of ?-globin expression. Knockdown of EHMT1/ EHMT2 by shRNA has been shown to increase the expression of ?-globin23,24. UNC6038 as an EHMT 1 / 2 inhibitor can induce HbF which can improve the beta thalassemia phenotype and is a potential drug candidate.

DNMT inhibitors:

Pharmacologically inducing fetalhemoglobin (HbF) is an efficacious treatment strategy for managing ß-hemoglobinopathies. In preclinical as well as clinical studies, DNA methyltransferase inhibitors like, 5-azacytidine and decitabine have been reported to cause the induction of HbF but are not approved for hemoglobinopathy. Recently in a GSK study, orally bioavailable reversible DNMT1-selective inhibitors were discovered as represented by GSK3482364 which increased HbF in sickle cell anemia by significantly inhibiting the methyltransferase activity

of DNMT125. As the imbalance in a-globin/ß-globin chain caused by decreased or absence in ß-globin synthesis is the main mechanism for anemia in ß-thalassaemia, improving this imbalance can be beneficial in beta thalassemia treatment.

HDAC inhibitors:

Histone deacetylation plays a major role in gamma-globin silencing through chromatin and transcription factor activity modification in the human ß-globin locus. HDAC1 and HDAC2 inhibition resulted in the induction of ?-globin and HbF in in vitro studies26. Histone deacetylase inhibitor drugs, like Vorinostat, used for cutaneous T-cell lymphoma, has the potential to suppress a-globin in beta thalassemia patients alongwithHbF induction27.

Pyruvate kinase activators:

Mitapivat (AG-348) is an oral small molecule allosteric pyruvate kinase activator. Mitapivat is being assessed in clinical trials for many hereditary hemolyticanemias, including pyruvate kinase deficiency (PKD), thalassemia and also sickle cell disease28. Currently two phase 3 multicenter, randomized, double-blind, placebo-controlled trials ENERGIZE and ENERGIZE-T are underway to study the efficacy and safety of mitapivat in non-transfusion dependent and transfusion dependent thalassemia patients.

Minihepcidin:

Minihepcidins are small peptides which are hepcidin agonists. Previously these peptides were shown to prevent iron overload in hemochromatosis mice models. They are known to lessen iron absorption and transferrin saturation29,30.

In recent studies, minihepcidins were reported to increase RBC count, RBC lifespan and hemoglobin concentration, decrease reticulocyte count, in Hbbth1/th1 mice model of beta thalassemia31.

Oral Ferroportin Inhibitor:

Vamifeport (VIT-2763) is a small-molecule oral inhibitor of the iron transporter ferroportin. Vamifeport treatment improved hemoglobin level and RBC count, showing improved erythropoiesis and amelioration of anemia as well as reduced iron levels in organs32,33.

Combining vamifeport with deferasirox (iron chelator) in the NTDT preclinical model, showed no negative effect of these drugs on each other34. VIT-2763 is undergoing a phase 2 study in NTDT is already underway (VITHAL, NCT04364269).

Discussion

These are the novel and/or repurposed drug candidates which are showing promising results in preliminary studies. Thus, in the near future, there will be a potential to improve the ineffective erythropoiesis in thalassemia which can help in increasing the transfusion interval or decreasing the transfusion dependency in beta thalassemia patients.

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Recent Advances in Management of Kawasaki Disease

Sayani Pan, Taraknath Ghosh
Department of Paediatrics, Burdwan Medical College and Hospital, West Bengal

Introduction

Kawasaki disease (KD) is the most common cause of acquired heartdisease in children in developed nations. This acute systemic vasculitis is more prevalent in Asian races, occurs mainly in infants and children under 5 years of age1 and predominantly affects the medium-size arteries. It is a multisystem vasculitis characterized by prolonged fever, polymorphous skin rash, nonpurulent conjunctival injection, extremity changes, oral mucosal changes, and cervical lymphadenopathy. Kawasaki disease is liable to be complicated by coronary artery lesions (CALs), which develop in approximately 15–25% of untreated KD children2, 3, 4 and in approximately 5% of KD children after intravenous immunoglobulin (IVIG) therapy.5, 6 The etiology of KD remains unknown and may be attributed to combined effects of infection, immune response, and genetic susceptibility.1

Making a timely and accurate diagnosis is essential for appropriate treatment, and incomplete KD poses a great challenge in this regard. While there are guidelines available for diagnosis, including clinical and echocardiographic findings, there is no definitive laboratory test, given the still unclear etiology. The best treatment option for recalcitrant disease is also debatable, as are the factors for those at high risk for coronary dilation. Although scoring systems are now available to risk stratify, these have variable success. It is envisaged that with the further development of novel biomarkers and genotyping, timely identification of those at risk will be a possibility.The present article reviews previous important publications with a special focus on the management of KD.

Correspondance : Sayani Pan, *Department of Paediatrics, Burdwan Medical College and Hospital Email : sayanipan92@gmail.com*

Management

IVIG and Aspirin :

Reducing inflammation or “putting out the fire” is key in the management of KD. This is achieved with the use of pharmacological “fire extinguishers”, for which the efficacy of IVIG has been well described by Newburger and colleagues in 1986.7 There is a strong inverse relationship between the IVIG dose and prevalence of coronary artery abnormalities(CAA)8,9 with described improved coronary outcomes from 15–25% to 3–5%.10,11

Current standard first-line management of KD include the use of IVIG (2 g/kg) as a single infusion plus oral Aspirin (80 to 100 mg/kg/day in USA or 30 to 50 mg/kg/day in Japan divided in 4 doses) until 48 hours afebrile or day 14 of illness. This is followed by oral aspirin (3 to 5 mg/kg/day) for 6 to 8 weeks which can then be discontinued if no further CAA are present on follow-up.

The role and dosing of oral aspirin in the acute management remains controversial 8,12-19, with regards to IVIG resistance rates and CAA. Although a reduction in fever duration has been reported with the use of high-dose aspirin 13,15,19, the role of CAA outcomes is not so straightforward. Furthermore, clinical bias with higher rates of high-dose aspirin prescription to those with early CAA would confound the results.

Kim and colleagues 13 reported a large retrospective study including 8,456 children managed in Korea comparing IVIG with medium to high-dose aspirin versus IVIG with low-dose aspirin. They observed

higher rates of IVIG resistance 10.5% vs. 16.9% (P<0.001) in those managed with low-dose aspirin. Higher rates of overall CAA were observed in those managed with IVIG and medium-high-dose Aspirin, with no differences in giant aneurysm rates.

Alternatives include oral clopidogrel (0.1–1.0 mg/kg/day) for Aspirin resistance or allergy or oral dipyridamole (1–5 mg/kg/day) for patients who require ibuprofen for alternative diagnosis, aspirin resistance and allergy or at risk of Reye syndrome 20.

Corticosteroids :

Steroids were once the first-line management of KD prior to the emergence of IVIG-directed therapy21. However, data on its role as first line has been controversial22-31. In 1979, an initial published report suggested that the use of steroids might actually worsen coronary artery abnormalities if used as part of the initial therapy of children with Kawasaki disease32.As an adjuvant therapy though, this appears more promising. Various case series, retrospective studies, and prospective studies suggested that corticosteroids may be beneficial in preventing coronary artery aneurysms. In particular, two trials from Japan and one from the USA found benefit from corticosteroids 33-35. Similarly, a meta-analysis concluded that the addition of steroids to initial therapy with IVIG and aspirin reduced the incidence of coronary artery aneurysms 36 ,Another meta-analysis suggested that steroids reduced the incidence of IVIG failures but did not have an impact on coronary artery aneurysms 37. Recently, in RAISE23 study, a multicenter, prospective, randomized, blinded, endpoints study conducted in Japan, 3% patients in the IVIG plus steroids group compared with 23% patients in the IVIG alone group were found to have coronary artery abnormalities (P < 0.0001). Additionally, patients in the steroid group had a lower incidence of needing second-line therapy (13 vs. 40%, P < 0.0001) and had significantly lower median z-scores for all coronary arteries measured at all three time points.In view of the promising early results, low-dose corticosteroids as an adjuvant to IVIG and Aspirin has been proposed in the most recent guidelines 20,23in the management of higher risk groups. The role of monotherapy with steroids is however not indicated.

Taking into account these recent studies, updated guidelines have been recently proposed for management of KD in the UK 59. UK guideline confirms that IVIG should be administrated in a single-dose at 2 g/kg and suggests aspirin administration during the acute phase of the disease at lower doses (30-50 mg/kg/day). As previously recommended, the anti-inflammatory dose should be reduced to an antiplatelet dose of 3-5 mg/kg/day once fever and inflammation subsided 59. UK guideline is particularly innovative compared with those of AHA because for the first time it proposes corticosteroids administration for the primary treatment of severe KD 59. The authors suggest that corticosteroids should be considered in:

1) IVIG-resistant patients
2) Children with features of severe disease (< 1 year old; those with markers of severe inflammation, including persistently elevated C-reactive protein (CRP) despite IVIG, liver dysfunction, hypoalbuminemia, and anaemia)
3) Children who develop features of hemophagocytic lymphohistiocytosis and/or shock
4) Patients who already have evolving coronary and/or peripheral aneurysms with ongoing inflammation at presentation
5) Kobayashi risk score = 5

In the absence of robust evidence, UK guideline provides two suggested regimens:

1) Intravenous preparation equivalent to 2 mg/kg prednisolone (ie, methylprednisolone 0.8 mg/kg twice daily) for 5-7 days or until CRP normalizes, followed by oral prednisolone 2 mg/kg/day, weaning over the next 2-3 weeks
2) Methylprednisolone 10-30 mg/kg intravenous (IV) once a day for three days, followed by oral prednisolone 2 mg/kg/day until day seven or until CRP normalizes, weaning over the next 2-3 weeks.

IVIG Resistance: Despite adequate and timely

therapy, the risk of IVIG resistance is documented in 9.7% to 32.2% 38-45of KD children, with an up to nine-fold increased risk of CAA 46. Response to IVIG is defined as resolution of fever (T <37.5 °C) and mucocutaneous features, and may take up to 36 hours from end of IVIG infusion1,20.

Multiple risk factors have been identified for IVIG resistance. Two meta-analysis 47.48identified multiple risk factors including higher total bilirubin, polymorphonuclear leukocytes (PMN), pro-brain natriuretic peptide (pro-BNP), aspartate aminotransferase (AST), alanine aminotransferase (ALT), ESR and CRP levels, with lower sodium levels, albumin level, haemoglobin, and platelet count. Even clinical variables have been associated with IVIG resistance including fever duration 49, perianal changes 50, cervical lymphadenopathy 51, changes in oral mucosa, cervical lymphadenopathy, swelling of extremities, and polymorphous rash 48.

To expand on these variables, multiple scoring systems have been proposed 51-54. These included various variables and different scoring algorithms. Cross translation of these data to different populations has however been variable in populations of different ethnic backgrounds 54-55, with generally poor sensitivities. The use of four of the more commonly cited scoring methods including the Egami 44, Kobayashi 45, Sano 43 and Fukunishi51 in our local Singaporean Chinese population had poor sensitivities resulting in 42–85% of patients with IVIG resistance missed 56. It is possible that the baseline genetic profile of the different populations would result in different risks.

Moving forward into an era of personalised medicine, a genetic risk profile could help tailor targeted therapy. Jaggi and colleagues 57generated a genomic score that was higher at baseline in IVIG resistance (median 12,290 vs. 5,572 in responders, P=0.009) and independently predicted IVIG response. In addition, Kuo and colleagues 58calculated a weighted genetic risk from 11 single nucleotide polymorphisms (SNPs) identified by genome-wide association study recognizing a significant association between weighted genetic risk score (P=4.518×10-3) and the response to IVIG (P=8.224×10-10).

With further work, new algorithms combining clinical, biochemical and genetic data would facilitate more accurate and population-specific risk estimations, allowing for more appropriate targeted therapy.

Treatment of IVIG non-responders:

About 80% of children who do not respond or have an incomplete response to a first infusion of IVIG respond to a second dose of IVIG, 2 g/kg60,61. This is our preferred therapy for those who do not respond to an initial dose of IVIG with aspirin. Other therapeutic options for non-responders include intravenous pulse steroid infusion and infliximab(5mg/kg).

Because some patients with acute KD have elevated serum tumor necrosis factor a (TNF-α) levels 62and such patients may be at increased risk of developing coronary artery abnormalities 63, investigators postulated that infliximab, a chimeric murine/human IgG1 monoclonal antibody that binds specifically to human TNF-α, might be effective therapy in KD. An initial report of apparent efficacy of this treatment in a group of refractory KD patients 64 was followed by a multicenter trial in which a second IVIG infusion was compared with infliximab for initial IVIG nonresponders65. This study showed that the two therapies were safe and well-tolerated, and that most patients treated with either therapy appeared to respond. A recent report indicated that 2.3% of US patients with KD received infliximab for IVIG-resistant KD in 2006 66.

Etanercept (Enbrel) is another TNF-α inhibitor that has been studied in a small number of Kawasaki disease patients. Etanercept is a soluble TNF receptor and functions as a TNF antagonist with a proposed similar mechanism of action to infliximab in the treatment of Kawasaki disease. Similar to infliximab, etanercept has been widely used in a wide array of autoimmune and inflammatory diseases. Etanercept (three doses at 0.8 mg/kg/dose weekly) was recently shown to be safe and well tolerated in a small study (n = 15) of children with Kawasaki disease as adjunctive initial therapy with IVIG [67].

An emerging therapy for IVIG-resistant disease is the use of the calcineurin inhibitor cyclosporine A (CSA). Two recent studies support the use of CSA in the treatment of Kawasaki disease. A prospective case

series of IVIG-resistant Kawasaki disease patients in Japan demonstrated efficacy, as measured by defervescence and decreased CRP, using an oral regimen of 4–8 mg/kg/day in 18 of 28 (64%) patients [68]. Similarly, a multicenter case series in the USA demonstrated the efficacy of using CSA in nine of nine (100%) patients with IVIG-resistant disease (a tenth patient was treated and responded to another calcineurin inhibitor, tacrolimus) [69]. On the basis of their experience, these researchers have proposed a detailed protocol for the use of CSA which recommends a dose of 3 mg/kg/day intravenously divided every 12 h followed by a switch to Neoral (oral CSA) once the patient is afebrile for 24 h.

Another Chinese study showed an effect of IL-1B polymorphism on the association with IVIG resistance in Taiwanese children with KD,70 which suggests the potential usefulness of monoclonal antibodies to IL-1, such as Anakinra, for IVIG-resistant patients.71

Several other therapies have been tried for IVIG-resistant disease. Two case series and a case report in Korea have documented success in using methotrexate (10 mg/body surface area weekly) in a total of 22 patients with IVIG-resistant disease [59–61]. Several case reports and one large retrospective case series (125 patients) in Japan have reported favorableoutcomes for plasma exchange in IVIG-resistant disease [62–66]. Ulinastatin, a urinary trypsin inhibitor that protects tissues against neutrophil-mediated injury, has also regained some attention in the literature. Ulinastatin has been shown to be inferior to the use of IVIG in the treatment of Kawasaki disease [67], but a large, recent retrospective study in Japan suggests that it may have some utility as initial adjunctive therapy in combination with IVIG [68].

Cyclophosphamide (2mg/kg/dose, IV) is another immunosuppressive agent that has been used in the management of IVIg non-responders in some cases.

Although these various therapies are now being tried and tested, no definite conclusions can be reached from these rare individual cases. Prospective clinical trials are warranted to determine the role of these therapies.

Conclusion

Management of KD is still of particular concern for paediatricians. However, recent advances have been important in improving the prompt disease diagnosis as well as developing a more effective treatment for KD. Identification of patients at increased risk of IVIG resistance and consequentially of acute and long-term heart complications is a goal for the future. Novel clinical scores should be proposed to identify non-Japanese children at the highest risk of CAA

Although several promising second-line therapies have been studied in a limited number of patients, most clinicians currently use IVIG as the second-line therapy. Of other therapies in this review, infliximab and steroids have the most experience as alternative second and third-line therapies. Further studies are urgently needed to identify what optimal therapy is needed for high-risk Kawasaki disease patients.

It is envisaged that with rapid advances in research and collaborative work among physicians in this field, that we will be even better equipped with knowledge to risk-stratify, diagnose and manage KD, especially the incomplete and complex variants, in achieving better outcomes.

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Predictors of Vaccine Hesitancy in Under-5 Children

Kamirul Islam

Medical Officer, Department of Paediatrics, Burdwan Medical college and Hospital.

Objectives: The study was conducted to estimate the prevalence of vaccine hesitancy among under-5 children, its predictors, and the reasons behind it. Methods: This cross-sectional, community-based study was conducted in Burdwan town between March, 2022 and February, 2023. Parents of children selected by stratified random sampling were approached for inclusion. Children whose parents refused consent, who were absent despite 2 home-visits, and whose Mother and child protection cards were not available were excluded. A pre-designed, pre-tested, semi-structured schedule was used for data-collection by interview of parents/ caregivers and review of immunisation records. P <0.05 was taken as the level of statistical significance.Results: Vaccine hesitancy was noted in 447 (46.6%) children, most commonly in Diphtheria-Pertussis-Tetanus booster (331, 74%). Waiting period <1 hour at vaccination site was the most important predictor (AOR- 0.35). Conclusion: Waiting period at vaccination area was the most important predictor of vaccine hesitancy among the under-5 children.

Key-words: Immunization, Schedule, Delay, Quality

Vaccination is a useful and economic strategy to get rid of morbidity, and mortality from grave infectiousdiseases. Delay in acceptance or refusal of vaccine despite the availability of vaccination service is known as vaccine hesitancy (VH), and is a crucial indicator of quality of immunization in a community [1]. It is the major reason of large unimmunised population in India, leading to decrease in herd immunity which in turn is responsible for outbreak of infectious diseases [2].Recently World Health Organisation declares VH as one of the top ten threats to public health [3].

Identification of risk factors of VH is important to reduce the burden of unimmunised population, and vaccine-preventable deaths.But literatures on this topic are limited, and suffer from methodological issues (e.g. conducted predominantly in countries of Europe and Africa, inappropriate sample size, inclusion of variable age groups, hospital-based study, addressing hesitancy to specific vaccines-like, COVID-19, influenza, measles etc) [4-6]. This study was therefore conducted to estimate the prevalence of VH among under-5 children, its predictors and, the reasons behind VH in a tier II city of West Bengal.

Correspondance : Dr Kamirul Islam, Medical Officer, *Burdwan Medical College and Hospital. Email kamirul.islam7@gmail.com*

Methods:

This cross-sectional, community-based study was conducted in Burdwan town between March, 2022 and February, 2023 after taking approval from Institutional ethics committee. Informed written consents were taken from parents/ legal guardians of each participant. According to the findings of Dasgupta, et al., the prevalence of vaccine hesitancy was approximately 83% [7]. Considering 95% confidence level, and 2.5% precision, required sample size would approximately be 904. Assuming 10% non-response, we planned to include 995 children in the study. The town comprises of 35 wards.Total sample size was divided in each ward proportionately to total number of children in that ward. Required numbers of children from each ward were selected by simple random sampling. Data were collected by home-visit (accompanied by local health workers) using a pre-designed, pre-tested, semi-

structured schedule by interviewing the parents/ caregivers of selected children, and reviewing the Mother and child protection (MCP) card. Children whose parents refused consent, who were absent despite 2 home-visits, and whose MCP cards were not available at the time of interview, were excluded.Socio-demographic variables[age, sex, education of parents,type of family, socioeconomic status, mode of delivery, birth order, exclusive breast feeding for 6 months, and waiting period for vaccination] and vaccination status were recorded.Questions related to cause of vaccine hesitancy were also asked to respondents. Modified BG Prasad scale was used for determination of socioeconomic status [8].Any vaccine administered more than 2weeks after due date was considered as vaccine hesitancy [7]. Only vaccines included in National Immunisation Schedule (NIS) [Bacillus Calmette–Guérin (birth dose), Hepatitis B (Birth Dose), Oral Polio Vaccine (Birth dose, and 10th week), Pentavalent (6th, 10thand 14th week), Inactivated Polio Vaccine (6th, and 14th week) Rotavirus vaccine (6th, 10th and 14th week), Pneumococcal conjugate vaccine (6th, 14th week and 9th-12th month) Measles vaccine (9th-12th month, and 16th-24th months), Japanese Encephalitis vaccine (9th-12th and 18th-24th months), and Diphtheria-Pertussis-Tetanus vaccine (16th-24thmonths and 5-6 years)] at the time of inception of study were considered for determining vaccine hesitancy. The highest age is considered for calculating vaccine hesitancy for vaccines with an age-range.

Statistical Analysis: Shapiro-Wilk test was used to check normality of distribution. Chi-square test was used to check significance of difference between proportions. Student's t test and Mann-Whitney U test were used respectively for normal and skewed data. Cut-off values for continuous variables were calculated from receiver-operator characteristic curve with the help of Youden's index. Binary logistic regression was used to identify contribution of each predictor, and for calculation of adjusted odds ratio. $P<0.05$ was taken as the level of statistical significance. IBM SPSS Statistics for Windows, version 23 (IBM Corp, Armonk, NY, USA) was used for data-analysis.

Results:

Parents of 995 children were approached for inclusion in the study, and 39 were excluded (21- absent despite two home-visits, 14- refusal of consent, 4- MCP cards were not available) to finally include 959 (46.5% boys) children in this study with a median (IQR) age of 32.3 (23.3- 42.5) months. Majority of them were Hindu (515, 53.5%), and belonged to lower socioeconomic status (598, 62.4%). Vaccine hesitancy was noted in 447 (46.6%, 95% CI: 43.4-49.8%) children. Vaccine hesitancy was most commonly due to delay in Diphtheria-Pertussis-Tetanus booster (331, 74%), followed by measles (244, 54.6%) and Japanese Encephalitis vaccine (194, 43.4%). Sociodemographic characteristics of children with vaccine hesitancy and who did not have vaccine hesitancy are represented in table I, and different reasons behind vaccine hesitancy are summarised in table II. Binary logistic regression model could correctly explain 78.1-79.8% variation of dependent variable (i.e. vaccine hesitancy). Waiting period <1 hour at vaccination site was the most important predictor (AOR- 0.35, 95% CI: 0.26-0.47) of vaccine hesitancy which could alone explain 59.1-59.5% variation. Other three significant predictors were, education of mother: secondary and above (AOR- 0.60, 95% CI: 0.45-0.79), lower socioeconomic status (AOR- 1.36, 95% CI: 1.03-1.79), and maternal age >26.5 years (AOR- 0.93, 95% CI: 0.89-0.97).

Discussion:We found that vaccine hesitancy was present in nearly half children, and waiting period at vaccination area was the most important factor associated with it.

Inclusion of only urban Bengali children might affect the external validity of the study. Also, only the vaccines included in NIS were considered for estimation of vaccine hesitancy. Few data were solely based on memory.

Estimated prevalence of vaccine hesitancy was higher than previous reports (5.3%-40%) [4,6,9-12]. This difference could be attributed toalteration in socioeconomic status across study population, inclusion of sample from out-patient or immunization clinic, and differences in operational definition of VH among the studies. Dasgupta, et al. observed a much

Table I: Distribution of the study population according to presence of vaccine hesitancy and different socio-demographic variables (n=959).

Socio-demographic variables	Vaccine hesitancy present (n= 447)	Vaccine hesitancy absent (n= 512)	Significance
Age (m)*	32.3 (22.2-42.8)	32.4 (24-42)	Z score= -0.20, P=0.42
Male Sex#	207 (46.3)	239 (46.7)	χ^2= 0.01, P=0.91
Hindu religion#	238 (53.2)	277 (54.1)	χ^2= 0.07, P=0.79
Education of father (Graduate and above)#	104 (23.3)	138 (27.0)	χ^2= 1.71, P=0.19
Education of mother (Secondary and above)#	134 (30.0)	211 (41.2)	χ^2= 13.07, P=0.0002
Lower Socioeconomic Status#	295 (66.0)	303 (59.2)	χ^2= 4.72, P=0.03
Nuclear family#	214 (47.9)	276 (53.9)	χ^2= 3.47, P=0.06
Maternal age (y)†	26.1±2.9	26.7±2.9	Student's t=3.51, P=0.0005
Normal Delivery#	354 (79.2)	397 (77.5)	χ^2= 0.38, P=0.53
Exclusive breast feeding#	327 (73.2)	381 (74.4)	χ^2= 0.20, P=0.66
Birth order: First#	213 (47.7)	237 (46.3)	χ^2= 0.18, P=0.67
Waiting Period at vaccination site <1 hour#	244 (54.6)	395 (77.1)	χ^2= 54.6, P<0.001

**Median (IQR), Mann-Whitney U test was used; #no (%), Chi-square test was used; †Mean (SD), Student's test was used.*

Table II: Reasons behind vaccine hesitancy (n=447).*

Reason	Frequency (%)
Prolonged waiting at vaccination site	256 (57.3)
Fear of COVID-19 infection	167 (37.4)
Lack of awareness/ information	132 (29.5)
Fear of adverse effect	91 (20.4)
Sickness of child	84 (18.9)
Influence of social media/ internet	77 (17.2)
Family problem	75 (16.8)
Travel	64 (14.3)
Influence of spiritual leaders	48 (10.7)
Others	33 (7.4)

**Multiple reasons may be there for single child*

higher prevalence (˜83%) might be due to inclusion of slum-dwellers who were predominantly migratory in nature, and belonged to lower socioeconomic status [7]. Otherauthors also noted waiting period at vaccination site is an important determinant of VH [10,13]. Multiple Indian authors identified higher socioeconomic status, and higher education of parents (particularly mothers), weresignificant protective factors for VH [7,10,12,14]. Educated parents are more likely to understand the beneficial effects of timely vaccinations.Unlike previous studies we did not find nuclear family, mode of delivery, and

child's age as risk factor of VH, probably due to presence of confounders [4,7,12].Various reasons cited for vaccine hesitancy were similar with the previous observations from India and abroad [4,10,15]. Fear of COVID-19 emerged as a new cause in the present study due to conduction of the study in context of pandemic.

To conclude, waiting period at vaccination area is the most important predictor of vaccine hesitancy among the children. These issues need to be properly addressed for success of Universal immunization program in the country.

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Vitamin B12 Deficiency Encephalopathy- A Killer in Disguise

Debjani Bandhopadhyay*, Mihir Sarkar, Arundhati Banerjee**, Sankar Das**, Asraf Uz Zaman***, Manas Kumar Mahapatra***, Subhayan Mukherjee*****

**PGT, **Professor, ***Senior Resident, Department of Paediatrics, Medical College & Hospital, Kolkata*

Introduction:

Vitamin B12 is a water soluble vitamin that has a key role in normal functioning of CNS and RBC formation.

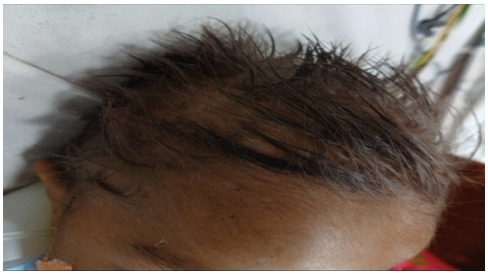
Vit-B12 deficiency can present with anaemia (macrocytic), gastrointestinal disorder and neurological abnormalities. Neuropsychiatric manifestations of vitamin B12 deficiency include:

- Dementia
- Delirium
- Mood disorders
- Psychosis
- Personality changes

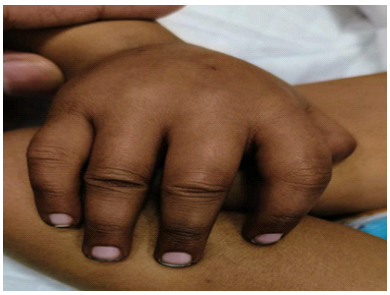
Encephalopathy due to VitB12 deficiency is very rare. Here we report a 2½ years old boy presented with acute encephalopathy due to Vit-B12 deficiency.

Case History

A 2yrs 6months old boy presented with:

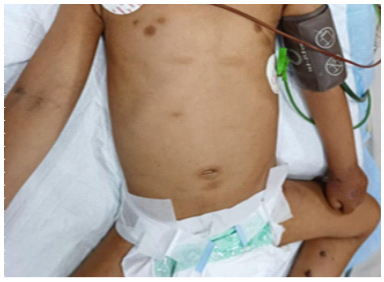


Sparse hairs (easily pluckable)



Hyperpigmented knuckles

Correspondance : Mihir Sarkar, *Professor, Resident, Department of Paediatrics, Medical College & Hospital. Email : drmihir09@gmail.com*



Pale skin (Pallor) & diffuse skin pigmentation

This was associated with:

- Decreased feeding
- Frequent vomiting
- Weakness
- Oral ulcers

} Duration- 6 months

- coryzal symptoms
- shortness of breath

} Duration- 2 days

Past History of hospitalisation for two times with pallor, fatigue and diarrhoea,H/o blood transfusion (2 times) for severe pallor.

Examination on presentation:

(a) Alert/conscious(GCS: 15/15)
(b) Afebrile
(c) Pallor(+), Icterus(-), Cyanosis(-),
(d) Edema(-), Neck Veins(n), L.N(n)
(e) SpO2- 88-90% (at Room air)
(f) Pulse- 112/min, good pulse vol.,sinus rhythm
(g) R.R- 52/min( ) [Retractions/Grunting(-)]
(h) CVS- S1,S2 (+), M(-)
(i) Chest- B/L VBS & Crepitations (+)
(j) P/A- Soft, IPS(+),
(k) No organomegaly
(l) CNS- WNL
(m) U/S- passed

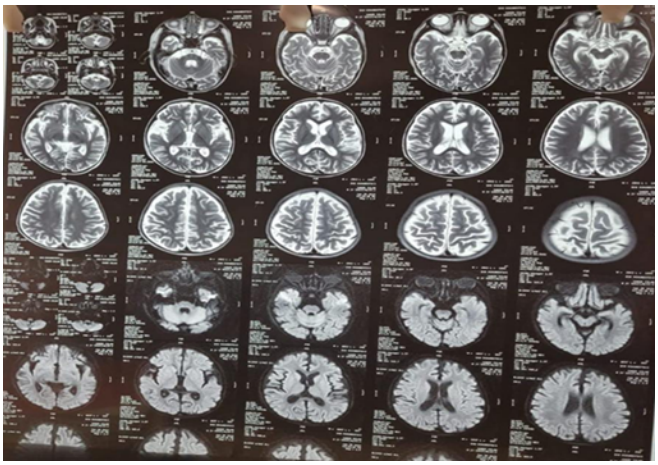
Next day, he developed- drowsiness, 2 episode of fever, followed by refractory generalised convulsions.

Investigations

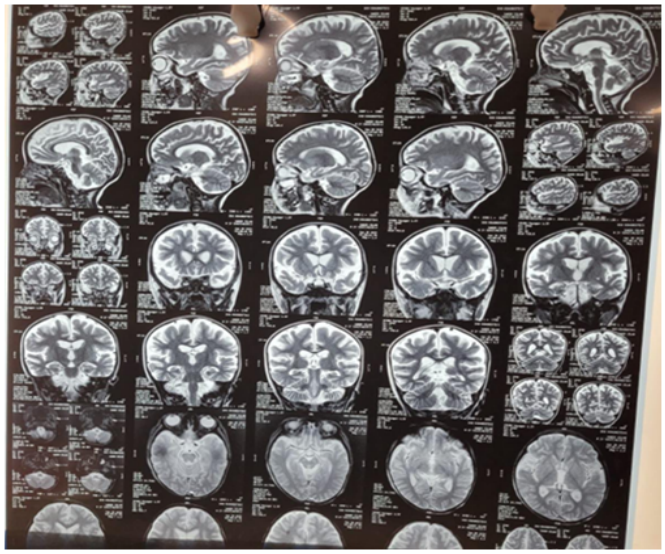
Hematological Investigations	Reports
Hb	6.5 g/dl
MCV	115 fl
MCH	37 pg
TLC	13,510/mm3
Platelet Count	1.8 L/mm3
CRP	14 mmol/L
Blood C/S	No growth
LFT	WNL
RFT	WNL

Metabolic Investigations	Reports
Random Blood Glucose	126 mg/dl
Serum Ammonia	26 mmol/L
Serum Lactate	1.37 mmol/L
Serum Folic Acid	11.5 ng/ml
TMS	WNL
Biotinidase (FEA)	WNL
Serum Vit B12	145 pg/ml
Serum Homocysteine	58.7 micromole/L

Other Relevant Investigations	Reports
CSF Study	2 cells/mm3 (all mononuclear) Protein - 24 mg/dl Glucose - 72mg/dl C/S – No Growth CBNAAT - Negative HSV DNA PCR – Negative
Respiratory Viral Panel	Negative
EEG	Generalised slowing of the background
Imaging:	
CXR	Hyperinflated Lung fields (b/l)
MRI Brain	1. Hyperintensities in bilateral temporal lobe 2. Cortical sulci widening and cerebellar folios with slightly dialated lateral ventricles.



T2 W image showing hyperintensities in bilateral temporal lobe



T2 W image showing cortical sulci widening and cerebellar folios with slightly dialated lateral

Differential Diagnosis:

(a) AES

(b) Metabolic disorders

(c) Autoimmune encephalitis

TREATMENT:

(a) Patient was intubated.

(b) Other neuroprotective strategies were followed.

(c) Antibiotics were started as per acute encephalitis syndrome (AES) protocol.

In view of no improvement of sensorium despite above treatment, Parenteral administration (I.M) of Vit-B12 (1000 mcg) was given:

alternate days in first week

↓

Weekly for 2 months

↓

Monthly for 6 months

Folate supplementation was also added.

(picture taken with consent)

This leads to dramatic improvement of the condition:

(a) Neurological symptoms improves within 2-3 days.

(b) Haemoglobin levels started increasing in 1 week.

(picture taken with consent at 3 months of follow up)

Discussions

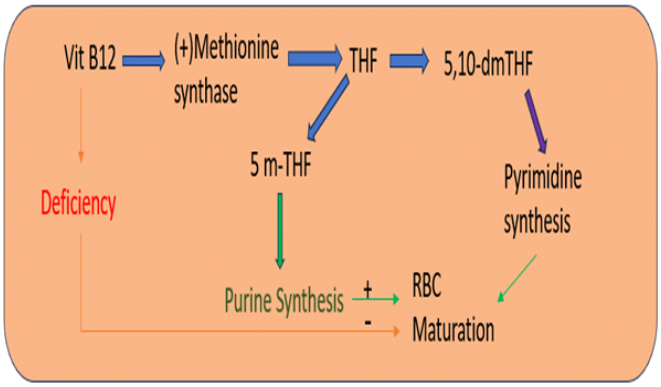
(a) Studies have shown that about 10% of patients with Vit B12 deficiency show knucle hyperpigmentation.

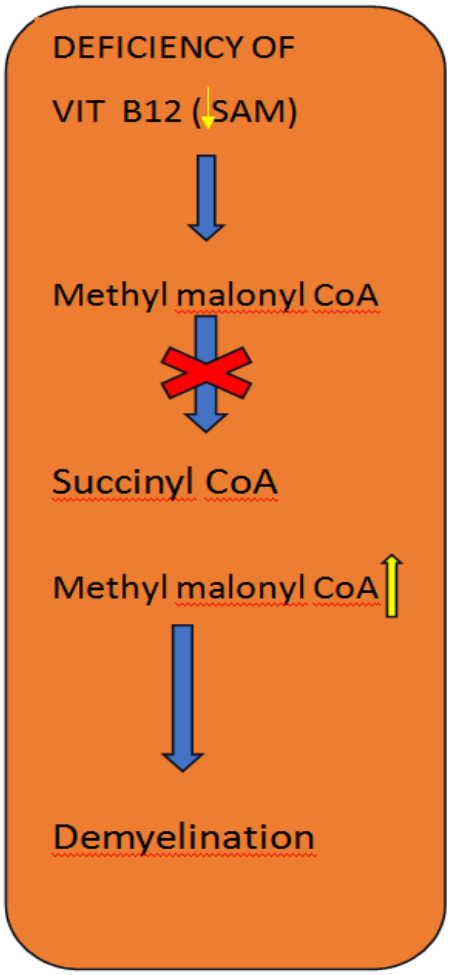
(b) The skin changes, bone marrow failure and demyelinating nervous system disorders are reversible.

(c) suggests, several conditions can falsely elevate or decrease serum cobalamin concentrations, hence the metabolites upstream (Homocysteine and MMA) should always be checked.

(d) Data suggests that prevalence of Vit B12 deficiency in Indian Population was found to be 47%.

(e) About 25% of patients with Vit B12 deficiency present with neurological signs.





Conclusion

(a) Though infective and autoimmune causes are common aetiologies of AES, reversible neurometabolic conditions are often neglected.

(b) Temporal lobe involvement in vit-B12 deficiency is not reported in literature.

(c) Hence any child presenting with macrocytic anaemia and encephalopathy should be investigated for reversible neurometabolic causes.

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WBAP EB Member 2023

Name	Post	Email
DR KALPANA DATTA	PRESEDENT,CIAP EB	drkalpanadatta@gmail.com
DR INDRANIL CHOWDHURY	SECRETARY	indranil.chowdhury1234@gmail.com
DR ASOK KUMAR DATTA	PRESIDENT ELECT	asokdatta31@yahoo.com
DR SUSHMITA BANERJEE	IMM. PAST PRESIDENT	sushmitabanerj@gmail.com
DR DIBYENDU RAYCHAUDHURI	VICE PRESDIENT	dr.dibyenduraychaudhuri@yahoo.com
DR MADHUMITA NANDI	IMM PAST SECRETARY	madhumitabanik@rediffmail.com
DR MIHIR SARKAR	JT. SECRETARY	drmihir09@gmail.com
DR PRIYANKAR PAL	TREASURER	mailme.priyankar@gmail.com
DR KALPANA DATTA	CIAP EB	drkalpanadatta@gmail.com
DR KAUSTAV NAYEK	CIAP EB	kaustav25@yahoo.co.in
DR KRIPASINDHU CHATTERJEE	CIAP EB	kschatterjee@gmail.com
DR ABHIJIT SARKAR	EXECUTIVE MEMBER	dr.sarkar@yahoo.com
DR AGNI SEKHAR SAHA	EXECUTIVE MEMBER	agnisekhar@hotmail.com
DR AMITA SINHA	EXECUTIVE MEMBER	amitasinhamandal@gmail.com
DR ASHIM KUMAR GHOSH	EXECUTIVE MEMBER	akgasn@gmail.com
DR BIPLAB BANERJEE	EXECUTIVE MEMBER	biplabjoy19@gmail.com
DR NILANJAN GHOSH	EXECUTIVE MEMBER	niltughosh@gmail.com
DR RUPA BISWAS	EXECUTIVE MEMBER	drrupa.biswas@gmail.com
DR SAMIK HAZRA	EXECUTIVE MEMBER	samik.hazra@gmail.com
DR SHUBHADEEP DAS	EXECUTIVE MEMBER	shubhadeepnrsdoc@gmail.com
DR SUMANTRA KUMAR RAUT	EXECUTIVE MEMBER	drsuman.raut@gmail.com
DR KAUSTAV NAYEK	Editor-in-Chief, CIAP EB	kaustav25@yahoo.co.in
DR SAMIR RANJAN DAS	Chairperson,Constitution Committee	das.samir2006@gmail.com
DR DEBAJYOTI BURMAN RAY	Chairperson, WBAP Board of Trustee	drdebajyotibroy@gmail.com
DR SWAPAN KUMAR RAY	Chairperson, Scientific Committee	drswapanray@gmail.com
DR VINAY ASAWA	Chairperson, Finance Committee	vinayasawa91@gmail.com
DR INDU SURANA	Chairperson, Community Action Plan	Indu.paed@rediffmail.com
DR ASAMANJA HAJRA	Coordinator, WBW Week	ahajra008@rediffmail.com
DR KAUSIK CHAKRABARTI	Coordinator, Immunisation Committee	drkausik.chc@gmail.com
DR ABUL FAZL A RAHAMAN	SPECIAL INVITEE	afardgp54@yahoo.com
DR ATANU BHADRA	SPECIAL INVITEE	atanu4bhadra@gmail.com
DR CHAMPAK DAS	SPECIAL INVITEE	champakdas23@gmail.com
DR SUBROTO CHAKRABARTTY	SPECIAL INVITEE	chakrabartty.subroto@gmail.com
DR SUKANTA CHATTERJEE	SPECIAL INVITEE	sukantachatterjee@hotmail.com

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