The Child and newborn

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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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Special Correspondance
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

Dear esteemed dignitaries and members of the West Bengal Academy of Paediatrics,

As I pen down this farewell note, a flood of emotions overwhelms me – a year has swiftly passed, marked by moments of growth, collaboration, and shared dedication to the field of pediatrics. Serving as President has been an immense honor and a truly enriching experience.

I am overwhelmed with gratitude for the confidence and faith you reposed in me and for having the privilege of serving as President during this transformative phase over the last one year. It has been an incredible journey we've shared during my tenure as the President of this esteemed body. The 42nd West Bengal State PEDICON is a testament to our collective dedication, endeavours and unwavering commitment to our body in pursuit of excellence in delivering quality healthcare.

Our accomplishments in 2023 are the result of our commitment to grow and progress. As I reflect upon the accomplishments, we've achieved together fills me with immense joy. The initiatives undertaken by the West Bengal Academy of Paediatrics in 2023 stand as milestones of our commitment to progress.

The formation of several Sub-Committees has not only increased member participation but has also infused a rich tapestry of evidence-based activities across various districts, fostering a stronger and more inclusive community.

Sandhya Pathshala program launched in this year has been well received with significant and active participation of resident doctors and practicing pediatricians. The introduction of Sandhya Pathshala, our online bedside clinical meeting held every month, has been instrumental in enhancing our clinical acumen and has been pivotal in refining our clinical expertise. Complementing this, the series of monthly workshops on diverse topics have been instrumental in fostering continuous learning and has contributed significantly to ourprofessional growth.

The establishment of new district branches has been a cornerstone in expanding our reach and cemented our connection with paediatricians in varied regions. Collaborating closely with these branches for their annual conferences has further strengthened our bond, has provided us a platform enabling us to exchange knowledge and expertise seamlessly.

Our participation and partnership as a key entity in national conferences such as RESPICON, ISPNCON, ASTHMACON, and VACCICON has not only elevated our stature but has also showcased our commitment to shaping the future of paediatric healthcare at a national level.

Yet, amidst these remarkable accomplishments, our vision should propel us forward to

achieve greater excellence. We should aim to stay at the forefront of paediatric care by continuously updating ourselves with the latest guidelines, meticulously implementing immunization practices and government programs. Our body's aspiration is to disseminate this knowledge down to the grassroots level, ensuring equitable access to top tier paediatric care for every child across the state of West Bengal.

However, the road ahead beckons us with challenges and opportunities. To further our impact, we must embark on a vigorous membership drive, encouraging more paediatricians, especially those in remote far flungareas, to join our collective pursuit of excellence. Their involvement, inputs and unique perspectives will be invaluable in shaping comprehensive paediatric care for all.

WBAP envisions a future where community participation becomes the bedrock of our endeavours. Collaborations with government agencies and esteemed entities like the WHO, UNICEF and others (NGOs) will fortify our efforts and exponentially magnify our impact manifold.

As I step away from this honoured position and handed over the baton of presidency to my esteemed successor, I am confident that the Academy will continue to thrive and reach new heights.I urge each of you to carry forward the torch of excellence. Let us persevere in our relentless pursuit of excellence and continue to work tirelessly, transcending boundaries and creating a lasting legacy, which I'm sure will leave an indelible mark on the landscape of paediatric healthcare.

Thank you for entrusting me with the privilege of serving as your President. It has been an honour to lead such a dedicated and passionate group of individuals. Together, we have ushered in a new era of paediatric excellence which has made a difference in healthcare, and together, we shall continue to shape a brighter and healthier future for paediatric population in our state and beyond.

I am grateful for the tireless efforts of each member, committee, and staff who contributed to the success of the Academy during my tenure.I extend my deepest gratitude to each one of you for your support, collaboration, and the privilege of serving as a President of this august body.

Wishing the WBAP, continued success and prosperity.

May God bless us all…

Happy New Year 2024

Will end with profound gratitude and warms regards,

Jai Hind

IAP for all.

Editorial

As editor in chief, this is the fourth occasion I'm writing the preface to the Child and Newborn. We started the year with the dream to revive our own Paediatric Journal from West Bengal Academy of Pediatrics. We were very hopeful but sceptical at the same time. That, we are able to publish the fourth edition of the journal this year is a testimony to the fact , that we are on the right path. Yes, the journey has been gruelling. I am greatful to all fraternity members who have contributed to the journal. It is because of your efforts this journal stands on firm grounds today. I thank all of you who have given your feedbacks. I'm trying my best to include all your thoughtful suggestions for the future issues. Please continue to send your feedbacks. Our ultimate target is to make this journal peer reviewed indexed journal. With all your support we will surely reach our goal in the near future.

It has been an excellent year of academics for West Bengal Academy of Pediatrics. The horizons of Clinical Case Presentation by Medical Colleges has expanded with one on line and one off line mode presentation each month. So most of the Institutes with PG students got the opportunity for clinical case presentation this year. "Sandhya Pathshala" the brain child of our President Dr.Kalpana Dutta was also very fruitful for young budding Pediatricians. Icing on the cake was the annual conference, State PEDICON. It was exceptional in all aspects. All the pre conference workshops were fully attended, there were numerous scientic talks, debates, panel discussion spread over two days. There was also a creative stall by our pediatricians with their paintings, photographs and books authored by them. The number of delegates who attended the conference was highest in recent years.

Child and Newborn will continue it's journey in the coming year . Your active participation for its improvement is very important. With your active participation it will surely reach its goal. Still there are lots of drawbacks. It's distribution is still not perfect. I will try my best to improve upon these aspects. Thank you all and have a great new year ahead.

Dr Kaustav Nayek
Editor-in-Chief

Micronutrient Status in Children with Autism Spectrum Disorder

***Kamirul Islam, **Kaustav Nayek**
**Medical Officer, **HOD, Department of Paediatrics, Burdwan Medical college and Hospital.*

Abstract:

Objectives: To find the relationship between status of micronutrients (iron, zinc and vitamin D) and autism spectrum disorder.Methods: This hospital-based,case-control study was conducted in the Pediatric out-patient clinic of a tertiary care centre between January, 2020 and December, 2022. Sociodemographic characters, iron status indicators (hemoglobin, iron, total iron binding capacity, and ferritin), serum zinc, and 25-hydroxy vitamin D levels were compared between 344 cases of autism spectrum disorders selected by complete enumeration, and 344 controls.P <0.05 was taken as significant.Results:Iron (55.2% vs 47.4%, P= 0.04)and zinc (77.3% vs 44.2%, P <0.001) deficiency were more common among cases.Iron (OR=1.37, P=0.04) and zinc deficiency (OR=4.31, P<0.001) were significantly and positively associated with the disease, while no significant association was observed with vitamin D insufficiency (OR=0.93, P=0.63).Conclusion: Iron and zinc deficiency were significantly associated with autism spectrum disorder.

Key-words: Iron, zinc, vitamin D, anemia

Autism spectrum disorder (ASD), a neurodevelopmental disorder characterised by impairment in the social interaction, communication, and restricted and repetitive behaviour; and is a leading cause of psychiatric morbidity among the under-fives [1]. The World Health Organization reported that prevalence of ASD was1-1.5% in developed countries [2]. Iron and zinc deficiency are major public health problems in developing countries. Both of them are important constituents of different enzymes related to neurotransmitter synthesis, and degradation [3]. In addition, iron play role in myelination, synaptogenesis, and functioning of monoamine neurotransmitter system [3, 4].Vitamin D reduces the inflammatory mediators in brain, promotes DNA repair, and also activates the expression of enzymes related to synthesis of serotonin precursors [5].

But literature regarding association between micronutrients status and ASD are limited, especially in Indian context. They also suffer from methodological issues (e.g.small sample size, no control group, predominantly includes western population) [6, 7].Hence, this study was conducted to identify the relationship between status of micronutrients (iron, zinc, and vitamin D) and ASD, if any.

Methods:

This hospital-based,case-control study was conducted in the Pediatrics Out-patient department (Pediatric Neurology and Pediatric Psychiatry super-speciality clinic- conducted every Tuesday of week) between January, 2020 and December, 2022 after taking permission from Institutionalethics committee.Informed written consents were obtained from parents/ legal guardians of each participant. Gunes,et al. estimated that prevalence of iron deficiency in ASD cases and controls was respectively, 25% and 15% [8]. Fixing a and ß error respectively at 5% and 10%, minimum sample required would approximately be 336 in either groups(case and control). Assuming 5% non-response, 353 children with ASD needed to be recruited. Parents/ legal guardians of all children

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

freshly diagnosed as ASD were approached for recruitment in the study.ASD was diagnosed according to Diagnostic and Statistical Manual of Mental Disorders 5th Edition (DSM-5) criteria [1]. Children who were taking supplement of any of the micronutrients under study, developed features suggestive of infection in previous 2 weeksor seriously ill requiring hospitalisation, and whose parents refused consents, were excluded. Age and sex-matched controls were selected from children undergoing elective surgery (with pathologies that do not alter iron, zinc, and vitamin D level).A pre-designed, pre-tested, semi-structured schedule was used for data collection. Socio-demographic features (age, sex, socioeconomic status, religion, and place of residence), iron status indicators [hemoglobin, ferritin, iron and total iron binding capacity (TIBC)], serum zinc, and 25-hydroxy vitamin D level were recorded. Socio-demographic status was estimated by modified BG Prasad scale. Three to 4 ml of blood sample was drawn from the children for estimation of different micronutrients after overnight fasting. Serum iron and TIBC were assessed by ErbaChem 5+V2 using Ferrozinc method while serum ferritin was estimated using Tosho AIA 360. Hemoglobin level <11 g/dl was labeled as iron deficiency.Serum zinc was estimated colorimetrically using2-(5-bromo-2-pyridylazo)-5-(N-n-propyl-N-3-sulfopropylamino)-phenol. Cut-off for zinc deficiency was set at 65µg/dl. Serum 25-hydroxy vitamin D was estimated using an automatic immunoassay analyzer (Human Maglumi 600), and serum level of <30 ng/ml was taken as vitamin D insufficiency.

Statistical Analysis:

Collected data were entered in IBM SPSS Statistics for Windows, version 23 (IBM Corp, Armonk, NY, USA) after double-checking. Shapiro-Wilk test was used to check normal distribution (as sample size <2000). Categorical data were expressed in proportion. Mean and standard deviation were used for normally distributed data, while skewed data were represented using median and interquartile range. Chi-square test was used to check significance of difference between proportions. Student's unpaired t test and Mann-Whitney U test were respectively used for normal and skewed data. Odds ratios (OR) were calculated with 95% confidence interval (CI). P <0.05 was accepted as the limit of statistical significance.

Results:

Three hundred and sixty two children presented with freshly diagnosed ASD in the specified time-period, and 18 were excluded (3- refusal of consent, 6- on oral iron supplement, 3-oral zinc supplement, 4- on vitamin D and calcium supplement, 1- seriously ill, 1- blood sample was lost during transport). Mean (SD) age of the study population (79.8% boys) was 3.6 (0.7) y. Majority of the study population belonged to middle socioeconomic status (431, 62.6%), rural area (439, 63.8%), and Hindu religion (467, 67.9%).Base-line characteristics of cases and controls are summarised in table I. Status of serum iron, zinc and 25-hydroxy vitamin D among them are depicted in table II. Iron deficiency [OR (95% CI)=1.37 (1.02-1.85)] and zinc deficiency [OR (95% CI)=4.31 (3.10-5.99)] were significantly and positively associated with ASD while no significant association was observed between vitamin D insufficiency and ASD [OR (95% CI)=0.93 (0.68-1.27)].

Discussion:

In thecurrent study, we observed that iron and zinc deficiency were significantly associated with ASD. Inclusion of only Bengali children in this hospital-based study limits its generalizability. We used DSM-5 criteria for diagnosing ASD which explicitly mentions that ASD might overlap with other disorders that may cause iron deficiency (e.g. Asperger's syndrome).

Iron and zinc deficiency were previously also reported in ASD [8-10]. Observed frequency of iron deficiency was different among different authors, probably due to alteration of study population across the studies. The reason of association of iron deficiency and autism is multi-factorial and bidirectional. Both iron and zinc act as cofactor of different important enzymes involved in neurotransmitter synthesis, particularly monoamines [3].Iron also plays important role in synaptogenesis and myelination of nervous system [4]. Due to restricted movement, children suffering from iron deficiency also receive lesser stimuli from environment.Difficulty in feeding and impaired absorption due to gastrointestinal symptoms in autism might also be responsible for iron deficiency in them. Iron deficiency was also previously reported

in literature to cause cognitive impairment, neurological, and neurodevelopmental disorders [11].However, Reynolds,et al. did not observe any significant association between iron deficiency and ASD, probably due to using serum ferritin as a sole marker of iron deficiency which is also an acute phase reactant [12]. Zinc plays important role in sensory processing, sensory stimulus induced neuroplasticity, and intracellular signalling of neurons. Multiple previous reports did not find any significant association between serum 25-hydroxy vitamin D level, and ASD [13, 14]. However,Kocovska,et al. reported significant association between vitamin D deficiency and ASD [15]. Conduction of the studies in different latitudes, variation in the ethnicity of study population, and difference in cut-off level in 25-

Table I: Socio-demographic features of cases (n=344) and controls (n=344).

Variables	Cases (n=344)	Controls (n=344)	Significance
Age (y)*	3.6 (0.6)	3.6 (0.6)	t= 0.04, P=0.96
Sex†			
Males	273 (79.4)	276 (80.2)	χ^2= 0.08, P=0.78
Females	71 (20.6)	68 (19.8)	
Socio-economic status†			
Upper	31 (9.0)	35 (10.2)	χ^2= 0.99, P=0.61
Middle	212 (61.6)	219 (63.6)	
Lower	101 (29.4)	90 (26.2)	
Place of Residence†			
Rural	213 (61.9)	226 (65.7)	χ^2= 1.56, P=0.46
Urban	131 (38.1)	118 (34.3)	
Religion†			
Hindu	226 (65.7)	241 (70.1)	χ^2= 1.50, P=0.22
Muslim	118 (34.3)	103 (29.9)	

**Mean(standard deviation), Student's unpaired t test was used; †no (%), chi-square test was used.*

Table II: Distribution of different parameters in cases (n=344) and controls (n=344).

Parameters	Cases (n=344)	Controls (n=344)	Significance
Hemoglobin (mg/dl)*	10.8(1.2)	11.1(1.9)	t= 2.48, P=0.01
Serum iron (µg/dl)*	74.1(9.3)	78.5 (5.7)	t= 7.48, P<0.001
Serum feritin (µg/l)†	42.2(31.5-52.4)	44.5(35.1-53.2)	z= -2.45, P= 0.01
TIBC (µg/dl)*	276.4(22.1)	242.4(15.7)	t= 23.3, P< 0.001
Iron deficiency‡	190 (55.2)	163 (47.4)	χ^2= 4.24, P=0.04
Serum zinc (µg/dl)*	62.2(3.3)	65.6(3.5)	t= 13.1, P<0.001
Zinc deficiency‡	266 (77.3)	152 (44.2)	χ^2= 79.2, P<0.001
Serum Vitamin D (ng/ ml)*	28.5(3.8)	28.8(2.6)	t= 1.21, P=0.23
Vitamin D insufficiency‡	221 (64.2)	227 (66.0)	χ^2= 0.23, P=0.63

**Mean(standard deviation), Student's unpaired t test was used; †median (interquartile range), Mann-Whitney U test was used; ‡no (%), chi-square test was used.TIBC- Total iron binding capacity.*

hydroxy vitamin D might be responsible for these discrepancies. Nutritional status of study participants was also different among different researchers.

To conclude, iron and zinc deficiency are associated with ASD. However, further research (preferably longitudinal multi-centric studies including children of different ethnicities) should be undertaken to confirm the relationship we observed, and to identify whether generalised supplementation with micronutrients will be helpful in treating ASD.

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Optimising Dose of BCG. What is the Controversy?

Kripasindhu Chatterjee
Member IAP ACVIP 2020-21, 2022-23.
Professor & HOD, Deptt of Pediatrics, Santiniketan Medical College

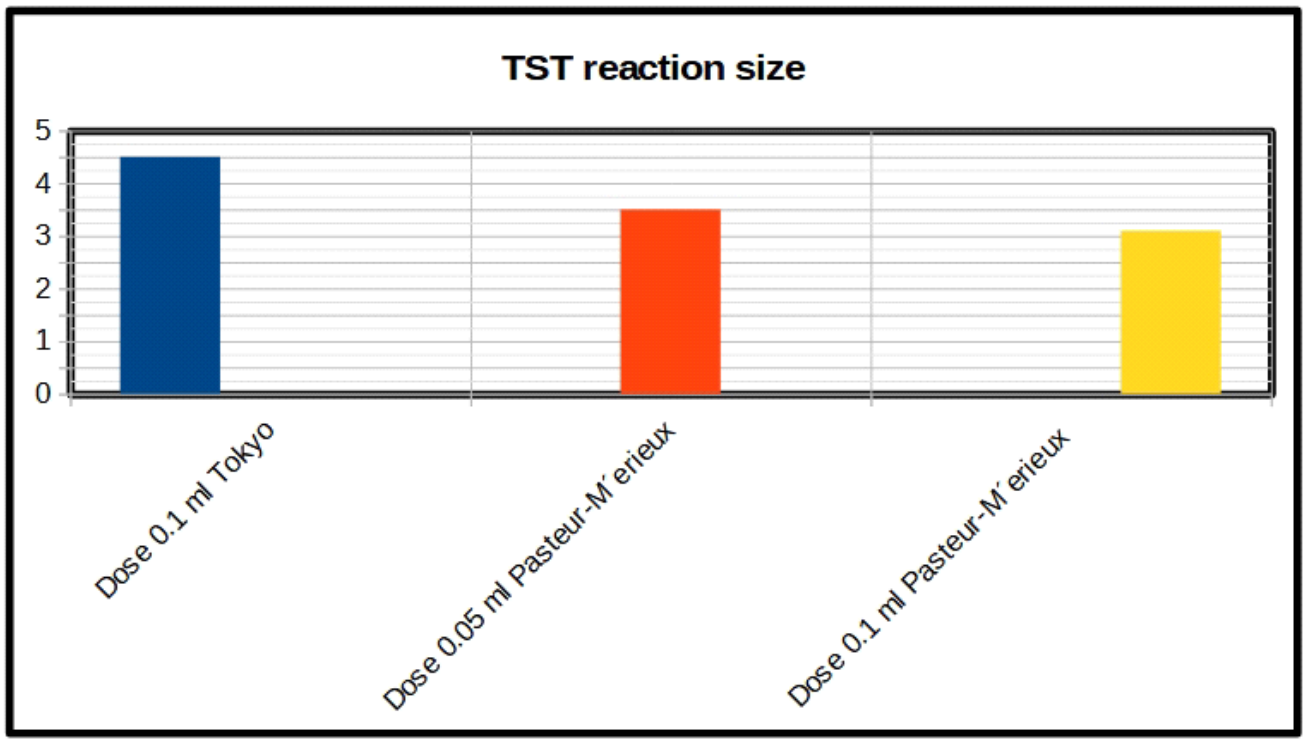
In 1993, WHO and UNICEF recommended the administration of 0.05 ml doses of BCG, instead of 0.1 ml, to newborns.

Study was conducted to assess the efficacy of two vaccine types and different doses BCG vaccination. Newborns of two public hospitals of Santiago were randomly assigned to receive the Tokio or Mérieux BCG strains in doses of 0.05 or 0.1 ml. Ninety five to 125 days after vaccination, vaccine scar was measured and immunogenicity was assessed using the tuberculin test.

The percentage of children with a PPD reaction of 0 mm was 9.3, 3.7, 7.8 and 0% with the Mérieux vaccine in doses of 0.1 ml, Tokio vaccines in doses of 0.1 ml, Mérieux vaccine in doses of 0.05 ml and Tokio vaccine in doses of 0.05 ml, respectively. In the same groups the scar diameters were 6.4 +/- 3.4, 7.3 +/- 2.7, 5.6 +/- 2.8 and 7.3 +/- 2.9 mm. The observed differences for each group are significant, depending on the type of strain and dose, but favoring the Tokio type of vaccine.

Therefore the use of 0.1ml doses for vaccination, that result in better scars and PPD response, is recommended.[1]

Post-vaccination tuberculin reactivity is not an indicator of protective efficacy of BCG vaccination, because it is not an indicator of immunity to M. Tuberculosis.[2]



Correspondance : Kripasindhu Chatterjee, Professor & HOD, Deptt of Pediatrics, Santiniketan Medical College, Email : kschatterjee@gmail.com, Mobile: 9434758969

Tuberculin skin test response after three modalities of neonatal BCG vaccination that is, [0.1 ml Tokyo (n = 104), 0.05 ml Pasteur-M´erieux (n = 137) and 0.1 ml Pasteur-M´erieux (n = 100)] was compared in a cohort of healthy newborns 5 months after vaccination at birth. Among the 341 infants, 91.2% had a response to TST, and the mean±SD TST reaction size was significantly larger in infants receiving the Tokyo strain than in those receiving the 0.05 ml or 0.1 ml Pasteur-M´erieux strains (4.4±2.0, 3.5±1.3 and 3.1±1.4mm, respectively; P < 0.0001). The mean±SD of the BCG scar size was significantly lower in infants vaccinated with the Tokyo strain than in those vaccinated with the 0.1 ml Pasteur-M´erieux strain (3.9±1.2 vs. 4.3±1.1 mm; P = 0.03) and no significant difference was found between infants receiving the Tokyo strain and the 0.05 ml Pasteur-M´erieux strain [3]

A study was carried out in India to evaluate tuberculin sensitivity and side effects following 0.05 ml and 0.1 ml of BCG at birth and 0.1 ml of BCG at 4-6 weeks of age. Two hundred and thirty eight newborns were vaccinated randomly with 0.05 ml and 0.1 ml of BCG vaccine (Copenhagen 1331 strain) containing 69 million culturable particles per ml. One hundred and eight infants 4-6 weeks of age were vaccinated with 0.1 ml of BCG. One hundred and fifty five (44.7%) infants were evaluated by Mantoux test using ITU PPD RT23 10-12 weeks after vaccination and 105 (30.6%) followed up till 6 months for any side effects. No significant difference in mean tuberculin reaction, tuberculin positivity and mean scar size was observed in groups receiving 0.1 ml at birth or 4-6 weeks of age. However, the group receiving 0.05 ml at birth had a significantly lower mean tuberculin reaction, tuberculin positivity and mean scar size. No loco-regional side effects were observed in the present study as compared to 0.76% to 2.42% reported by others. WHO had reported the mean risk of loco-regional complications to be 0.38/1000 though it varies from country to country and 76% of complications are seen in the first 6 months. It is concluded that the present practice of giving 0.1 ml of BCG at birth using Danish 1331 strain should be continued. Similar studies with larger number of infants and longer follow up should be carried out to substantiate or negate the present study.[4]

Comparative studies of tuberculin skin sensitivity following BCG vaccination using vaccines of high and low viable counts were carried out in tuberculin-negative students leaving secondary school. After intradermal vaccination using high-count BCG vaccine (14.2 million viable units per mg. BCG), a significantly higher degree of tuberculin skin sensitivity was found upon Mantoux testing with tuberculin PPD, 5 TU, than following low-count vaccines (5.4 and 4.5 million viable units per mg. BCG). [95.9% vs 74.3%].[5]

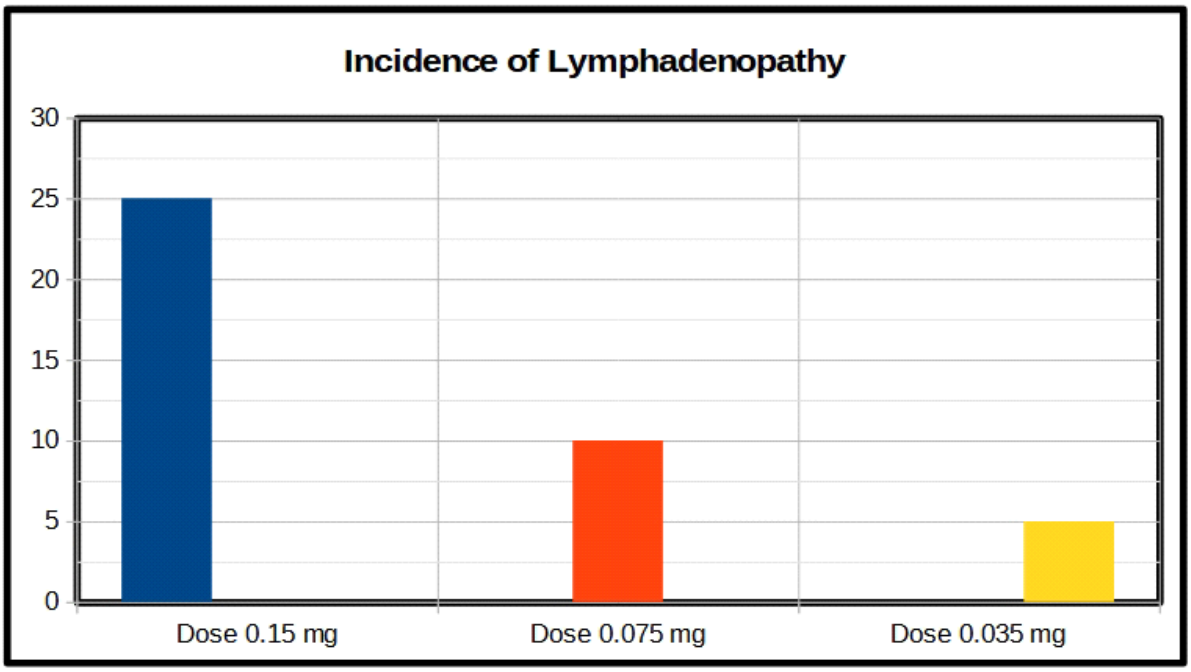
In a 1971 study by Belcourt [6], 30 neonates aged 7–21 days were vaccinated with Connaught BCG (0.1 mg) at twice the recommended infant dose. Two infants developed lymphadenitis, and 57% developed suppurative nodules at the injection site. Subsequently, 72 neonates were vaccinated with 0.0125 mg (one-fourth the infant dose). None of the children developed lymphadenitis or suppurative nodules at the injection site, and 8 weeks later, tuberculin reactivity was not different in the two groups [89%–91%].

A study by Guld et al. [7] that investigated suppurative lymphadenitis after intradermal BCG vaccination in the newborn revealed that the frequency of enlarged glands or local skin ulceration after BCG vaccination was related to the dose [The 0.15 mg. dose has given rise to complications in 25 % of the babies examined, the 0.075 mg. dose in 10%, and the 0.0375 mg. dose in less than 5 %]. The degree of tuberculin sensitivity is also directly related to the dose of vaccine, although halving the total dose results in a reduction of only about 1 mm. in the average size of the reaction to the 5 T.U. The reactions increased in size up to about four months after vaccination, then remained stable throughout the remainder of the year.

The researchers found that a smaller dose of BCG vaccine was associated with a significantly lower rate of suppurative enlarged glands and ulceration after BCG vaccination.

Conclusion

Immunogenicity studies of 0.05 ml and 0.1 ml BCG vaccine were based on tuberculin conversion and BCG reaction size and there was no homogeneity of results. Conclusive results measuring T cell cytokine response are absent. Also studies do not confirm



any corroboration between tuberculin conversion and efficacy.

Safety studies that has been studied so far show increased numerically incidence of lymphadenopathy in 0.1 ml group but they are not statistically significant.

So, in the pre text of recommendations of 0.05 ml BCG dose by WHO, UNICEF and NIS and in absence of any conclusive data against it, I would recommend to continue 0.05 ml BCG dose for newborn.

But it practical scenario it is some times difficult to give 0.05 ml intradermal in exact dose and produce 5 mm induration. So some experts follow the process that they inoculate that much to produce 5 mm induration.

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An Analysis on The Outcome of Available Treatment Options In Paediatric Aplastic Anaemia Patients

***Rojina Yasmin, *Sarmistha Adhikari, **Kaustav Nayek, **Paramita Mandal**
**Biomedical Genetics Laboratory, Department of Zoology, The University of Burdwan, West Bengal, India*
***Department of Paediatric Medicine, Burdwan Medical College & Hospital, West Bengal, India*

Abstract:

Aplastic anaemia (AA) is a rare haemopoietic stem-cell disorder that results in pancytopenia and hypocellular bone marrow (BM). In most cases, the pathophysiology of acquired aplastic anaemia is immune mediated. Most of the paediatric patients present with symptoms such as pancytopenia, easy bruising or petechiae, epistaxis, menorrhagia, pallor, fatigue. There is an apparent geographic variation in the incidence of AA. Bone marrow transplantation (BMT) and immunosuppressive therapy (IST) are the only treatment options available to such patients. In children with severe aplastic anaemia (SAA), BMT from an HLA-matched family donor (MFD) is the treatment of choice. Graft rejection, acute and chronic graft-versus-host disease (GVHD), and infectious complications are limitation to BMT whereas, a lack of response, relapse, and clonal evolution pose problems in case of IST. Because of the delay in the proper diagnosis, costly treatment, lack of proper supportive care, limited availability of the expertise centre, and the patient's affordability, the management of this disorder is a challenge in our country.

Keywords:

Aplastic anaemia, Paediatric, Bone marrow transplantation, Immunosuppresive therapy, Management

Introduction

Aplastic anaemia (AA) is a rare haemopoietic stem-cell disorder that results in pancytopenia and hypocellular bone marrow (BM). Although most cases are acquired, there are unusual inherited forms. The pathophysiology of acquired aplastic anaemia is immune mediated in most cases; autoreactive T lymphocytes destroy the haemopoietic stem cells (Brodsky, 2005). Acquired AA has to be distinguished from inherited bone marrow failure syndromes (IBMFS) for proper treatment. IBMFS are more frequent in the paediatric population, 25–30% of cases of bone marrow aplasia in children are of inherited type. The severity of AA is characterised by peripheral blood cell counts in the presence of a hypocellular bone marrow. According to the disease severity, AA is of three types; Non-Severe (NSAA), Severe (SAA), Very-Severe (VSAA). Age specific differences are present in case of choice of treatment, response to treatment, treatment outcome (Hartung et. al., 2013). Most patients with aplastic anemia have pancytopenia, with decreased platelets, white blood cells (WBC), and erythrocytes (Young, 2018). Most children with AA show symptoms resulting from advanced pancytopenia. Thrombocytopenia may manifest as easy bruising or petechiae. Epistaxis and menorrhagia are also common in postmenarchal girls along with pallor and fatigue. Patients are susceptible to infections due to neutropenia and thus fever or focal signs of infection are initial complaints. Hepatosplenomegaly and lymphadenopathy are hardly ever seen (Hartung et al., 2013). The disorder has been associated with exposure to chemical agents (benzene, pesticides) and drugs. It can also follow viral infections, as post-seronegative hepatitis, and it is a rare complication of pregnancy and other immunological diseases (Montané et al., 2008). Treatment options include HLA matched Bone marrow transplantation or Immunosuppressive therapy (Young, 2018).

Correspondance : Paramita Mandal, *Biomedical Genetics Laboratory, Department of Zoology, The University of Burdwan, email: pmandal@zoo.buruniv.ac.in*

Prevalenceof AA worldwide & in India

The incidence of acquired AA is about 2 per 1,000,000 children per year in North America and Europe and 2–3 fold higher in Asia. There is a peak in incidence in young population as well as in the elderly. Incidence is equal in male-to-female ratio (Hartunget al., 2013). There is an apparent geographic variation in the incidence because it is more common in the East than in Western countries. Geographic variation should probably be due to certain nvironmental rather than genetic causes (Locasciulli, 2002). The precise incidence of AA in India is unknown due to a lack of epidemiological study. Almost 20-40% of pancytopenia cases in referral centres are of aplastic anaemia. The disease is prevalent in northern states of India such as Uttar Pradesh, Bihar, Delhi/NCR and Haryanaetc. (Fig.1)(Mahapatra et al., 2015). Chakrabarti et al. estimated the prevalence in northern districts of West Bengal to be 2.98/million populations per year (Chakrabarti et al., 2013). The prevalence of aplastic anaemia in children was calculated to be 1.96/million population of children/year in the northern districts of West Bengal (Goswami et al., 2009). Most of the patients are 15 to 25 years of age however, this peak at young age is not found in European or American studies (Locasciulli, 2002).

Treatment options available

Bone marrow transplantation (BMT) and immunosuppressive therapy (IST) are the main options available for improved survival in AA. However, the choice of type of treatment for paediatric cases is dependent on the severity of AA and the availability of a HLA-matched family donor (MFD) (Kooket al., 2016). For children with SAA, BMT from an HLA-matched family donor is the treatment of choice. Studies suggest that overall survival (OS) with MFD stands at aproximately 90% in paediatric patients (Kook et al., 2016; Yoshida et al., 2014; Dufour et al., 2015). However in an Indian study, OS was found to be almost 61.6% among paediatric cases (Kharyaet al., 2023). Graft failure, graft-versus-host disease (GVHD), and infectious complications are the limitations for BMT (Yoshida et al., 2014).

For those without a matched family donor, IST with a combination of antithymocyte globulin (ATG) and cyclosporine (CsA) is a way out (Yoshida et al., 2014). The ATG brands available in India are AtgamVR (Pfizer Inc., USA) or ThymogamVR (Bharat Serums, India) with the latter being more cost effective (Jain et al., 2019). An Indian study reported that paediatric patients appeared to respond faster to IST. The overall response with ThymogamVR of paediatric patients in India was found to be 69.6%, at the end of 24 months (Shah et al., 2019).The 3-year overall survival (OS) in a north Indian cohort was 63% and the OS at 3 years was reported to be 62% and 64% after treatment with Thymogam and Atgam, respectively (Fig.2) (Jain et al., 2019). There are reports of adverse effects following IST. bleeding or other significant hemorrhage being most frequently reported side

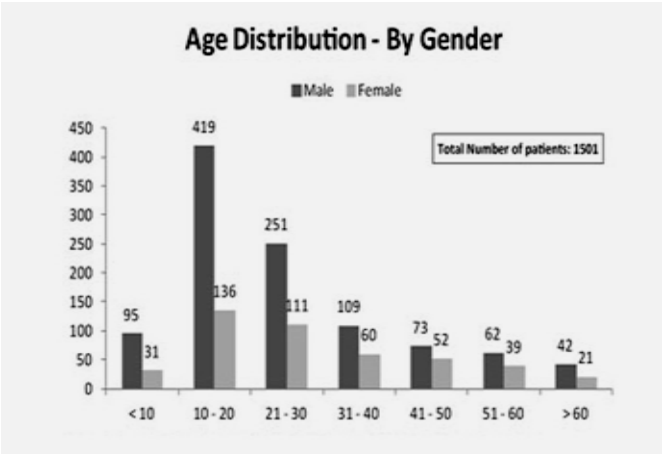

Fig 1: Distribution of age and sex of the AA patients (Mahapatra et al., 2015).

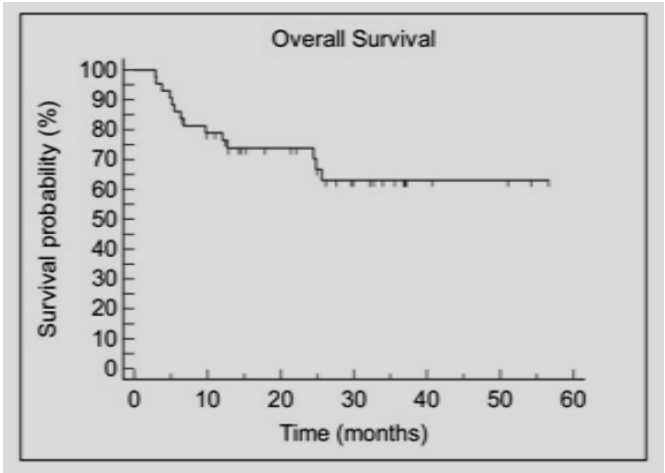

Fig 2: Overall survival in children with Aplastic naemia after (Jain et al., 2019).

effects. Other than that, bacterial, fungal infections, pneumonia, hypertension are also some of the complications in paediatric cases (Rogerset al., 2019; Shah et al., 2019). Almost 30% of the patients do not respond to the IST and 30-40% of patients that respond eventually relapse(Shin, 2013; Dhingra, 2023). About 30-70% of relapsed patients respond to the second line of IST or CSA alone (Shin, 2013;Scheinberg, 2012;Dhingra, 2023). For severe AA patients who were non-responsive or had an insufficient response to IST, supportive care (e.g., blood transfusion) was found to be the prime treatment option. But the US FDA approved the oral thrombopoietin (TPO) receptor agonist eltrombopag in combination with IST in 2014 as the first-line treatment for refractory AA (Dhingra, 2023).

TPO analogs can effectively improve the bone marrow function of SAA patients. As an agonist of the TPO receptor, eltrombopag significantly restores trilineage hematopoiesis in patients with refractory aplastic anemia (Fang et al., 2021). Addition of eltrombopag with IST regimen is reported to improve response rate in adult patients. One study reported 68% overall response rate from the combined therapy of IST and eltrombopag (Dhingra et al., 2023;Peffault et al., 2022). A Chinese study on paediatric AA patients reported an overall response rate of 94.4% for patients receiving IST+eltrombopag comapred to 69.2% for IST alone (Fang et al., 2021). Another TPO receptor agonist, Romiplostim, a peptide body that stimulates endogenous TPO production. The possible mechanism of hematopoietic recovery by romiplostim is the stimulation of hematopoietic stem and progenitor cells (HSPCs). The response rate of romiplostim+IST is higher than the combination of ATG+CsA alone (Dhingra, 2023). A temporary moderately elevated bilirubin levels along with fever, serum sickness, mild nausea, vomiting, and dizziness were few side effects of eltrombopag regimen (Fang et al., 2021). There is a lack of study involving thse TPO analogs. So, more studies are needed to explore the role of thrombopoietin receptor agonists for patients with AA, especially children.

Challenges in the management of AA in India

In our country, there is a lack of uniformity of treatment strategies and many children are managed only with supportive care due to cost affordability. The main focus of treatment is to prevent infections and bleeding (Danewa et al., 2022). HSCT is not readily available to the majority of the patients in low middle-income countries primarily due to the cost involved, as well as due to absence of a matched donor. In India, cost as well as time to HSCT goes up significantly in case an unrelated donor for HSCT is required, as a result of insufficient bone marrow donors registries. Most of the cost is borne by the patient's family. Due to cost and donor unavailability, HSCT remains inaccessible to the majority (Jain et al., 2019). In India, the availability of indigenous preparation of hATG, Thymogam is a hope for the financially weak patients for its less cost (Shah et al., 2019). The cost of the drugs is often an important deciding factor for use in treatment which is a concern (Jain et al., 2019).

Conclusion

Because of the delay in the diagnosis, lack of proper supportive care, the patient's affordability pose a challenge to the management of AA in India. The cost of therapy become a limitation for the use of HSCT. Another challenge with immunosuppressants is the relapse of the disease or its evolution to myelodysplasia or paroxysmal nocturnal haemoglobinuria (PNH) in some of the patients. Unfortunately, in India, increased cost and limited availability of HSCT and ATG, leads the majority of the AA patients to receive only CsA with or without androgens.

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Conflict of interests

None.

Ethics statement

Not applicable.

Author contributions

RY, SA & PM: concieved the idea, performed formal analysis& wrote the manuscript, KN: performed formal analysis

Eventration: An Unusual Association of Poland Syndrome

Joydeep Das, Manas Kumar Mahapatra, Debabrata Debnath
Department of Paediatrics, Jagannath Gupta Institute of Medical Sciences and Hospital, Buita, Budge Budge, West Bengal

Abstract:

Recurrent pneumonia in childrenneeds meticulous search for underlying cause which may be due to underlying structural lung disease or immunological lung disease(1). Diaphragmatic eventration causes hypoplasia of ipsilateral lung and predisposes the Childrens for recurrent pneumonia. Association of Diaphragmatic eventration in Poland syndrome (PS) is a rare entity and only few cases have been described in literature(2).Clinical Description: A 1 year old boy with Poland syndrome presented with intermittent high grade fever and difficulty in breathing. He had past history of multiple hospital admission with similar complains and was treated with IV antibiotics.Management: The child was managed with IV antibiotics and other supportive care .Investigations revealed Neutrophilic Leucocytosis (TLC-19600/cumm, Neutrophil-76%) with raised CRP levels(6.5mg/dl). X-RAY chestsuggested bilateral pneumonia with elevated left dome of diaphragm. HRCT chest was advised which was suggestive of left sided Diaphragmatic Eventration. After initial stabilization the child undergone left sided thoracotomy followed by diaphragmatic plication and was discharged in stable condition following operation Conclusion:A high index of clinical suspicion is required for an early diagnosis of Diaphragmatic eventration in Poland syndrome to guide appropriate treatment. Thoracotomy and Surgical plication of diaphragm may be required for severe cases of Diaphragmatic eventration in children who failed to respond toconservative care.

Keywords: Recurrent pneumonia, Poland syndrome, Diaphragmatic eventration

Recurrent Pneumonia (RP) is defined as two or more episodes of pneumonia in 12 months or three episodes altogether with radiographic clearance in between(1). It should be differentiated from persistent pneumonia, which is defined as persistence of symptoms and radiological changes for 6 weeks or more despite treatment.Undiagnosed hyperactive airway disease, recurrent aspirations, structural lung disease, immune deficiency, pulmonary hemosiderosis, cystic fibrosis, ciliary dyskinesia, congenital heart disease etc. are commonly identified entity. Poland syndrome consists of anatomic anomalies that include the absence of the sternocostal head of the pectoralis major muscle with other varied manifestations that include hypoplasia or absence of the pectoralis minor muscle as well as digital anomalies such as syndactyly .Poland syndrome affects about 1 in 36,000 to 50,000 newborns, with males more likely to be symptomatic than females. Furthermore, right-sided predominance occurs more frequently in men than women. Cases usually are sporadic, with rare familial cases also described in the literature.Patients with Poland syndrome usually present for cosmetic and aesthetic complaints and are usually asymptomatic. Patient history of cardiopulmonary complaints, although rare, can be important given the association of dextroposition and lung herniation with Poland syndrome(3).Diaphragmatic eventration (DE) is the abnormal elevation of a portion or entire hemidiaphragm due to a lack of muscle or nerve function while maintaining its anatomical attachments. The abnormality can be congenital or acquired, thus presenting in both the pediatric and adult populations. Patients with eventration of the diaphragm have variable presentations. Most patients are asymptomatic and discovered incidentally on chest X-ray; however, some may present with

Correspondance : Joydeep Das Department of Paediatrics, Jagannath Gupta Institute of Medical Sciences and Hospital, Buita, Email : dr_joydeepdas@yahoo.com

significant respiratory distress or gastrointestinal symptoms(4).

Clinical Description

The parents of a 1 year old boy brought their child with the complaints of intermittent high grade fever for 4 days and difficulty in breathing for 1 day. The child had multiple episodes of similar complaints since 2 months of age for which he was admitted multiple times in hospital and was treated with intravenous antibiotics.

The child was born out of nonconsanguineous marriage at term with a birth weight of 2.6 kgs by normal vaginally delivery. The antenatal, natal and postnatal periods were uneventful.The boy was the first in birth order and the only child of his parents . He had achieved his developmental milestones as per normal limits. .The child was on breast feeding and complementary feeding and was immunized as per date.

On examination the child was underweight for his age(6kg), height was 75 cm(50th centile) and the body mass index was. The child had dysmorphism in the form of brachydactyly and syndactyly of left had without any facial dysmorphism. On primary survey the child was sick looking and was in distress. He was alert, active , febrile (temperature- 100.3 F), heat rate 130/min with thready pulse, blood pressure 86/54mmhg, respiratory rate 48/min, capillary blood glucose 90mg/dl and oxygen saturation of 90% at room air.

Respiratory system examination revealed asymmetrical chest wall with hollow left sided chest (hypoplasia of pectoral muscle). There was marked intercostal and subcostal retraction and on oscultation crepitations were heard over right Upper chest and eft lower chest.

Management

The child was in respiratory distress and was immediately provided supportive care with oxygen through mask followed by Heated Humidified High Flow nasal Cannula (HHHFNC) with 10 litres of oxygen flow and 30 % Fio2. Nebulization with Levo salbutamol was given at emergency room.IV cannulation was done for collecting blood samplesfor investigations and normal saline bolus at 10 ml/kg was given followed by 100% maintenance fluid. The

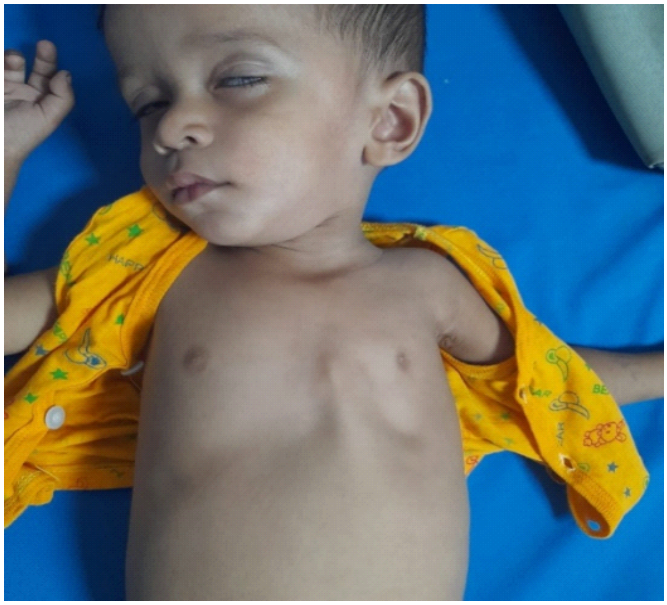

Fig: Hypo plastic left pectoral muscle

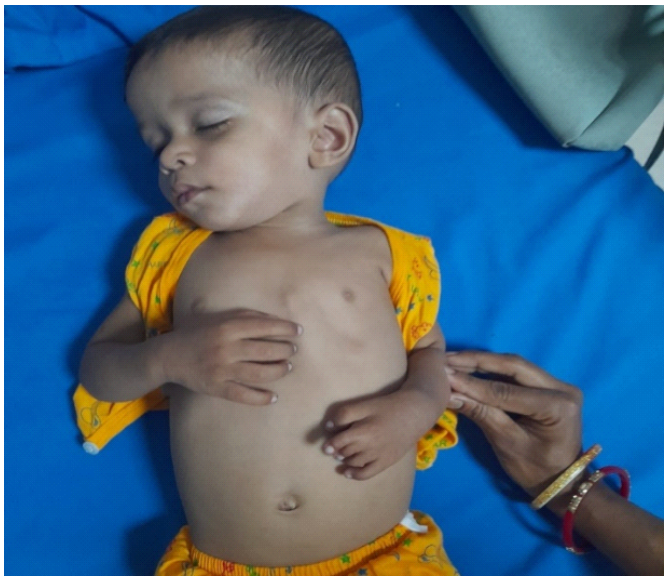

Fig: Hypo plastic left pectoral muscle with brachy-syndactyly

child was started on empirical antibiotic(Injection Ceftriaxone and Injection Vancomycin) in view of pneumonia and other supportive care were optimised .

Venous blood gas at admission PH-7.38, PCO2-28, P02-43, HCO3- 20.1, Lactate-3.4,Na-137, K-3.6. Routine laboratory tests revealed hemoglobin of 10.7 g/dL,total leukocyte counts of 19,600/mm3, with neutrophils 76.%,lymphocytes 24%, platelet count of 2.1 lakhs/mm3, and erythrocytesedimentation rate

of 34 mm/1st hour, C reactive protein 6.5mg/dl. His kidney function tests were normal with urea of 16 mg/dL and creatinine of 0.5.mg/dL.Alanine aminotransferase and aspartate aminotransferase were34 and 40 IU/dL, respectively.Serum albumin was 3.8 gm/dL, total bilirubin0.6 mg/dL and PT/INR 15.2/1.2.

Initial X-RAY chest at emergency was suggestive of bilateral pneumonia and the left dome of diaphragm appeared slightly elevated than the right dome . For diagnostic confirmation high resolution computed

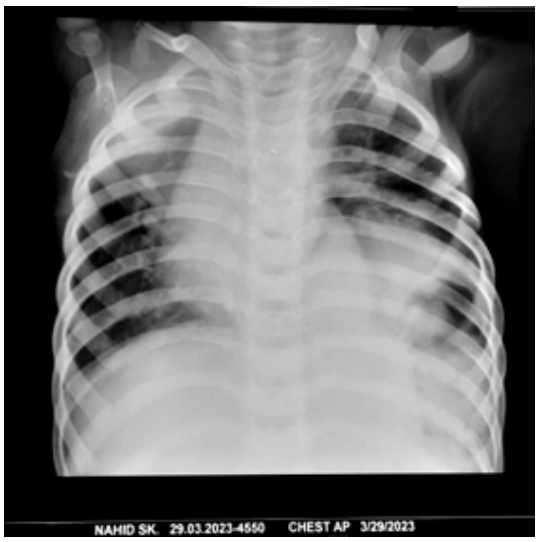

Fig: X-RAY chest : Right upper and left lower zone opacities with elevated fundic gas shadow in left side

tomography scan of thorax was performed which confirmed Left sided Diaphragmatic Eventration.

Intra operatively Membranous diaphragm was seen in left hemithorax with Stomach,Spleen ,Left kidney and few loops of small intestine in the left hemithorax beneath the diaphragm.All the thoracic contents were brought down to there original anatomical position as mush as possible maintaining blood supply to those organsDiaphragmatic plication was done on left side and chest was closed after putting 2 chest drain in situ.

Post operatively the child was kept in PICU and was given oxygen by face mask which was gradually withdrawn over 4 hours .IV antibiotics, IV fluids were continued and oral feeding were gradually started. There was minimal chest drain output and for which chest drain was removed on post operative day 5 and daily physiotherapy was started.The child was

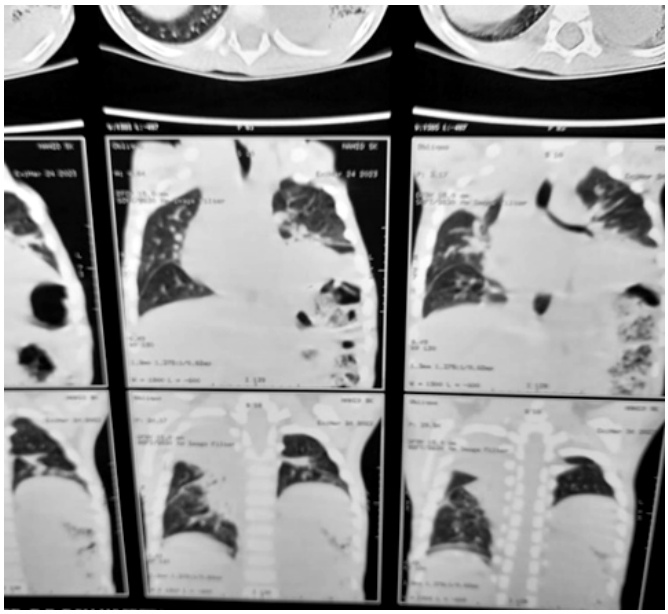

Fig: HRCT chest coronal section : Elevated left hemi diaphragm with few gas filled bowel loops beneath it

discharged on stable on post operative day 10 following removal of stitches .

At follow-up, nearly 30 days after discharge, the childwas clinically stable with no further episodes of respiratory distress. The child gained 1 kgs of weight at one month following discharge.

Discussion

The above described child is a case of Poland syndrome with hypoplasia of left chest wall, ipsilateral symbrachydactyly and left sided eventration of diaphragm presenting as recurrent pneumonia. In this case abnormally elevated left dome of diaphragm on chest x-ray in the back ground of recurrent pneumonia made us thought about possibility of underlying structural lung disease. With a grain of suspicion, we went ahead with high resolution computed tomography scan of thorax which confirmed Left sided Diaphragmatic Eventration.

The characteristic features of PS is a combination of pectoral hypoplasia and symbrachydactyly of the ipsilateral hand.The aetiology of PS is still debated. Several theories and aetiological factors have been suggested with the vascular disruption theory being the most accepted to date.The pathogenic hypothesis of subclavian artery supply disruption sequence (SASDS), introduced by Bavinck and Weaver, points to an insult variably interrupting the

blood supply to the subclavian artery, resulting in the underdevelopment of the pectoral muscles in the embryo along with a range of associated hand anomaliesIncidence of Poland syndrome ranges from around 1:17?000 live births in Japan to 1 in 52?530 live births in Hungary. PS occurs in men with a predominance of 3:1 ratio, and right side is more affected than the left in 75% of the cases(2).

Diaphragmatic eventration (DE) is the abnormal elevation of a portion or entire hemidiaphragm due to a lack of muscle or nerve function while maintaining its anatomical attachments. The abnormality can be congenital or acquired, thus presenting in both the pediatric and adult population. Due to the rarity of diaphragmatic eventration, there is limited data on the incidence and prevalence of this condition. A limited number of case reports have suggested the incidence is as low as less than 0.05% with male predominance and more commonly affecting the left hemidiaphragm. Others have suggested the incidence to be 1 in 10,000 live births. The incidence is likely higher than reported as most patients are asymptomatic, and many remain undiagnosed(4).

According to a previous study only 3 cases of eventration of diaphragm reported in Poland syndrome(2) and most probably this is the first case reported from India. This makes it a rare entity but notable when investigating aone year old child having subtle stigmatas of Poland Syndrome with respiratory symptoms. Congenital EOD is a developmental defect of part or entire muscular portion of the diaphragm, where the diaphragmatic muscle is replaced by fibroelastic tissue, loosening its attachment to ribs, sternum and spine, causing the weak hemidiaphragm to move into the thorax.

Often patients with isolated EOD are asymptomatic and diagnosed on chest X-ray incidentally. Diagnosis of EOD is by using X-ray/CT of the chest, as noted in our case. There is no specific timing for the repair of EOD as most cases can be asymptomatic and could resolve by appropriate ventilation support.The indications for surgical plication are- respiratory distress unresponsive to conservative treatment, dyspnea that is not due to another process (i.e., heart failure or primary lung diseases), infants with inadequate nutritional intake or failure to thrive, life-threatening or recurrent pneumonia, inability to be removed from mechanical ventilation(4). In our case the boy had recurrent pneumonia with failure to thrive for which he underwent Diaphragmatic plication.

PS can be diagnosed clinically at birth if the distinctive features of unilateral chest hypoplasia and ipsilateral limb defects are present. Regardless, many cases are diagnosed at various ages and sometimes presented to medical care for reports not related to the PS itself. Imaging modalities are crucial in PS to identify the specific location and characteristics of chest wall deformity. The chest radiograph is the first and most basic study, which usually shows lung field hyperlucency in the affected side. Both CT and MRI are used to enable accurate diagnosis, to show the extent of lesions in the musculoskeletal component, and to help the surgeon's decision-making regarding the best modalities for reconstruction(2).

Conclusion

Association of congenital EOD with PS is rare and the one year old boy in our case was symptomatic from 2 months of age requiring an early intervention. Usually cases can be missed in infancy as the presentation might be subtle and widely variable. PS is a clinical diagnosis but needs detailed imaging such as XRAY/USG/ CT to precisely identify the musculoskeletal defects aiding surgeons in reconstruction. Overall, the outcome of PS is favourable except in rare cases like ours which require early surgical intervention due to EOD causing respiratory compromise.

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A Short Review on Pathogenesis & Epidemiological Study of Eastern Equine Encephalitis Virus: Causative agent of Tropical Neglected Mosquito-borne Disease

***Kaustav Nayek, **Arghya Nath**

**Principal, **Research Scientist-B, ICMR-DHR Viral Research & Diagnostic Laboratory, Burdwan Medical College, Burdwan-713104*

Introduction

Eastern equine encephalitis virus (EEEV) is a rare but potentially fatal mosquito-borne virus that affects both humans and horses. The virus is found primarily in the eastern and Gulf Coast regions of the United States, and the majority of human cases occur between June and September.[1] Despite its rarity, EEEV is considered a significant public health concern due to the high mortality and neurological sequelae rates among those who become infected.[2] This review paper will provide a comprehensive overview of the current understanding of the epidemiology, transmission, and clinical manifestations of EEE, as well as current and potential control measures. The paper will delve into the details of the epidemiology of EEE, including the geographic distribution and seasonal patterns of the virus. The transmission dynamics of EEE will also be discussed, including the role of birds and mosquitoes in maintaining the virus cycle. Additionally, the paper will provide information on the clinical manifestations of EEE infection, including symptoms and outcomes, as well as current and potential control measures. The paper will provide a valuable resource for public health officials, healthcare professionals, and researchers working to understand and control the spread of EEE.

Background

Eastern equine encephalitis virus (EEEV) is a mosquito-borne virus that belongs to the family Togaviridae and the genus Alphavirus. It is primarily found in the eastern and Gulf Coast regions of the United States, as well as parts of Central and South America.[1] While EEEV is a rare virus, it can cause severe neurological disease and has a high mortality rate among those who become infected.[2] Epidemiology studies have shown that the majority of human EEEV cases occur between June and September, with the highest incidence in the Atlantic and Gulf Coast states. The virus is primarily maintained in a sylvatic cycle involving birds and mosquitoes, with horses and humans being dead-end hosts. However, recent studies have shown that human cases have been associated with outbreaks in marshy, freshwater habitats, suggesting that human cases may be more closely linked to the sylvatic cycle than previously thought.[3]Clinical manifestations of EEEV infection range from mild febrile illness to severe encephalitis and death. The severe form of the disease primarily affects the central nervous system and can result in long-term neurological sequelae, such as seizures and cognitive impairment. [3,4]

Epidemiology

Eastern Equine Encephalitis (EEE) is a rare but serious viral illness that affects the central nervous system. The virus is transmitted to humans through the bite of an infected mosquito.The disease is most common in the eastern United States, particularly in the Atlantic and Gulf Coast states, however, cases have also been reported in Canada and South America.[1]Epidemiology studies have shown that the incidence of EEE varies depending on the location and year, with a range of a few to several cases per year. The highest incidence of EEE is usually seen during the late summer and early fall. This is because the mosquitoes thattransmit the virus, such as Culisetamelanura, are most active during this time of year.

Additionally, the virus can replicate well in the warm, humid conditions that are typical of summer and early

Correspondance : Kaustav Nayek Principal, Burdwan Medical College, Email : kaustav25@yahoo.co.in

fall. The case fatality rate is around 35%. The population at the highest risk of EEE are people who live in or visit areas where the virus is known to circulate, especially during the summer and fall months. This includes people who live in or visit wooded areas, swamps, or other areas where mosquitoes are commonly found. People who spend a lot of time outdoors, such as farmers, hunters, and outdoor enthusiasts, are also at increased risk of contracting the virus.[5] Symptoms of EEE can include fever, headache, nausea, vomiting, fatigue, and muscle and joint pain. In severe cases, the virus can cause inflammation of the brain, which can lead to seizures, paralysis, and even death. Thereis no specific treatment for EEE, and the best way to prevent the disease is to avoid mosquito bites. It is important to note that people who live in or visit areas where EEE is known to circulate should take steps to protect themselves from mosquito bites, such as using insect repellent, wearing long-sleeved shirts and pants, and staying indoors during peak mosquito-biting hours.[6] Asper CDC, Eastern equine encephalitis virus human disease cases by year of illness onset, 2003-2022 & their sex ratios were illusted in figure 1 & 2 respectively.

During 2003 to 2022 human disease cases reported 189 and hospitalization cases were 169 individuals. Among them 78 deaths were reported as per CDC.[8]

A case report illustrated that A 4-year-old girl, who had been in good health before, was brought to the emergency department after losing consciousness while playing on a trampoline. By the time she arrived at the hospital, she had already regained consciousness and was behaving normally. There were no noteworthy issues in her birth or medical history. Her parents mentioned that she had a fever and had been complaining of headaches in the days leading up to the incident. A physical examination showed no signs of neurological problems, and the doctors suspected that she had experienced a febrile seizure. [8]Clinically significant Eastern Equine Encephalitis Virus (EEEV) infections in the human population are exceedingly rare, with only 4 to 5% of EEEV infections leading to encephalitic disease. Symptomatic cases are more likely to occur in children and elderly individuals. Children have a case-to-infection ratio of 1:8, whereas adults have a lower ratio of 1:29.4. The Centers for Disease Control and Prevention (CDC) reports an average of 6 cases of EEE per year in the United States, with the highest incidence observed in southeastern states. From 1964 to 2010, a total of 270 cases of probable or confirmed EEE have been documented. Notably, this case is the sole documented pediatric case of EEEV in the past 10 years in Onondaga County.

Pathogenesis

Eastern Equine Encephalitis (EEE) virus is a member of the family Togaviridae and the genus Alphavirus. The primary host of the EEE virus is the Culisetamelanura mosquito, which acquires the virus by feeding on infected birds. Humans and horses can also be infectedthrough the bite of an infected mosquito. [6] After the virus enters the body, it replicates in the lymphoid tissues, then spreads to the bloodstream and finally to the central nervous system, where it causes inflammation of the brain (encephalitis) and the surrounding tissues.

The transmission cycle of the Eastern equine encephalitis virus in North America involves wild birds as asymptomatic carriers, while horses, pheasants, and humans usually experience devastating effects, with many cases resulting in death or neurological complications for survivors. The primary enzootic cycle occurs during the summertime and is primarily concentrated in freshwater marshes. The virus is transmitted through Culisetamelanura mosquitoes

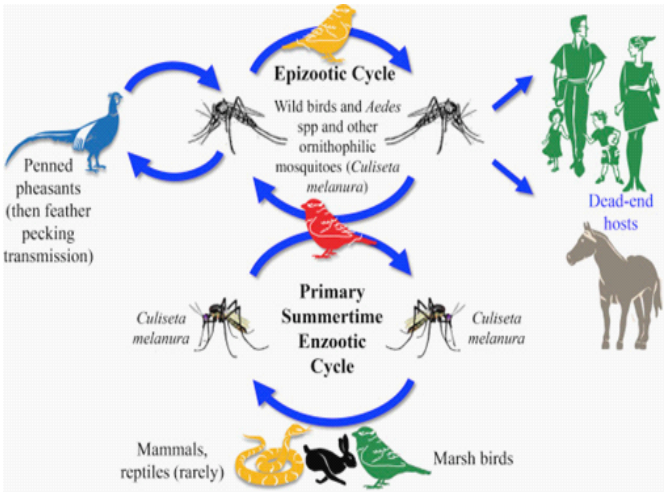

Fig 2. Transmission cycle of eastern equine encephalitis virus in North America.[7]

in this cycle. The epizootic cycle, on the other hand, often occurs in areas near these marshes.

Though horses and humans are considered "dead-end" hosts from an epidemiological standpoint, some horses can have high enough levels of viremia to transmit the virus to mosquitoes that feed on them. This further contributes to the spread of the virus in the affected areas.[7]

The virus damages the blood-brain barrier, allowing inflammatory cells to enter the brain, which results in edema and eventually neuronal damage and death. The virus replicates in theneurons and glial cells of the brain, which leads to inflammation and damage of the neural tissue. The severity of the symptoms of Eastern Equine Encephalitis (EEE) infection is directlycorrelated with the viral load in the brain, with a higher viral load leading to more severe disease. This is because as the virus replicates in the brain, it causes inflammation and damage to the neural tissue, leading to a wide range of symptoms such as fever, headache, nausea, vomiting, fatigue, and muscle and joint pain. In severe cases, the virus can cause inflammation of the brain, which can lead to seizures, paralysis, and even death. The virus also stimulates an immune response in the body, which can contribute to the inflammation and tissue damage seen in EEE. The virus-induced inflammation can cause a cascade of events that lead to the activation of microglia and astrocytes, which are the resident immune cells of the brain, and the release of inflammatory mediators. These mediators can cause further damage to the neural tissue, leading to cell death. [10] The host immune response to EEE virus infection is a complex and dynamic process, which involves the activation of different immune cells, such as macrophages, dendritic cells, T cells, and B cells. These cells play a critical role in controlling viral replication and limiting the damage caused by the infection. However, the immune response can also contribute to the pathogenesis of EEE virus infection, as excessive inflammation can cause tissue damage and lead to neurological deficits.[11]

In summary, the pathogenesis of EEE virus infection is a multi-faceted process that involves the replication of the virus in the brain, the host's immune response, and the consequent inflammation and tissue damage. An understanding of the mechanisms involved in the pathogenesis of EEE virus infection is essential for the development of effective therapies and vaccines.

Treatment

The treatment for equine encephalitis virus (EEV) in humans primarily involves supportive care to manage symptoms and complications. This may include hospitalization, fluid replacement, and medication to control fever and reduce inflammation in the brain [1]. In severe cases, intensive care may be required to support vital organ function and manage complications such as seizures or coma [13].There is no specific antiviral treatment for EEV in humans, and treatment options are limited [14]. However, some studies have found that the antiviral drug Ribavirin may be effective in reducing the severity of symptoms and improving outcomes in infected individuals [15,16].

In addition to medical treatment, rehabilitation and physical therapy may be necessary to help individuals recover from the neurological effects of the virus [18].It is important to note that prevention is key when it comes to EEV. This can include avoiding mosquito bites and getting vaccinated [19].Control measures

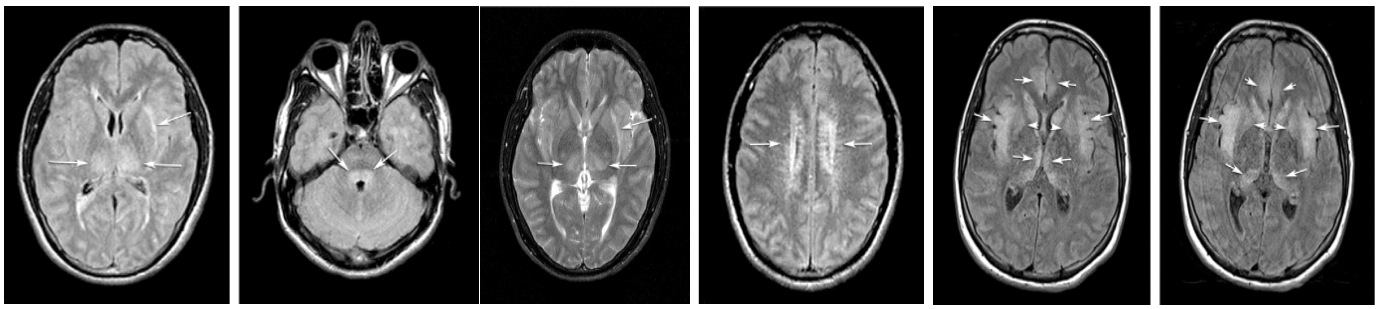

Fig 2 : 1-6:- Eastern equine encephalitis: MRI findings in two patients[10]

for EEEV are primarily focused on preventing mosquito bites through the use of insect repellents and wearing protective clothing. In addition, reducing mosquito breeding sites through elimination of standing water and use of larvicides can also help to reduce the transmission of EEEV. Potential control measures that are currently being researched include the development of effective vaccines and antiviral drugs.

Conclusion

EEEV is a rare but potentially fatal mosquito-borne virus that primarily affects the eastern and Gulf Coast regions of the United States. Despite its rarity, EEEV is considered a significant public health concern due to the high mortality and neurological sequelae rates among those who become infected. This research paper has meticulously reviewed the current understanding of the epidemiology, transmission, and clinical manifestations of Eastern equine encephalitis virus (EEEV), as well as current and potential control measures.Eastern equine encephalitis (EEE) is a rare but potentially severe neurological infection. Those most vulnerable to infection are children, the elderly, and individuals who live, work, or travel near freshwater swamps where the virus is prevalent. The primary preventive measure is to avoid such areas. For those unable to do so, protective clothing and insect repellents can be used to guard against mosquito bites. In cases where there is a clinical suspicion of EEE, serologic testing should be conducted. Neuroradiology studies showing signs of encephalitis, especially lesions in the basal ganglia and thalamus, should raise further concerns about EEE. If clinical findings suggest EEE, confirmatory testing using MRI is recommended as it is a more sensitive modality.

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Intervening Haematopoietic Stem Cells Regulation With The Association of Nutrients (Amino Acids And Vitamins) And Diets For The Management of AA in Children

***Sarmistha Adhikari, **Kaustav Nayek, *Paramita Mandal**

**Biomedical Genetics Laboratory,Department of Zoology, The University of Burdwan, West Bengal, India*

***Department of Paediatric Medicine, Burdwan Medical College & Hospital, West Bengal, India*

Abstract:

Aplastic anaemia (AA) in recent days, considered as fatal and related to higher mortality rate. Various factors are associated with the progression of this disease that includes cellular, mechanical and environmental aspects. Till date, haematopoietic stem cell transplantation (HSCT) is the only definitive cure for acquired AA. But after therapy it was reported that several complications can arise with time that may impair the overall survival. For this reason, it is necessary to understand how haematopoietic stem cells regulated their cellular and metabolic functions via different mechanical way to protect from various hazards and combat infections. In this context, we are majorly focusing on how nutrients (amino acids, vitamins) modulate the HSCs and their niche via several sensing pathways. In Paediatric form of AA, if we understand those dimensions that could be helpful for the younger generation to sustain a healthy and better after treatment life. Small measures in children's diet could lead to change the after-surgery scenario in social as well as medical aspects.

Key words: Aplastic anaemia (AA), Haematopoietic stem cell diet, HSCT, HSC nutrients and vitamins

1. Introduction:

Aplastic anaemia (AA) is geographically varied (in India), rare haematological disorder with heterogenous clinical representation of bi or pancytopenia, hypocellular bone marrow with no characteristics of dysplasia, fibrosis or infiltration, and absence of splenomegaly (1). Aplastic anaemia is also represented as an auto immune disorder where CD34+ Haematopoietic progenitor stem cells (HPSCs) devastated and destructed by cytotoxic T lymphocytes and the antigenic alterations includes infections, medications, exposure to hazardous chemicals (2). Haematopoietic stem cells (HSCs) or HPSCs are seem to be the "topper of the lineage tree" and have the multipotent ability to differentiate, regenerate or self-renewal or remain quiescent. HSCs are also capable to regulate the blood system homeostasis and can generate any lineage of mature blood cells through the hypoxic Bone Marrow (BM) microenvironment niche. So, HSCs and HPSCs in a conditioned BM niche are continuously making the decisions whether to differentiate, or proliferate, or regenerate to a mature cell path or remain dormant. "The path of making the cell fate" in HSCs are interestingly regulated by various internal and external factors. As internal factors, cellular and metabolic dysfunction could also be associated with dysregulated energy balance and nutrition status of the being. Whereas, environmental factors and hazards have the potentiality to epigenetically alter various pathways that could be alarming for the incident of the disease scenario. Decreased number of HSCs are often associated with age-related diseases. But in case of AA, it was found that loss of HSCs is independent of age and in case of Paediatric Aplastic anaemia (PAA) the rate of prevalence of this disease in children is increasing day by day with a higher rate. For this reason, it is needed to be understand what are the probable factors for the onset of the disease and what measures should be taken for the wellbeing of those patients even after treatments. A healthy bone marrow is much needed for blood homeostasis, we have to understand how the BM microenvironment

Correspondance : Paramita Mandal, *Biomedical Genetics Laboratory, Department of Zoology, The University of Burdwan, email: pmandal@zoo.buruniv.ac.in*

works in their finest capabilities and realize what direction of treatment or management options need to be taken even after Immunosuppressive treatment (IST) or Haematopoietic stem cell transplantation (HSCT) in AA and also in paediatric ones for their overall survival (OS). For this reason, this review focuses on the bone marrow from a nutrient or dietary perspective how HSCs actually work in conditioned way and finding the most suitable options or regime to understand this disease from a close look perspective.

2. Incidence And Epidemiology:

From a global scenario, the disease is 2-3 times higher in case of Asia than the western countries and almost 6.8 million individuals are affected per year considering this as a life-threatening disease with higher mortality rate. In India, being geographically varied the epidemiology is seem to be higher in the Northern states of India. From a single centre study (AIIMS, New Delhi) it was reported in 2015 that, over 1501 patients were diagnose with AA over 7.5 years of time period (3). In case of PAA, it was reported from Lucknow that, almost 6.8 million children are affected per year with an increasing rate (4). Though the median age is reported as 25 years (Range 2-83 years) and 36.5 years (Range 19-77 years) for the onset of the disease (5) but the alarming rate of elevated disease scenario could be dangerous for a generation in near future. If we have a close look on the scenarios of West Bengal, it was found that Northern districts are found to be associated with higher rate of prevalence. The percentages are 33.33% in case of Severe Aplastic anaemia (SAA) and 57.14% in case of non-severe aplastic anaemia (NSAA) (6). This incidence rate is itself challenging in terms of diagnosis and treatments as the only definitive cure is HSCT till date. But the associated complexities like infections, transfusion support, elevation of several associated symptoms after HSCT or IST treatment are facing more challenges. For this reason, it is needed to be realized the scenario and management of this disease.

3. Treatment Options:

From 3-4 decades till date there are several treatment options are being used. The popular options are Immunosuppressive treatment with ATG+CsA and Allogenic Haematopoietic stem cell transplantation (HSCT) (7,8). In case of HSCT, there is a huge risk for allogenic graft rejection. This could be happened via various infectious disease whereas, in IST long term transfusion support could also responsible for other disease evolution associated with AA. IST is not seemed to be effective in general cohort of patients and does not have much response or effectiveness. Sometimes androgen treatment and platelet-elevated drugs like Eltrompobag (51) and Danazol are being used (52). But the overall survival is still depended on the follow-up checkups and also a healthy lifestyle management.

For these instances, it is again necessary to understand the BM microenvironment or niche and how it regulates different processes of HSCs via nutrient or diet to achieve their matured cell fates.

4. Haematopoietic Stem Cells (Hscs) & Their Associated Nutrient Factors For Keepin The Stemness

Havin unique multipotent capabilities like differentiation, proliferation, regeneration, the HSCs are always known for their stemness. These cells are generally resided in the bone marrow and can self-regenerate to conduct a steady-state haematopoiesis sustained by HSCs and HPSCs into lineage-restricted cell states (9,10). It is necessary to know in which ‘space’ and ‘time’ and ‘conditions’ the HSCs reside at BM niche and regulate the fates of biological systems. There are various metabolic and molecular factors which can modulate these cell paths (11). The ‘space’ in which HSCs are resides, are perivascular in nature and well protected and constructed by mesenchymal stem cells (MSCs) and endothelial cells (53,55). The whole system is located near trabecular bone and the niche is maintained a hypoxic condition along with some HIF factors (12,13). For this favourable condition of BM, they can regulate the oxidative phosphorylation to maintain their proliferative properties (12,14). Along with proper space and conditions, it is necessary to understand in which ‘time’ or ‘measures’ other factors can affect the “conditioned space”.

4.1.Essential Nutrients For Hscs:

“Minimal living and High thinking” are probably the best suitable phrase for HSCs and its niche. They

are constantly maintaining the low energy state and low biomolecular requirements to achieve their full potency to differentiate, proliferate, regenerate or to remain quiescent. Oxidative phosphorylation, Glycolysis and Fatty acid oxidation can play major roles to maintain its original properties like self-renewal and maintenance (14,15).

4.1.1. *Amino Acids:*

Not only in HSCs, but also in other different biological processes, Amino acids play a vital role for healthy maintenance. Valine is regarded as most important essential amino acids along with three others. The main sources of valine are red meat, dairy products and other protein rich sources. In a study, Taya et al., reported that, HSCs maintenance is dependent on Valine and dietary restriction of Valine may potentially reduce the number of HSCs (16). Cysteine also plays a role in ex-vivo HSC proliferation. Apart from these two amino acids, reducing amount of threonine could also play as a negative regulator in HSCs function via biosynthesis of glutathione. So, it is evident that, restricted events of dietary nutrients could be essential for maintaining the right anaerobic conditions (13) to maintain all the properties of HSCs. Not only single amino acid is the only requirement for HSCs but in a study, it was revealed that, branched chain amino acids in an imbalance state where the amount of valine is low could be associated with poor HSCs maintenance (14,15).

In AA, as the HSCs are drastically losses its number, it is necessary to analyse right amount of dietary intake of those amino acids that could lead to maintain a proper oxidative state within BM niche and reframe the self-renewal or differentiation properties.

4.1.2. Vitamins:

For a healthy living, the mechanisms and properties of vitamins and their roles is quite interesting in case of HSCs. Vitamin A, D, C are being widely used to maintain BM niche.

VITAMIN A

According to Cabezas-walls-cheid et al., vitamin A and its oxidative derivative retinol can regulate the HSCs dormancy which is necessary for its maintenance. A loss of HSCs can be caused by Vitamin A free diet in mice via inhibiting the re-entry of HSCs into dormancy (17). In Retinoic acid (RA) metabolism, the downregulation of retinoic acid is unable to activate VE-cadherin expression in in-vivo endothelial cells because of the lesser production of retinol dehydrogenase-2 (18,19). This could completely abolish the development of HSCs. Therefore, the wnt-signalling could also be inhibited via RA modulators (19). This dysregulated or inhibited wnt-signalling then promptly shutdown all the pathways necessary for HSC development and maintenance.

VITAMIN D

Sunlight is the main source for the absorption of vitamin D in a healthy living system. Vitamin D is also essential factor for HSCs proliferation and self-renewal (15). In a study, it was observed that loss of vit D could slower the rate of HSCs proliferation in mice after a 14-17 weeks experiment with vit D free diet (20,17). Targeting via Vit D modulators could restore the ability to self-renewal and proliferation via active Vit D metabolite 1,25(OH)D3. This could initiate the ex-vivo proliferation in human umbilical cord blood (17). Thus, vitamin D is necessary tool to sustain and renew stemness.

VITAMIN C

Acidic fruits like lemon, orange, apple etc and green pepper and all is known sources of ascorbic acid aka Vitamin C. This antioxidant is known for their ROS level reduction. According to Agathocleous et al., systemic ascorbate depletion could increase HSCs frequency in case of mice (21,22). Not only this, Vit C is also a key factor for enzymatic activity of TET family of DNA hydroxylases (23). This antioxidant acts as a negative regulator of HSCs self-renewal via TET-2 dependent and independent pathways to limiting their renewal (24).

Not only Vitamin A, D, C is important for HSCs regulation but also Vitamin B3 and Vitamin K can affect enormously via different time and scenario.

4.2. "Soaking Up" The Nutrients Into Hscs Via Various Nutrient-sensing Pathways:

A s we previously discussed, nutrients (amino acids, vitamins) are important for protecting the BM niche or environment. But it is important to sensing all the nutrients from dietary supplements via blood homeostasis. Thus, HSCs are maintaining their activity and processes. This nutrient uptake could happen via various pathways.

4.2.1. Restriction on Calories:

A cycle of 48h prolonged fasting in mice shows the regain of regeneration capabilities in HSCs. This regeneration is occurred via inhibiting the insulin growth factor 1 (IGF1) signalling during prolonged fasting period (25,26). Restriction on calories in dietary nutrients could be modulate BM microenvironment by elevating Lgr5+ intestinal stem cells and a decreased number of mature erythrocytes in mice model. This result leads to the fate where caloric restriction plays a role in shifting intestinal stem cells (ISCs) towards their self-renewal (27). In haematopoietic system, caloric restriction (CR) preserves the muscle stem cell function during aging. Thus, CR intrinsically influences the stem cell function and its residence (27,28). That's why, it may be helpful to understand the mechanism of insulin inhibition associated with dietary caloric restriction could be one of the regimes to follow.

4.2.2. High fat diet:

Accumulation of adipocytes in the BM is the main concern in AA. Adipocytes tends to reservoir of energy and protector of HSCs. They are capable to initiate or enables various cytokines [such as, stem cell factors (SCF)] to promote HSCs regeneration after irradiation or any injury (29,30,31). Limiting high fat diet (HFD) is crucial for maintaining HSCs numbers. Excessive amount of adipocytes can impair the mobility and number of HSCs in the time of self-renewal and influence the HSCs differentiation at the cost of self-renewal.

4.2.3. Maintaining the Microbiome:

Loss of HSCs, BM suppression and microbiome depletion generally caused by chronic antibiotic treatments and resulting anaemia or pancytopenia (32,33). The absence of mature blood cells with its heterogenous clinical representation is a well-known characteristic feature of AA. 'The path of happiness must be through gut' is a known fact. The symbiotic microbiome residing in gut is performing their tasks to stay immune and healthy. A healthy gut regulates all the metabolic products in a biological system and this mechanism is closely associated with HSCs differentiation (32). Prebiotic and Probiotic intake can reduce the chances of infection or graft rejection and strengthen the immune system via gut or intestinal system (34,35). Microbiome is also thought to modulate HSCs activity via MSCs and maintain the whole differentiation process (36).

Along with these, if we can play the act of balancing via nutrient sensing pathways and eliminating or reducing excess metabolites from HSCs biological environment, then the excess ROS production or regulating the metabolites can maintain a healthy bone marrow microenvironment for proper functioning.

4.3. Stress Sensing Pathways Of Hscs:

Above mentioned nutrient availability can regulate the HSCs metabolism. There are various sensing pathways are associated with nutrient uptake mechanisms and resulting in activation of several maintenance processes.

4.3.1. Integrated stress sensing pathways and mTOR signalling:

As discussed earlier, cycles of prolonged fasting are necessary to HSCs differentiation. Fasting states are regarded to induce ketogenesis. In a low carbohydrate diet, the elevation of ketone bodies is shown in circulation and forces to use as an alternate energy source (37,38). This state while fasting can promote the resistance against DNA damage (39,40,41).

In case of nutrient limitation, metabolic activity like protein synthesis could be disrupted. This could lead to mammalian target of rapamycin (mTOR) signalling and generate integrated stress sensing pathways (42,47). mTOR complex 1 (mTORC1) is a central node of metabolic signalling and sensing (43). In nutrient deprived conditions, two repressors of mTORC1 are seizure threshold 2 (STZ2) and tuberous sclerosis (TSC1) which are important in HSC homeostasis. The loss of STZ2 in HSCs are associated with reducing repopulation capabilities in HSCs pool. Loss of both STZ2 and TSC1 led to marked synergistic effect in increased mTORC1 activity and increase the production of ROS by 10 folds (44). So, overnutrition in a form of obesity can subsequently impair the HSCs function. Whereas, availability to adequate nutrients, amino acid leucine is thought to regulate mTORC1 activity via GTPase Rag A (45) and interestingly Rag A is found to be associated with HSCs resilience in certain nutrient stress conditions (46).

4.3.2. RAS-MAPK Signalling:

This signalling is also reported to participate in HSCs maintenance and homeostasis. Spred1, the negative regulator of RAS-MAPK, modulates HSCs self-renewal negatively through Rho kinase activity (48). Absence or deficiency of Spred1 can mitigate HSCs failure induced by pathogen, and therefore limiting the lifespan of HSCs.

4.3.3. TGF-ß Signalling:

TGF-ß Signalling have an impact in HSCs for their reconstitution (49). Disrupted TGF-ß receptor localization within lipid rafts lead to impair smad2/ 3 dependent TGF-ß Signalling.

4.3.4. PPAR?2 Signalling:

Metabolic stress can affect the bone marrow microenvironment by altering the gut microbiota and create a imbalance between osteoblast and adipocytes. This alteration leads to activation of PPAR?2 Signalling therefore hindered osteoblastogenesis and promoting adipogenesis inside the bone marrow (50, 54).

5. Conclusions:

From the background study about HSCs and their microenvironment on different conditions now it may be easier to understand the actual scenario of BM niche before and after treatments of AA. In India, the challenge is to identify and diagnose the disease onset and its pathophysiology. Response rate in the treatment is not quite satisfying in different patient cohort. Increasing number of pesticides, chemicals and other hazardous exposure rate is increasing day by day. The increased rate of the disease progression in Paediatric AA is much alarming. As the number of HSCs are high in younger subjects in AA it could be possible to manage the overall situation via those measures. Various lifestyle related factors and daily dietary intake could be associated with this increasing rate.

In recent days, stem cell therapy or HSCT used in several life-threatening diseases. HSCT is the only definitive cure of AA till date but associated with several complexities after transplantation. Chronic antigenic resistance, evolution of other haematological disorders, disrupted metabolism can be found. For this reason, we must evaluate every cellular mechanism associated with metabolic regulation can be important in future to take different measures. Small measures like Intermittent fasting or lowering the high fat diet or caloric restriction could also be helpful for the overall survival and long-term healthy BM niche. These changes in daily life and daily diet can change the whole paradigm of the onset of the disease scenario. Last but not the least quoting Great poet of Bengal, Sukanta Bhattacharjee until other dimensions is being revealed:

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"এ বিশ্বকে শিশুর বাসযোগ্য ক'রে যাব আমি নবজাতকের কাছে
এ আমার দৃঢ় অঙ্গীকার।"

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Ethical Approval
As the study is based on review of the topic therefore no ethical permission approved by Institutional Clinical Ethical Committee of The University of Burdwan is not necessary.

A Review On Epidemiological & Pathogenicity Of Nipah Virus: A Relatively Rare And Transmissible Disease

*** Kaustav Nayek, **Arghya Nath**
**Principal, **Research Scientist-B, ICMR-DHR Viral Research & Diagnostic Laboratory, Burdwan Medical College, Burdwan-713104*

Abstract

Fruit bats, especially Pteropus species, serve as the natural reservoir hosts for the biosafety level-4 pathogen known as Nipah viral illness, a zoonotic ailment brought on by the Nipah virus (NiV). After being discovered in Malaysia for the first time in 1998, the illness has subsequently spread to other nations in South and Southeast Asia. Due to its high human fatality rate, zoonotic origin, potential for human-to-human transmission, and absence of a vaccine, NiV has been identified by the WHO as a worldwide health hazard. Outbreaks are still happening in Bangladesh and India, with contamination of date palm sap in Bangladesh and India and contact with pigs in Malaysia and Singapore being the main modes of transmission. This virus, which may infect both people and animals, is primarily found in bats. In the acute phase, isolation and nucleic acid amplification or antibody detection might be used to confirm the diagnosis. The majority of acute encephalitis syndrome treatment focuses on syndromic management and supportive care. The condition is characterised by fast escalating severe illness, such as fatal encephalitis and/or respiratory illness. The development of respiratory disease and neurological symptoms is possible in pigs younger than six months. Enzyme-linked immunosorbent tests and molecular techniques using the polymerase chain reaction are examples of diagnostic techniques. However, supportive care and prevention are the cornerstones of therapy because there are presently no viable medicines for the NiPah virus. Only ribavirin, m102.4 monoclonal antibody, and favipiravir have some anti-NiPah virus efficacy. Comprehensive infection prevention and control methods are built on the pillars of standard precautions, hand cleanliness, and personal protective equipment.

Introduction

Nipah virus (NiV) infection is a viral disease caused by the Henipavirus genus, a novel RNA paramyxovirus closely related to the Hendra virus. It is an emerging zoonosis, accounting for 60% of emerging infectious diseases, with about 70% originating from wildlife. The disease is also widely described in pigs, with clinical signs involving the respiratory and nervous systems. The natural reservoir of the virus is represented by frugivorous bats called "flying foxes" belonging to the Pteropus genus.The main outbreaks of NiV infection have occurred in Malaysia, Singapore, Bangladesh, India, and the Philippines. The emergence of the virus and its zoonotic potential of transmission to animals and humans seem to be related to losses in the bats' habitat. The modes of transmission are different: Pteropus-swine-man, human contagion through the consumption of contaminated food, inter-human contagion, and direct bat-human contagion.When outbreaks occur in pigs, the only possible measures are isolation, blocking of movements, and killing of infected animals. A definitive diagnosis can be performed using molecular techniques, but serological tests are also available. NiV infection is an emerging and potentially dangerous disease whose spread must be curbed. Current strategies include prevention via limiting contacts with reservoir species, using proper pig farming practices, and improving hygiene and feeding habits of some populations living in areas where the disease occurs[1-5].

Further studies are necessary to improve knowledge about the interaction between NiV and the immune response, apply prevention methods, and develop

Correspondance : Kaustav Nayek Principal, Burdwan Medical College, Email : kaustav25@yahoo.co.in

effective prophylactic and curative therapies. Experimental vaccines based on the main NiV immunogenic proteins or peptides have been developed to investigate their immunogenicity, which could potentially counteract the infection and induce a cell-mediated response to mediate viral clearance. Remote sensing and geographic information system (GIS) technologies have proven useful tools in investigating animal distribution in relation to environment/human settlements and diseases in wildlife.Climate change has adversely affected the adaptive capacity of flying foxes to new environmental conditions, especially in relation to demography and species survival and thus NiV diffusion. Therefore, a "One Health" approach, considering humans, domestic and peridomestic animals, as well as the environment, is required to effectively control the disease.[6-10].

Viral Structure

An enveloped paramyxovirus with negative stranded polarity and a non-segmented RNA genome made up of helical nucleocapsids is known as the nipah virus. When compared to a conventional paramyxovirus, NiV exhibits minor structural changes. In contrast to other paramyxoviruses, it includes reticular cytoplasmic inclusions near the endoplasmic reticulum. NiV is also often bigger than other paramyxoviruses. Since Hendra virus (HeV) and NiV show considerable cross reactivity on serological testing and just slight ultrastructural variations, they are categorised as henipaviruses [11]. The Malaysian (MY) and Bangladesh (BD) strains of NiV have been identified as two distinct strains. Despite having a 92% identity in terms of sequencing, the pathogenicity and transmissibility of the two strains appear to be very different [12-14].

Nipah virus (NiV) is a paramyxovirus that can cause fatal encephalitis and severe respiratory disease in people. It is an RNA virus with helical symmetry that is single-stranded, nonsegmented, and enclosed in the negative sense. Six genes are included in the RNA genome: long polymerase (L), fusion glycoprotein (F), attachment glycoprotein (G), matrix (M), and nucleocapsid (N). The viral RNA is joined with the N, P, and L to create the virus

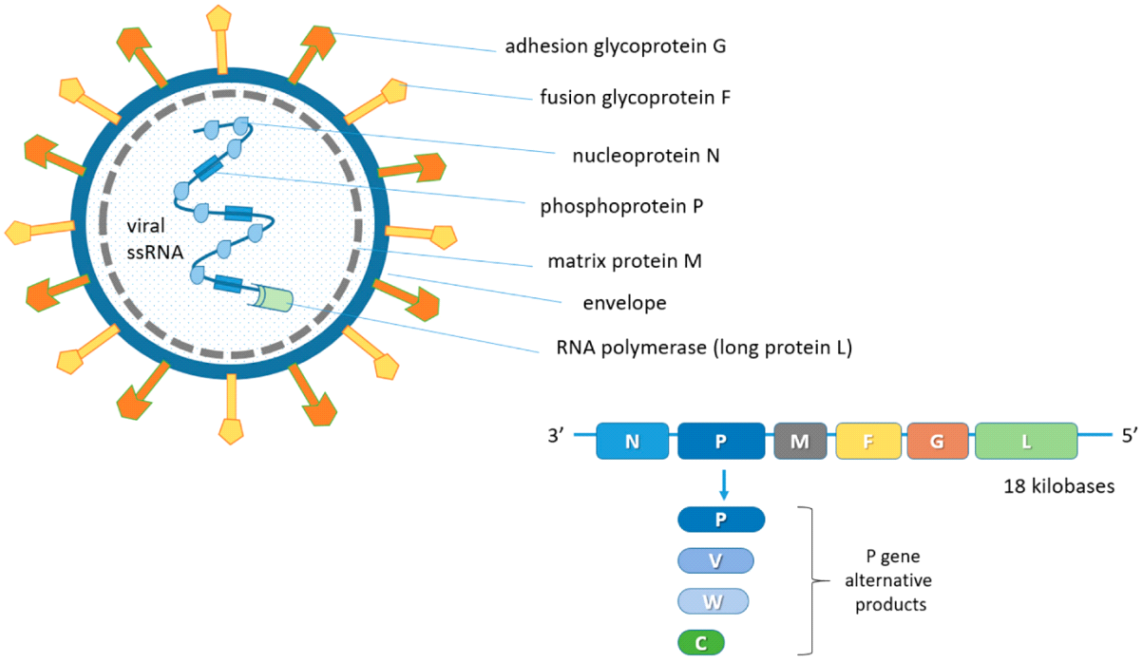


Fig 1: The NiV structure and viral genome organisation are shown schematically. The ribonucleoprotein (RNP) complex is formed when the N, P, and L proteins connect with the unsegmented single-stranded negative-sense viral RNA genome. The inner side of the envelope, which includes the G and F glycoproteins for attachment to ephrin-B2 and -B3 receptors and, correspondingly, fusion, is connected with the matrix M protein, which is needed for viral assembly and budding. The V, W, and C proteins encoded by the P gene are the results of mRNA editing and alternative open reading frames (ORF). A 3' leader and a 5' trailer region surround the six coded genes [15].

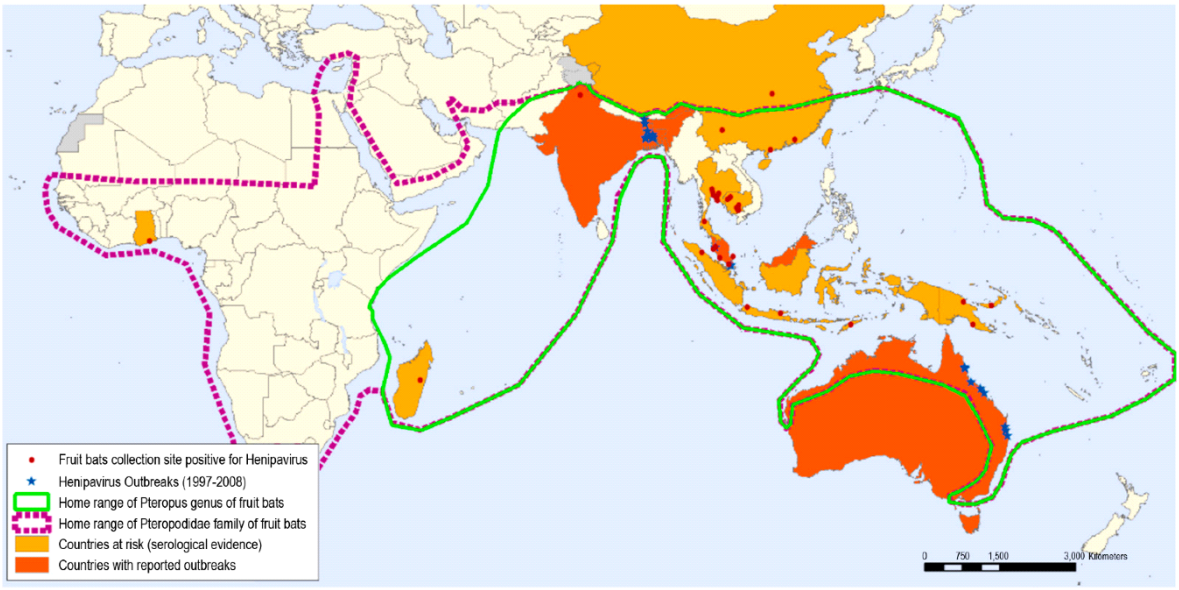
ribonucleoprotein (vRNP). The cellular attachment of the virion and subsequent host cell invasion are mediated by the F and G proteins. Host protease divides the freshly made precursor F protein (F0) into its two components, F1 and F2. For virus entrance, the F1 subunit's fusion peptide causes the viral and host cellular membranes to fuse. The viral M protein controls morphogenesis and budding, and an anti-G protein antibody is necessary to stop NiV infection. G and F proteins are two glycoproteins that allow NiV to infect its host cells. While the fusion protein facilitates the fusing of the virus-cell membranes for cellular entry, the G glycoprotein promotes attachment to host cell surface receptors. Inducing conformational changes in host ephrin B2/3 receptors, the G protein of NiV causes F protein refolding. The nucleolar DNA-damage response (DDR) pathway is the focus of viral control of the host cell machinery, which boosts henipavirus production. Mango fruit or fruit juices may keep NiV alive for up to 3 days, while fake date palm sap can keep NiV alive for at least 7 days. In fruit bat urine, it has an 18-hour half-life. NiV is rather stable in the atmosphere, lasting an hour at 70°C until becoming fully inactive after being heated for more than 15 minutes at 100°C. However, according on several factors, its viability in its native habitat may change [16].

1. Epidemiology

The map shows the geographic distribution of Henipavirus outbreaks and fruit bats of the Pteropodidae family. Countries at risk are highlighted in orange, while countries with reported outbreaks are highlighted in red. Violet spots indicate fruit bats that tested positive for Henipavirus, while blue stars indicate outbreaks between 1997 and 2008. The map also shows the home range of the Pteropus genus of fruit bats and the Pteropodidae family of fruit bats. The data source is the Global Alert and Response Department, World Health Organization. [17].

Transmission

High-risk infections including the Nipah, rabies, and Marbug viruses are reservoir hosts for bats. These viruses do not, however, significantly alter the pathology of bat populations. Understanding the pathways of Nipah virus transmission from bats to pigs, pigs to humans, and from date palm sap to humans requires more investigation [18]. Nipah viruses are naturally stored in fruit bats, and outbreaks have been reported all across the world. beyond spilt over transmission, the virus has broken beyond its barrier of species to infect other animals, including humans. The major areas where transmission happens are near people, pigs, and bats. Close closeness, touching, feeding, or



The boundaries and names shown and the designations used on this map do not imply the expression of any opinion whatsoever on the part of the World Health Organization concerning the legal status of any country, territory, city or area, or of its authorities, or concerning the delimitation of its frontiers or boundaries. Dotted lines on maps represent approximate border lines for which there may not yet be full agreement.

Data Source: Global Alert and Response Department
World Health Organization
Map Production: Public Health Information
and Geographic Information Systems (GIS)
World Health Organization

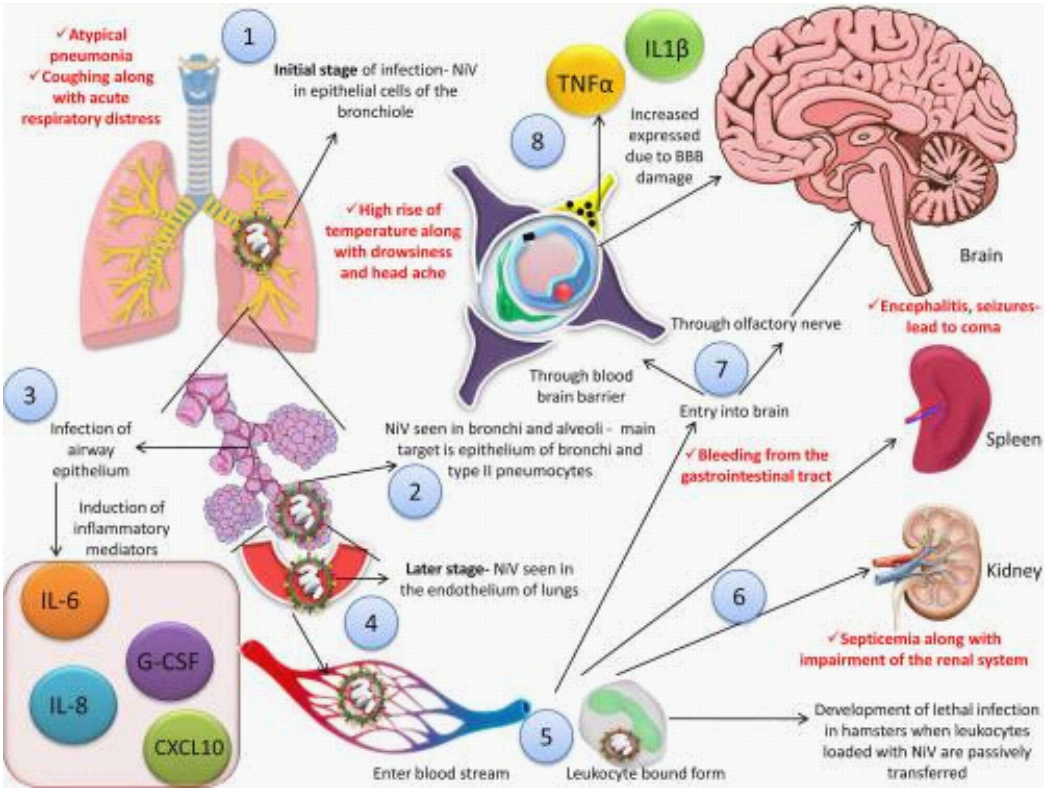
World Health Organization

attending sick people are risk factors. After research in Bangladesh, three mechanisms for the Nipah virus to spread have been found. The ingestion of fresh date palm sap is the most common route, with the drinking of tari (fermented date palm juice) being a possible route of viral transmission [19]. The NiV infection linked to tari can be avoided by restricting bat access to date palm sap. Date palm trees are frequently visited by bats like Pteropus giganteus, which lick them while collecting sap, according to studies utilising infrared cameras. It was discovered that drinking raw date palm sap was a contributing factor in the Nipah virus epidemic reported from Tangail district, Bangladesh. Patients in Bangladesh were diagnosed with symptoms between December and March, when date palm sap was being collected. Additionally, the data showed that Pteropusspp had a significant seroprevalence of anti-Nipah viral antibodies, indicating that the virus had undergone adaption successfully enough to spread among Pteropus bats [16].

It was discovered through research done in Bangladesh between May and December 2004 that man-to-man and bat-to-man transmission of the NiV virus both happened. In certain cultures, NiV infections were attributed to mystical or supernatural forces, necessitating the use of cooperative preventative and control methods. During outbreaks, secondary human transmission was seen, with NiV shed from Pteropus spp. infecting one or more people before spreading in an epidemic form through person-to-person contact. Patient handling and coming into touch with an infected person's secretion are risk factors for the illness[18-20].

Pigs were discovered to be the virus' intermediate and amplifying hosts in Malaysia. Domestic animals were found in Bangladesh searching for fruits tainted with infectious saliva, suggesting that they played a part in the spread of the disease. Infections with the Nipah virus have also been linked to illnesses contracted from pigs, goat saliva, and bat secretions in Naogaon. When ferrets were exposed to certain dosages of NiV particles, systemic illness was produced in the animals. Patients with respiratory tract infections have a higher risk of transmitting NiV. Direct close contact with pigs was the main cause of human NiV infections, according to a case-control investigation evaluating the risk variables for human NiV infection during the outbreak in Malaysia [22].

Although domesticated animals are important in big



outbreaks of bat-borne viruses, it is unclear exactly how they function as bridge or amplifying species. During the harsher winters, prevention tactics against NiV infections in people need to be bolstered. Understanding the dynamics of bat infections and spillover risk can be achieved by evolutionary research based on codon use patterns.

Pathogenesis:

NiV's pathogenesis. During the early stages of infection, NiV may be observed in the bronchiole's epithelial cells. Bronchi and alveoli both contain NiV antigen. 3. An infection of the airway epithelium causes the activation of inflammatory mediators. When the sickness is further advanced, the virus spreads to the lungs' endothelial cells.The virus enters the bloodstream, spreads, either freely or in a leukocyte-bound form, and reaches the kidneys, spleen, and brain.Viral entrance into the central nervous system (CNS) occurs via two pathways: the hematogenous route and anterogradely through olfactory nerve nerves.The virus's infection of the CNS ultimately results in the breakdown of the blood brain barrier (BBB), the expression of IL-1 and tumour necrosis factor (TNF), and the development of neurological symptoms. The human symptoms are displayed in red type [16].

2. Conclusion

The development and transmission of the Nipah virus illness have been extensively studied during the past 20 years. In order to introduce vaccinations and change risk factors to avoid infection, this understanding will be essential. Additionally, it will help with the development of medications and treatment methods for infected patients, lowering morbidity and mortality.

The Global Outbreak Alert and Response Network (GOARN) has emphasised the importance of a network that connects veterinary and medical services in order to prevent NiV outbreaks in India and Bangladesh. Precise preventative interventions must be planned and implemented using a multidisciplinary approach.NiV first appeared 20 years ago and has since spread throughout Bangladesh and India, causing significant morbidity and mortality in both humans and animals.The 'One Health' strategy, which involves collaboration across institutions and on an international scale among virologists from many domains, is essential. Education on both personal and food cleanliness is crucial. Infrastructure facilities and qualified staff should be available, together with appropriate isolation, quarantine, and disinfection methods. It's also crucial to maintain proper cleanliness while slaughtering cattle.To ascertain the frequency and forecast the likelihood of HIV transmission, ongoing observation of human health, animal health, and reservoir hosts is required. To effectively stop the spread of an outbreak and treat infected people, therapeutic antibodies or antivirals must be developed at an expedited rate. The development of a vaccine or treatment for NiV may be accelerated by collaboration between CEPI and biotech firms.

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Toilet Training

Subhabilas Bhunia
Consultant Pediatrician.Hooghly, West Bengal

Acquiring the skill of toilet training is an important milestone in child development. It is believed to be a normal process and eventually almost all normal healthy children become toilet trained with the assistance of parents and caregivers. In most of the cases, it is a rewarding experience for both parents and children but sometimes it may become frustrating for both and problem arises.

The parents may have unrealistic expectation about their child's capability or they may become very intolerant to normal accidents during the process. Sometimes power-struggle between the child and the parents comes into play and complicate the process very adversely. All these things may be the precipitating factors of child abuse or may lead to other behavioral problems in the children (1). Refusal to sit in the potty, hiding during defecation or soiling the pants may be a concern for the parents and ultimately, if untreated may spiral into physical, behavioral and developmental problems and can disrupt the process of toilet training (2). Chronic wetting and soiling may persist well into school years and may become refractory to empirical medical treatment.

Pediatricians are often asked about the timing and method of toilet training especially when problem arises. To help facilitate the process of toilet training, pediatrician should be prepared to offer anticipatory guidance to the parents as the child learns toilet skill.

But like many behavioral issues, there is no concrete guideline in this matter easily available to the practicing pediatricians. This article aims to review the literature and discuss the different methods and guidelines for toilet training.

Correspondance : Subhabilas Bhunia, Consultant Pediatrician., Email : kaustav25@yahoo.co.in

Epidemiology

The age at which the parents initiate toilet training is culturally determined rather than scientific evidences. For example, in East African Digo culture, some children between 2 to 3 months of age are conditioned to urinate or defecate when placed in certain position. This type of conditioning practice is carried out in certain places in China. The Chinese children are kept without diapers and the caregivers who are holding them sense a change in their bodies in response to a need to eliminate and they place their children in an appropriate position (1).

American cultures focus on the learning aspects of toilet training as opposed to above-mentioned conditioning aspects. They follow a 'child oriented' approach and focus on the cognitive development of the children and the children readiness to learn the complexities of the task.

Currently in the United State and several European nations, toilet training begins significantly later than in the past (3). In the 1940s, training commonly started before 18 months of age. Recent data show that training starts between 21 to 36 months of age and that only 40 to 60 per cent of children complete toilet training by 36 months of age (4).

The socioeconomic factors also influence parental beliefs about toilet training. Horn and colleagues found that higher family income was associated with parents favoring later initiation of toilet training (1). Girls tend to achieve this control at a slightly younger age than boys (5). The average time from the initiation of toilet training to the attainment of independent toilet training varies from 3-6 months (6). Most children (80%) are trained simultaneously for bladder and bowel control. Approximately 12% are trained first for bowel control and 8% for bladder control (7).

The night time urinary continence may coincides with day time continence or occurs several months or years later (7).

Pathophysiology

Infant's voiding is not merely a spinal reflex in response to the sensation of full bladder. It requires the ability of the brain to inhibit bladder contraction and to achieve co-ordinated bladder contraction with sphincter relaxation. For the success of the process of toilet training, a certain degree of neurological and biological development is essential. Myelination of the pyramidal tracts and conditioned reflex sphincter control are necessary. Voluntary control is achieved by myelination of the pyramidal tracts by the age of 12 to 18 months. Conditioned reflex sphincter control occurs by 9 months of age and voluntary co-operation between 12 to 15 months.

"Walking" may be viewed as one of the milestone that indicates motor readiness for toilet training (1). Toilet training depends on both physiological and psychological readiness. Cognitive development is assessed by a child's ability to follow certain instructions. Two years of age has been suggested by many as the appropriate age to initiate toilet training in most children. Toilet training usually takes 2 weeks to 2 months to learn, although training may occur in less time using more intense conditioning methods (1).

Counseling and assessment of readiness

The pediatricians are often asked by the parents for advices on toilet training especially when problem arises. Anticipatory counseling about toilet training should address the family perceptions and misconceptions and should be structured to help parents to develop reasonable expectations. Ideally, parents are counseled at 18 to 24 months of age (American Academy of Family Physician). During counseling, the pediatrician should understand the family dynamics and should assess the readiness and also provide educational support to the parents.

As each child and family is unique, the ideal age for toilet training varies. Toilet training readiness should not be directed by a child's chronological age. Parents must judge when their child is ready. Remaining bowel-movement free overnight is the earliest attained skill while the ability to pull up underwear or training pants is typically the last skill mastered.

In child oriented approach, a child must be both physiologically and psychologically ready to begin the process. Physiological readiness precedes psychological readiness. When assessing a child's readiness for toilet training, the pediatrician must consider motor, language and social milestones as well as the child's demeanor and relationship with his or her parents(8). Child may be considered ready for toilet training if affirmative answers are obtained to the following three questions.

1) Do children exhibit bladder control as evidenced by –
   a) periods of dryness that last up to 2 hours
   b) facial expressions that show their physiological response to the elimination process?
2) Do children have the motor skill for the purpose?
3) Do children have the cognitive ability to understand the task ahead?

A check list of a child's toilet readiness is furnished in Table -1(9)

Table 1 :Adopted from Toilet training: Anticipatory guidance with a child-oriented approach – Paediatr. Child Health; 2000 Sep; 5(6): 333-335

- Able to walk to the potty chair or adopted toilet seat
- Stable while sitting on the potty or adopted toilet seat
- Able to remain dry for several hours
- Receptive language skills allow the child to follow simple (1&2 steps) commands
- Expressive language skills permit the child to communicate the need to use the potty or the adopted seat with words or reproducible gestures
- Desire to please caregivers based on positive relationship
- Desire for independence and control of bladder and bowel function

Pediatrician should advice the parents to delay toilet training if there is a stress in the family like

a) Family has moved recently

b) The birth of a new baby is expected

c) There is a major crisis such as a death or serious illness

Training Methods

There are several methods of toilet training (Table-2). Basically, there are two contrasting styles – one is child oriented and unregimented and the other is of intense conditioning and parent oriented.

Table-2. Different methods of toilet training

Child oriented approach
• The Brazeltone child oriented approach
• Dr Spock's "the common sense book of baby and child care"
Operant conditioning
The Azrin& Foxx "toilet training in a day method"
Other methods
Assisted infant toilet training
Elimination communication

The first description of standardized method of toilet training was published in 1962 by Brazeltone. He developed a "child readiness" approach which was child-focused and unregimented. The children started training at 18 months of age and in a group of1170 children day time continence was achieved by a mean age of 28.5 months (7). Children were considered "ready" to start training when they were physiologically capable of the process and when the child and parent were emotionally ready.

Spock discussed toilet training in "Baby and Child Care" published in 1968. Like Brazelton, Spock recommended a child oriented approach, starting when the child displayed signs of readiness. He opposed to absolute rules that could result in behavioral problems (8).

In 1973, Foxx and Azrin published a method that was structured and parent oriented. After the children achieve readiness a 4-step measure was used. The four steps were like this – 1) increase the amount of fluid consumed, 2) regularly scheduled time for toileting, 3) positive reinforcement when successful like affection, toysor candy and 4) overcorrection of accidents like cleanliness training, punishment, lack of positive attentionortimeout (i.e. negative enforcement) (12).

Other methods include assisted toilet training in infants which starts when the child is 2 to 3 weeks of age. The infant is placed on the toilet after a meal and also whenever the parent thinksthe child may need to evacuate his or her bowl or bladder. The parent makes a noise that is linked to the elimination and conditions the child to evacuate with noise. Variation of this method is elimination correction. There are no studies evaluating these methods.

American Academy of Pediatrics guidelines

AAP guidelines incorporate many components of child oriented approach. The guidelines recommend that training should begin after 18 months of age using a potty chair. Parents should assess readiness by looking the signs of readiness. AAP training steps are similar to Brazelton approach, although the AAP suggests using praise for reinforcement rather than treats.(10) AAP recommendations are based on expert opinion rather than on control trial evidences.

Indian Academy of Pediatrics guidelines

Indian Academy of Pediatrics, however has suggested an older age for initiation of toilet training. They recommend that ideal time to initiate toilet training should be 2-3 years of age depending upon the child's readiness and it should be gradual and too rigid training should be avoided. The guidelines suggest the following steps (13).

1. Assess the readiness of the child
2. Get the right type of equipment
3. Create a routine
4. Demonstrate the posture
5. Do not scold the child in case of incident of soiling
6. Encourage the habit

Advices to parents

To facilitate the toilet training process, the pediatrician may advice the parents to take the following approach (1, 9,10, 11,13).

1. Begin when the child shows sign of readiness generally after 18 months of age.
2. Decide on the vocabulary which will be used related to the toilet training process. This may include words like-potty,hago, hisu, poo, clean,peeetc.
3. Tell the children what is the purpose of the potty

chair. Placing the contents of a soiled diaper into the potty can demonstrate its function and educate the child about the purpose of the potty.

4. In general, a potty chair is recommended rather than the toilet during the early stages because children feel more secured and stable on the potty. The potty also provides the best biomedical position for the child. Children should sit on the potty with their feet on the floor giving them a greater sense of security.
5. Parents can encourage the children to decorate the potty by attaching stickers and can put their names on it.
6. The potty may be kept in a place where children spend much of their time, not necessarily in bathrooms.
7. Initially, the child is encouraged to sit fully dressed on the potty for a week or two.
8. After one to two weeks of fully-clothed sits, children should be encouraged to sit on the potty without their cloths on for a few minutes. But parents must not insist the child to use the potty chair in this point.
9. Thereafter, the child can be led to the potty several times a day and encouraged to sit on it for a few minutes.The child may be encouraged to sit on the potty after a wet or soiled diaper has been removed. It may be helpful to place the soiled diaper in the potty to demonstrate its function.
10. Finally, the child is encouraged to develop a routine of sitting on the potty at specific time of a day (e.g. after meals or snacks, after walking in the morning, before or immediately after naps).
11. The child needs to be praised whenever he or she expresses an interest in sitting on the potty. Positive reinforcement may be used by giving praise on success, but material rewards should be discouraged. Verbal praise will be more appropriate.
12. When away from home, the potty chair should be packed to maintain the established routine.
13. It is also important that all individuals caring for the child (like grandparents, babysitter) understands the parent's plans for toilet training. The cooperation of all caregivers should be ensured to provide a consistent approach.
14. Encourage cleanliness and dryness by changing children frequently. Parents should ask their children whether they need to be changed by using appropriate vocabulary. Some parents mistakenly do not change their soiled children as means of punishing them for having accidents. This gives the children a confusing message.
15. While sitting on the potty, the children can be entertained with reading a story or playing games. It is helpful to have designated toys or books only when the child is sitting on the potty.
16. Children who use the potty successfully should be rewarded. Rewards should be in the form of verbal comments and hand clapping.
17. Regression in a toilet-trained child may occur with stressors such as a recent move, new sibling or divorce. The parents should be supportive and any kind of punishment should not be used.
18. Once the child has used the potty successfully for one week or more, he or she may be ready to try training pants which are thickened underwear or pull-ups. These are diaper like underwear rather than diapers. After repeated success, parents may suggest the use of training pants or cotton underwear and should make this a special moment. Accidents are almost inevitable. However, the parents need to be supportive. A child who has experienced a series of accidents soon after trying training pants or cotton underwear should be allowed to return to diapers without shame or punishment.
19. Children should wash their hands following sessions sitting on the toilet
20. If the children are trained and using the potty chair successfully, they can generally begin using a toilet between 2.5 to3.5 years of age. Transfer from potty chair to toilet may be stressful. Toilet adapter rings or other devices may be used. Toilet adapter rings require the toddler to climb up on the toilet. A stool may be used to aid in climbing onto the toilet.

When problem arises

Toileting refusal

If the children demonstrate resistance to toilet training,

the most likely explanation for failure is that the child is not ready. If the child is not ready, parent's attempt to toilet train the child will be futile. Parent should be advised not to be engaged in "toileting battle", because this then may become the source of future bowel problems including constipation.

In this situation, the process should be delayed for one to two months. This allows trust and cooperation to be re-established between parents and child. After this break, most children are ready to begin training. However, if repeated attempts are unsuccessful or if the child is older than four years, a referral to a developmental pediatrician may be required. The referral is necessary to explore aspects of parent-child relationship and to rule out neurodevelopmental abnormalities.

Stool withholding

It involves the child physical maneuvers in an attempt to avoid defecation (e.g. potty dance or crossing the legs) Voluntary constriction of the sphincter during rectal contraction can lead to constipation. The most common interventions for stool withholding include treatment of constipation and resuming diaper use.

Hiding

Some children who are toilet trained hide while defecating rather than using the toilet. Onset of this behavior is most common around 22 weeks of age. These children are most likely to be constipated and likely to have toileting refusal or stool withholding also. However, the children who prefer to stand in a corner to defecate should be commended.

Conclusion

The process of toilet training has changed over years and within different cultures. The age at which the toilet training should be initiated does not depend on the chronological age but on the cognitive development and readiness of the child to learn the complexity of the task. The process of toilet training should be individualized and a child oriented approach is recommended. Though, almost all the children are eventually toilet trained, sometimes it may be a frustrating experience for children and parents. The problem arising out of the training process may be the precipitating factors of child abuse and if left untreated, may spiral into physical, behavioral and developmental problems.The pediatrician should be prepared to offer anticipatory guidance to the parents as the child learns theskill and should provide support when problem arises.

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