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A Study of Clinical and Laboratory Profile with Outcome and Follow up of Children with Infantile Tremor Syndrome in a Tertiary Care Center

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ABSTRACT

Infantile Tremor Syndrome (ITS) is characterized by anaemia, skin depigmentation, tremors and developmental delay or regression. Vitamin B12 deficiency has been found to be associated with ITS in many studies. To assess the clinical profile of infantile tremor syndrome (ITS) and to correlate serum Vitamin B12 level along with response to treatment and final outcome. It is a retrospective and prospective Observational study including total 50 patients, from 6 months to 2-year age group, admitted to Paediatric department of Vanivilas Hospital and Bowring Hospital attached to Bangalore Medical College and Research Institute, India from March 2017 to 2020 Jan and their follow up for 3 months. 45 (90%) among 50 study subjects were between 6 and 24 months, with mean age of presentation of 12.15 months. Mothers of 45 children (90%) were vegetarian by diet. 40 children (80%) were exclusively breast fed for prolonged period and had delayed initiation of complementary feeding. 40 (80%) and 10 (20%) children had features of ITS and pre-ITS respectively. 45 children (95%) had developmental delay, 5 children (10%) had developmental regression. Severe Acute Malnutrition was evident in 35 (70%) of children. 100 % children had anaemia and 100% children had skin hyper pigmentation. Hypotonia was predominant topographical finding observed in 35 (70%). Hyperopia in 5, dystonia in 2, seizures in 2 . Half of the children had dimorphic blood picture with predominant macrocytes. Pancytopenia was noted in 70%. All the children and their moms had evidence of anemia and low serum vitamin B12 level. Very Severe anemia was noted in 10 babies and 20 required blood transfusion, also due to cardiac failure. Other micro nutrient deficiency was noted in 30 babies (60%). Serum Homocysteine was also high in 54% . Low maternal vitamin B12 level was found in all. Two children succumbed to death due to pneumonia. 20 children (40%) required treatment for tremors with Propranolol and Clonazepam. Microcephaly was seen in 25% cases (12 cases) and MRI was abnormal in 20% cases (10) mainly showing cerebral atrophy and delayed myelination. Tremors seen were limited to hands in 10 (20%) and involving hands, feet and voice in 40 (80%). Most of the findings , clinical and laboratory, except developmental delay, fully reversed on follow up of 3 months and later lost to follow up. Most of the infants and young children with ITS will have hematological findings consistent with megaloblastic anaemia and evidence of vitamin B12 deficiency. Nutritional vitamin B12 deficiency is an easily treatable cause of pseudo-neuroregression and long-term neuro-deficits can result if treatment is delayed but are easily reversed with timely B12 treatment. Mothers with Vit B12 deficient diet are the main reasons for Vit B12 deficiency in children and ensuing ITS and hence they have to be screened and supplemented with VitB12 in pregnancy and 6 months post partum making available VITB12 also along with Iron Folic Acid IFA like IFAB12. Long term follow up is required to prevent recurrences especially in those on vegetarian diet and to look for complete recovery of developmental quotient above 70%.

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Key Words

ITS, malnutrition, vitamin B12, regression , developmental delay

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INTRODUCTION

Infantile tremor syndrome (ITS) is a clinical condition of infancy and early childhood characterized by acute or insidious onset with mental and psychomotor changes, pigmentary changes of hair and skin, pallor and tremors. Tremors are seen in the form of rhythmic, coarse, twitching of the angles of eye, mouth, eyelids and tongue with a tremulous cry resembling bleating of a goat, tossing movement of the head, wriggling movements of the trunk and coarse rhythmic continuous rapid movements of varying but usually of low amplitude in the extremities, most marked in the distal parts especially the fingers along with anemia, dull apathetic look, sparse scalp hair, expressionless face with drooling of saliva, pigmentation over extremities, mild hepatomegaly with or without splenomegaly, regression of mental development and hypotonia of muscles[1-3]. ITS is seen in infants and children of 6-36 months of age group[1]. It has been primarily reported from Southeast Asia including India and other developing countries. The exact incidence is unknown. In India, it accounts for 0.22% paediatric hospital admissions[2]. These children are listless, apathetic and disinterested in surroundings. The presence of tremors and neuromotor regression are the most prominent neurological manifestations attributed to structural and functional alterations of brain especially the extrapyramidal system[4,5]. The causation of ITS is still unknown. Malnutrition, vitamins and mineral deficiency like Mg, Zn,Vit.B12., infections, toxins, degenerative brain diseases, enzyme defects (e.g., tyrosine), all have been postulated as the cause of ITS[6,7].

Among all, malnutrition/ nutrition theory is the most accepted theory. It is usually seen in children who are exclusively breastfed for prolonged periods by Vitamin B12 deficient vegetarian mother[8]. The low levels of Vitamin B12 and its transport protein Transcobalamin II in the cerebrospinal fluid (CSF) may be responsible for the neurological features of this syndrome[9]. It is usual to find direct or indirect evidence of malnutrition associated other micronutrients deficiencies such as Vitamin A, D and Vitamin B complex[1]. ITS was first described by Dikshit AK who named it as "Nutritional dystrophy and anaemia"[10]. The current nomenclature of infantile tremor syndrome seems to be misnomer as this entity has been seen even beyond infantile age and the syndrome can present without tremors in early stage.

Aims: to assess the clinical profile of children with infantile tremor syndrome and its relation to vitamin B12 levels along with response to treatment and final outcome.

MATERIALS AND METHODS

It is a retrospective and prospective observational study including total 50 patients, from 6 months to 2-year age group, admitted to Pediatric ICU, wards and nutritional rehabilitation centre, Vanivilas Hospital and Bowring Hospital, Bangalore Medical College and Research Institute, Bangalore India from March 2017 to Jan 2020. Children who were diagnosed to have pre-ITS or ITS were included in the study. Those with perinatal asphyxia and other conditions causing global developmental delay were excluded . Pre-ITS condition is defined as those children who developed tremors after treatment. Detailed history of presenting illness along with past history, family history, birth history, diet history of child and mother and developmental history was taken. Socio-economic status was established on basis of modified Kuppuswamy classification. Malnutrition was classified according to WHO classification. Complete general physical examination and systemic examination was carried out including fundus. A complete haemogram which includes haemoglobin, total leukocyte count, platelet count, MCV, MCHC, MCH, peripheral blood film was done.Serum vitamin B12 level was done for all the children and mothers, values <83ng/ml was considered as low. Other micronutrients like Serum Iron, calcium, Magnesium, Phosphorus, Albumin, vit D were also checked. Serum Homocysteine levels were also done for all but TMS and Methylmalonic acid MMA levels could be done only for 2 . Urinary MMA levels were not done for anyone. MRI brain was done for those with microcephaly and free of cost in our hospital for < 1year and those with severe malnutrition through schemes. MRI brain could not be done for select few without microcephaly and those without any schemes as cost was not affordable in them. Bone marrow examination was not done for anyone. Neither was csf or EEG done. No nerve conduction studies could be done too. Visual Evoked Potentials , Brain stem evoked auditory response were not done . Chest radiograph, urine examination, blood cultures were done in cases associated with lower respiratory tract infection, urinary tract infection or sepsis. Children were managed in PICU and Nutrition Rehabilitation Ward according to WHO protocol for management of malnutrition. Children with low serum vitamin B12 level were treated with parenteral vitamin B12 injection 1000 mcg daily for 1 week followed by weekly

for a month and monthly regimen for a year. Vitamin B12 was also given to mothers with low vitamin B12 level. Persisting tremors were treated with Propranolol and Clonazepam. Diet counselling was offered to all. Physiotherapy and stimulation were offered to all via DEIC or District Early Intervention Centre. All babies were followed up for 3 months in OPD and later for another 3 months to note for reversibility in clinical and laboratory parameters . However MRI brain was not repeated for anyone. Statistical analysis was done using Microsoft Excel software.

RESULTS AND DISCUSSIONS

Clinical: Out of 80 children who were admitted with vitamin B12 deficiency anaemia in the study period, 50 children were included in the study who had features of Infantile Tremor Syndrome initially or later. Mean age of presentation was 12.15 months . 45 (90%) were between 6 months to 2 years. 45 children (90%) in the study were infants. Male to Female ratio among study children was 3:2. 10 children (20%) were born to consanguineously married couple. Siblings with similar illness was seen in 2 children. 25 (50%) were exclusively breast fed for prolonged period and had 25 had inappropriate complementary feeding. 100% mothers looked pale with knuckle pigmentation in 90%. Mothers of 45 children (90%) were vegetarians, consuming minimal animal products like dairy, 50% mothers had received blood transfusion during pregnancy for severe anemia. 50% mothers irregularly received vitamin supplements during pregnancy and 10 % only received supplements after delivery. 30(60%) had other micronutrient deficiency including signs of vit d deficiency, vit a, vit c deficiency. 100% had pallor, skin/knuckle pigmentation , severe malnutrition in 70% and apathy in 80%. 35 had hypotonia. 10 had normotonia and 5 had hypertonia, 2 had dystonia. 2 had seizures, probably due to hyoxia in those with severe pneumonia. No sensory or cerebellar involvement was noted in anyone. No other involuntary movements like chorea athetosis were seen . Microcephaly seen in 12 cases (25%) . Tremors at admission seen in 80% and in 20% after treatment and were limited to hands in 10 (20%) and involving hands, feet, lips, face, tongue and voice in 40 (80%). They increased in 24% cases after treatment. 35 children (70%) were immunised appropriate for age as per National schedule. 45 children (95%) had developmental delay of which, average Developmental quotient was around 50%, 40 had global delay and 5 had only motor delay. 5 children (10%) had developmental regression. 45 children (90%) belonged to Upper-Lower socio-economic class according to Modified Kuppuswamy Classification.

Table I: Distribution of Clinical Features among Study Children is Shown in the Below Table

Clinical Finding	Number of Cases [N=50]
Skin/ knuckle hyperpigmentation	50 (100%)
Tremors at admission	40 (80%)
Tremors after treatment	10 (20%)
Exaggeration of tremors after treatment	12 (24%)
Severe Acute Malnutrition	35 (70%)
Anaemia	50 (100%)
Other micronutrients deficiency features	30 (60%)
Bleed gums – Vit C deficiency	2(4%)
Frontal bossing/large Anterior fontanel/ Harrison sulcus/delayed teeth – vit d deficiency	25 (50%)
Bitot spots / dry eyes – vit A deficiency	3 (6%)
Lethargy/Apathy	40 (80%)
Developmental delay	45(90%)
Regression	5(10%)
Hypertonia	5 (10%)
Hypotonia	35 (70%)
Normotonia with exaggerated reflex	10 (20%)
Dystonia	2 (4%)
Chorea athetosis	0
Seizures	2 (4%)
Sensory and cerebellar	0
Microcephaly	12(25%)
Hand only Tremors	10 (20%)
Hands, feet , tongue, face, lips and voice tremors	40(80%)
Lustreless scalp hair / bald areas	40 (80%)
Dry skin	45 (90%)
Skin lesions	5 (10%)
Bald tongue	20 (40%)
Fundus normal	50(100%)
Vision hearing normal	50(100%)
Maternal knuckle pigmentation	50 (100%)
Maternal anemia	50(100%)
Respiratory infections	30(60%)
Gastrointestinal infections	10 (20%)
Congestive cardiac failure	10 (20%)
Death (severe pneumonia)	2(4%)
Prolonged exclusive breast-feeding	25 (50%)
Inappropriate complementary feeding	25(50%)
Mothers received blood in pregnancy	25(50%)

30 children (60%) had concurrent respiratory infections and 10 children (20%) had gastroenteritis. 10 children (20%) presented with features of congestive cardiac failure due to severe anemia.

Reversibility of tremors with vit b12 , complete 40 (80%). Reversibility of tremors with vitb12 partial 10 (20%). Requiring medication for tremor 20 (40%) Reversibility of physical findings, anemia, Laboratory findings 50 (100%). About 100 % had anemia of which 10 had severe anemia (20%), 35 (70%) had pancytopenia , 25 (50%) had bicytopenia. 45 (90%) had macrocytic blood picture whereas 5 had microcytic picture. 25 (50%) had dimorphic anemia. No bone marrow aspiration was done for anyone. Low serum vit B12 levels were noted in 50 (100%) children and all their mothers . 20 babies (40%) received blood transfusion either due to failure or very severe anemia. All babies and their moms received Inj. Vit B12. Other deficiencies noted were low Iron in 25 (50%) , low serum folate in 12 (24%), hypovitaminosis D in 25 Homocysteine levels were high in 27 (54%) children. Serum MMA (50%), hypocalcemia in 10 (20%),

Table 2: Laboratory Finding and Management of ITS among Study Children is as Follows

Laboratory parameter and treatment	Number of Cases (N=20)
Anaemia	50 (100%)
Hb <4g%	10 (20%)
Bicytopenia	25(50%)
Pancytopenia	35 (70%)
Macrocytic	45 (90%)
Microcytic	5 (10%)
Dimorphic	25 (50%)
Serum Vitamin B12 <83ng/ml	50 (100%)
Maternal Hb <11g%	50 (100%)
Maternal low vitB12	50 (100%)
Children received blood transfusion	20 (40%)
Children received vitamin B12	50 (100%)
Mothers received vitamin B12	50 (100%)
Vit d levels <20ng/ml	25(50)
Serum folate <3ng /ml	12(24)
Serum Iron <50 mcg/dl	25(50%)
Serum Calcium <7 mg %	10 (20%)
Serum Magnesium <1.6mg%	6 (12%)
Serum Phosphorus normal	50 (100%)
Serum albumin <3g%	6 (12%)
Serum Homocysteine >20mcmol /L	27(54%)
MMA levels high >400nmol/L	2 (4%)
MRI Brain abnormal	12(24%)
Response to Inj Vit B12	50(100%)

in 6 (12%) , hypoalbuminemia in 6 (12%). Serum levels could be done in only 2 and was high .Urinary MMA could not be done for any. MRI brain was abnormal in 12 (24%) of which 5 showed cerebral atrophy, 5 showed delayed myelination, 2 had T2 /FLAIR hyperintensities in periventricular areas Response to vit b12 injections were noted in all, complete recovery of tremors in 40 and partial recovery in remaining 10 during discharge in 2 weeks. The mental apathy had reversed in all. However on follow up in 3 months, they all had recovered physically like hyperpigmentation, other skin hair changes, pallor too . Severe acute malnutrition had recovered in 60% in 3 months and Regression reversed in all in 3 months, however grossly developmental delay continued in 30 (60%) even after 3 months. However no Bailey s or any validated developmental scrrening was done for that . For next 3 months , many lost to follow up and 5 of them had shown full recovery like severe malnutrition and delay.

Clinical: In the present study, males were more commonly affected similar to other many studies by Kalra, Gupte, Gupta, Kaul, Sachdeva[1-5]. In the present study,45 children (90%) were between 6 and 24 months which is consistent with Kalra *et al,* Gupte , Gupta, Kaul, Sachdeva, Khan, Holla, Dikshit, Ratageri , Bajpai, Ramakumar, Pathak, Garg, Gowda *et al.* who found it ranging from 88-96%[1-16]. 5 children were aged less than 6 months, which can be explained with maternal vitamin B12 deficiency. In the current study, skin hyper pigmentation (100%), pallor (100%) psychomotor changes and apathetic look (80%), were reported in the majority of cases as reported in the earlier studies by Gupte, Gupta, Sachdev , Khan, Bajpai, Gowda, Jadhav[2,3,5,7,12,16,17]. Prolonged breast feeding for >6 months was noted around 50% and in 50% more there was inappropriate complementary feeding in beyond 6 months age which is on similar lines as per Gupte[2], Kaul[4], Sachdeva[5], Holla[8], Ratageri[11] ranging from 43-70% and 60-30% respectively.

Around 100% mothers had pallor as consistent with other studies by Gupte[2], Pathak[12], Goraya[18], Ratageri[11], Gowda[17] ranging from 70-95% but ours was most all and around 25% had received blood in pregnancy too reiterating that they had severe pre-existing pallor not supplemented which has reflected in study by Ratageri[11], Gowda[17] and maternal dietary restrictions in pregnancy and post delivery, including dairy and the fact that few communities like Rajasthanis, Jains, Lingayats don't consume non vegetarian foods and in our study too 90% were vegetarians owing to their customs, religion, tradition consistent with Ratgeri[11], Gowda[17], Goraya[18] studies. Other infections like respiratory , gastrointestinal were noted in 60% and 20% respectively as against studies by Pathak[12], Ratageri[11], Gowda *et al.* which showed around 40-60% and 20-40% respectively owing to their severe malnutrition status , micronutrient deficiency status too. However 20% had cardiac failure due to severe anemia, reflected as 10-15% in studies by Khan[7], Ramakumar[13], Pathak[14], Goray[18]. Developmental delay was observed in 90% of children similar to Holla[8], Ratageri[11], Bajpai[12], Ramakumar *et al*. studies (80.3%)[13] , 10% had neuroregression in our study and studies from other centres also reported similarly like Gowda[16], Jadhav[17], Goraya[18], Dror[19] ranging from 4-8% . 70% of the children had severe acute malnutrition similar to Bajpai[12], Pathak[14], Gowda[16]. 60% had other nutrient deficiency of which 4% had vit c deficiency like features, 50% had clinical vit d deficiency ,6% had signs of vit a deficiency, which are similar to study by Ratageri[11], Bajpai[12], Goraya[18]. Out of the total cases, 80% had ITS and 20% had pre-ITS at the time of admission similar to Pathak[14]. study[14], Garg[15], Gowda[16]. 25% of the children had microcephaly similar to Gowda[16], Dror[19], Thora[20], Gupta[21], De souza[22] studies, ranging from 20-35%. Topographically, hypotonia was noted in 70% of the children similar to studies by Gupta[3], Sachdeva[5], Bajpai[12], Gowda[16],ranging from 70-90%. Other studies like Dikshit[10], Holla[8], Ratageri[11], Pathak[14]

showed a lesser degree of hypotonia around 60%. Notably 2 had dystonia and 10% had hypertonia as studied by Goraya[18], Wirthensohn[23], Kamate[25] which showed 2% to 5%. 2 had seizures due to severe pneumonia similar to Goraya[18]. Death was seen in same 2 cases due to severe pneumonia requiring ventilator, progressing to sepsis and death, ranged from 5-10% in studies by Gupta[21], Garg[15], Gowda[16]. Tremors was seen limited to only hands in 20% and generalized to feet, lips, face, tongue, voice in 80% which as shown as 70% to 93% in studies by Holla[8], Gowda[17], Goraya[18], Dror[19], Desouza[22], Chaudhary[24] reiterating that hand tremors are seen in 100% and lips and voice tremors in >70% like bleating of goat due to involvement of larynx. Interestingly there was no other movements like chorea athetosis/sensory or cerebellar involvement like in other studies by Gupta[21], Garg[15] but few reported rarely in studies by Gowda[16], Dror[19], Desouza[22].

Laboratory Tests/Imaging: Mean Hb was around 8g% and Very Severe pneumonia was seen in 10 children or 20% as against 10-40% in many studies done by many studies including Gupte[2], Gupta[3], Kaul[4], Sachdeva[5] etc . Pancytopenia was noted in 70% and bicytopenia in 50% as against many studies by above authors ranging from 85-47% respectively stressing that vit b12 deficiency is a bone marrow suppression like state affecting all cell lines most often than not. Majority had macrocytic indicators with MCV>90 fl >90%, however 10% had microcytic too due to reasons not sure but many had iron deficiency too. Most studies by all showed 90% to 95% macrocytic pictures[1-15]. However Dimorphic blood picture was seen in 50% of the cases compared to Vykuntaraju K. Gowda *et al.* study (7%) because of co-existing iron deficiency as incidence of severe malnutrition was higher in our study[16]. but many had similar experience ranging from 30-45% like in studies by Bajpai[12], Ratageri[11], Goraya[18]. Many reported low vitamin B12 , less than 83ng/ml in 100% of the children which was true in our study[1-20].Maternal low vit b12 was also seen in 100% here whereas seen in 80-100% in many others including by Bajpai[12], Ratageri[11], Gowda[16]. About 20 children(40%), those with cardiac failure and HB<4g% received blood transfusion here whereas as many as 30-55% had received in other studies by Goraya[18], Gowda[16], Ratageri[11] etc low folate seen in 24%, low iron levels in 50%, hypocalcemia in 20%, hypomagnesemia in 12%, hypovit d in 50%, hypoalbuminemia in 12%, hypophosphatemia in 100 % was seen as other deficiencies as with other studies like Ratageri[11], Goraya[18], Wirthensohn[23] as many are malnourished and have commonly these deficiencies plus associated infections can explain. About 27 or 54% had high serum homocysteine >20 mcmol/l as against high levels of 75-90% in many studies like Gowda[16], Goraya[18], Dror[19], De souza[22]. It is well known that homocysteine is an essential amino acid broken down by B6,B12 and also MMA are broken down by b12 and hence elevated in their absence . we are not sure why our findings are low, may be lab variation and also dietary modifications as many were sick. We could do serum MMA in only 2 due to cost constraints and was high and were not able to perform urinary MMA. many studies by Gowda[16], Dror[19], Desouza[22] had shown very high levels of serum and urinary MMA .

Many theories are postulated for tremors in ITS like studies by Kalra[1], Goraya[18], Gowda[16], Dror[19], Desouza[22], that due to delayed myelinated, demyelination, imbalance in ratio of S adenosylmethionine and S adenosylhomocysteine, neurotropic cytokine imbalances, neurotransmitter imbalances. It is a brain vitamin, requires sulphur amino acids, needed in myelin degradation, synthesis, axon regeneration, sprouting, production of catecholamines etc. MRI brain was abnormal in all those with microcephaly in 12 (24%) showing delayed myelination, cerebral atrophy, T2/FLAIR hyperintensities consistent with others like Gowda[16], Dror[19], Desouza[22], Thora[22], Gupta[21], Kamate[25] where in it ranged from 30-45%. We could not do MRI brain for those without microcephaly due to cost constraints. 10 children developed tremors after treatment (20%) and 12 children(24%) had exaggeration of tremors after starting vitamin B12. Other studies done by Gowda[16], Dror[16], Desouza[22] had shown tremors appeared after vit b12 injection in around 10-25% , similar and postulated due to sudden imbalance in neurotransmitters after starting B12 and also hypothalamopituitary axis dysfunction. 20 children (40%) required treatment for tremors like propranolol and clonazepam, again consistent with above studies. Gowda[16] studied that the mean duration for control of tremors as 35.3 days in contrary to our study, it was 10.2 days ranging from 5 days to 6 weeks. Mean duration of hospital stay was 15.6 days. Tremors reversed fully in 80% cases by discharge and in remaining on follow up in 3 months as consistent with all other studies by Gupte[2], Gupta[3], Holla[8], Ratageri[11], Bajpai[12], Pathak[14], Gowda[16], Goraya[18] showing 100% resolution. Likewise as quoted in same studies anemia, skin ,hair changes and apathy, anemia

all lab findings totally reversed in all including normal vit b12 levels , few on discharge and few follow up in 3 months. Severe acute malnutrition had recovered in 60% in 3 months.

Regression reversed in all in 3 months , however grossly developmental delay continued in 30 (60%) even after 3 months. However no Bailey s or any validated developmental scrrening was done for that For next 3 months , many lost to follow up and 5 of them had shown full recovery like severe malnutrition and delay. This was again consistent with above authors, 90-100 % recovery noted in all. The concern for microcephaly and cerebral atrophy on MRI noted in 5 patients as against 7 more who had delayed myelination and hyperintensities (who may have recovered fully) may point towards a relatively slow or no complete resolution of delay. This needs to be watched out for and with proper therapy and stimulation , hope for full recovery is there. Hence the need for early diagnosis and treatment to fully reverse. MRI was not repeated in anyone .

Limitations of the Study: Study was just observational and no comparison was done between any groups. Certain lab assays like urine MMA could not be done. Inspite of these sample size was good and it was a fairly well thought of and conducted study with resource limited settings. However no validated Developmental testing like Bailey s was done . Few of them were lost to follow up after 3 months.

CONCLUSIONS

Most of the infants and young children with ITS will have hematological findings consistent with megaloblastic anaemia and evidence of vitamin B12 deficiency. Nutritional vitamin B12 deficiency is an easily treatable cause of pseudo-neuroregression and developmental delay and long-term neuro-deficits can result if treatment is delayed but are easily reversible with timely injections. Long term follow up is required to prevent recurrences especially in those on vegetarian diet. Spreading awareness and imparting health education to mothers to take vitamin B12 supplements in pregnancy and after delivery for 6 months is essential for prevention. Dietary restrictions have to be clearly avoided. Government of all states should incorporate free vit B12 along with Iron and Folic acid tab combination urgently

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