Original Article

Pediatric Education and Research
Volume 2 Number 4, October - December 2014

Among Children with Anemia does Presence of Hyperpigmentation as Compare to Absence of Accurately Indicate Vitamin B_{12} Deficiency?

Amar Taksande*, Sheetal Nikose, Krishna Vilhekar*****

*Professor, Department of Pediatrics, Jawaharlal Nehru Medical College, Sawangi Meghe, Wardha, Maharashtra -442102.
**Senior Resident ***Professor, Department of Pediatrics, Mahatma Gandhi Institute of Medical Sciences, Sevagram, Wardha, Maharashtra -442102.

Abstract

Background: Hyperpigmentation of dorsum of hands and fingers though considered an important diagnostic sign for Megaloblastic Anemia (MA). **Objectives:** To evaluate the diagnostic accuracy and reliability of hyperpigmentation for detection of Vit. B_{12} deficiency among children. **Study Design:** A cross-sectional diagnostic study. We prospectively enrolled all children ages 2 months to 5 years presenting to inpatient or outpatient Pediatric departments. We identified the child who looks pallor, and did the hemoglobin (Hb.) and mean corpuscular volume (MCV) level. After that we included those patients who had a Hb. < 11 g/dl, and MCV > 100 fl. **Study Procedure:** *Index test:* After fulfilling the inclusion criteria, Pediatric nurse and Pediatric resident sequentially examined the knuckles and terminal phalanges of each study patient for hyperpigmentation (Index test) and the interval between the two observer's examinations ranged between 30minutes. **Reference standard:** Serum Vit. B_{12} level (reference standard) was performed after the clinical assessments of the children. **Results:** A total of 20 patients, in the age group of 2 months to 5 years were enrolled in the study. The children with Vit. B_{12} deficiency was best identified by the presence of hyperpigmentation of knuckle as indicated by the high sensitivity (Pediatric resident :94% and Pediatric Nurse 82%) and satisfactory specificity (Pediatric resident :66% and Pediatric Nurse 33%), compared with hyperpigmentation of terminal phalanges (Pediatric resident: sensitivity (Sn)=52%, Specificity (Sp)=66% & Pediatric **Nurse:** Sn=29%, Sp=66%). Thrombocytopenia was detected in only one case (5%). Leucopenia was detected in 3 cases (15%). Vit. B_{12} deficiency was detected in 17 cases (<80 pg/ ml) out of 20 cases. **Conclusion:** The presence of hyperpigmentation of knuckle in the anemic children can moderately raise the probability of Vit. B_{12} deficiency.

Key word: Vitamin B_{12}; Hyperpigmentation; Diagnostic accuracy; Mean corpuscular volume.

Introduction

Anemia is mainly related to impaired physical growth and mental development. It is also associated to a higher risk of child mortality, when it co-exists with malnutrition and other risk factors. Deficiency of Vit. B_{12} and folate commonly results in megaloblastic anemia (MA) which is common in vegetarian than in non-vegetarian families[1]. Vit. B_{12} deficiency seen in infants and young children has been particularly related to maternal deficiency which results in poor body stores at the time of birth. These underprivileged infants who are predominantly breastfed for prolonged period tend to develop Vit. B_{12} deficiency[2]. In developing countries, most cases of MA are caused by nutritional deficiency of folate, B_{12} or both. Serum Vit. B_{12} level as well as bone marrow examination is used to diagnose MA but this test is often not available in rural settings areas. Although physicians rely on physical signs such as

Corresponding Author: Amar M. Taksande, Department of Pediatrics, Jawaharlal Nehru Medical College, Sawangi Meghe, Wardha, Maharashtra -442102.
Email: amar.taksande@gmail.com

hyperpigmentation of the knuckle or proximal finger[3-5]. We conducted this study to know the accuracy of clinical sign to detect Vit. B_{12} deficiency .

Objective

To evaluate the diagnostic accuracy, reliability and validity of hyperpigmentation (at knuckle and at phalanges) for detection of Vit. B_{12} deficiency among 2month to 5 year children.

Material & Methods

Setting: The Mahatma Gandhi Institute of medical sciences, Sevagram is the rural medical college located in Maharashtra. It is a 648 bed teaching institution with 3,25,000 patient visits. ***Study Design:*** A cross-sectional diagnostic study was undertaken from Nov 2010 to July 2011. We prospectively enrolled all children ages 2 months to 5 years presenting to inpatient or outpatient Pediatric departments. We identified the child who looks pallor, and did the hemoglobin (Hb.) and mean corpuscular volume (MCV) level. After that we included those patients who had a Hb. < 11 g/dl, and MCV > 100 fl. We exclude those patients known to have a diagnosis before they were enrolled in the study, and those received injection Vit. B_{12} treatment within one month at the time of enrolment. We planned to determine diagnostic accuracy of the index test {Clinical assessment of hyperpigmentation (at knuckle and phalanges as two sites)} as compared to a reference standard (Laboratory confirmed Serum Vit. B_{12} level) in a blind and independent manner. We also planned to determine reliability of each sign across two professional categories who evaluated these signs independently, who had different educational background and years of experience.

Study Procedure

Index test

After fulfilling the inclusion criteria, pediatric resident (observer 1) and pediatric nurse (observer 2) sequentially examined the knuckles and terminal phalanges of each study patient for hyperpigmentation (Index test). The Clinical assessment for hyperpigmentation would be done in natural light. To access reliability of hyperpigmentation, pediatrics resident evaluated each child along with pediatric nurse independently and the interval between the two observer's examinations ranged between 30minutes.

Reference standard

After obtaining informed consent from parents, blood samples had been drawn from a peripheral vein. Serum Vit.B_{12} level (reference standard) was performed after the clinical assessments of the children. A written informed consent sought from one of the parents of the children for inclusion in the study.

Statistical analysis

The diagnostic accuracy of each clinical sign was measured by computation of sensitivity, specificity, positive likelihood ratios, negative likelihood ratios, and positive and negative predictive values. The precision of these estimates were evaluated by using 95% confidence intervals (95% CI). The likelihood ratios were computed by means of sensitivity and specificity values. We used 8 statistic (a chance corrected measure of agreement) to assess reliability of physical findings between the pair of physicians.

Results

A total of 20 cases, in the age group of 2 months to 5 years were enrolled in the study. Of these, 9 were boys and 11 were girls. Table 1 summarizes the anthropometric data of the study group. Out of 20 cases, 9 (45%) cases presented with failure to thrive, 3 (15%) with infantile tremor syndrome, 3(15%) with delayed motor milestone, 3(15%) with pneumonia and 2(10%) with acute gastroenteritis. No children presented with bleeding manifestation. Vitals were mean heart rate:134±21.07 beats per minute (bpm), mean respiratory rate: 41±13.33 per minute, mean systolic blood pressure: 74±5.83mmHg and mean oxygen saturation : 97±0.03. On general examination, all cases had pallor whereas cyanosis and icterus was not detected in any case. Systemic examination revealed hepatomegaly in 8 (40%) cases and splenomegaly in 5 (25%) cases, respectively. On auscultation, 13 (65%) cases revealed soft systolic murmur heard maximally in 3rd left intercostal space parasternally.

Children with Vit.B_{12} deficiency was best identified by the presence of hyperpigmentation of knuckle (Observer1 & 2), as indicated by the high sensitivity and satisfactory specificity, compared with hyperpigmentation of terminal phalanges as shown

Table 1: Anthropometric data of the cases

Sex	Number of cases	Age (mo) mean±SD	Height (cm) mean±SD	Weight (Kg) mean±SD	Head ircumference (cm) mean±SD
Boy	9	9±7.33	65±8.47	5.77±1.06	41.92±3.59
Girl	11	8.45±3.04	71.27±10.61	6.2±0.93	42.36±1.56
Combined	20	8.8±5.13	68±9.998	6±0.99	42.1±2.69

Table 2: Sensitivity(Sn), Specificity(Sp), positive predictive values (PPV), negative predictive values(NPV), likelihood ratio (LR) of clinical signs to detect children with Vit.B12 deficiency.

Clinical Sign	Sn(%)	Sp(%)	PPV(%)	NPV(%)	+LR	-LR
Hyperpigmentation of knuckle	95	66	90	80	2.76	0.20
Hyperpigmentation of terminal phalanges	85	66	85	66	2.50	0.23

Table 3: Inter-observer variability in assessment of hyperpigmentation (n=20)

Clinical Sign	Observer 1 Versus Observer 2	Percent Agreement	Kappa Value	Standard Error
Hyperpigmentation of knuckle		95	0.64	0.20
Hyperpigmentation of terminal phalanges		85	0.66	0.21

in table 2. The inter-rater agreement between the Observer 1 & observer 2 for the detection of hyperpigmentation of terminal phalanges and hyperpigmentation of knuckle were K = 0.64 and K = 0.66, respectively (Table 3).

All cases had anemia with Hb. levels ranges from 3 to 9 g/dl . Mean Hb. was 6.26±1.56gm%. Severe anemia (Hb<5gm%) was present in 9 (45%) cases. Thrombocytopenia was detected in only one (5%)case. Leucopenia was detected in 3(15%) cases. Peripheral smear showed predominantly macrocytes, macroovalocytes and pear shaped poikilocytes. Vit. B_{12} deficiency was detected in 17 cases (<80 pg/ ml). Mean serum B_{12} level was 89.76±47.17. Vit. B_{12} deficiency cases were put on intramuscular injection of Vit. B_{12} (Infant :250ìg/ day & older children: 500ìg/day) daily for a week followed by alternate day administration and then twice a week injection.

Discussion

Megaloblastic Anemia (MA) is a distinct type of anemia characterized by macrocytic red blood cells (RBC) and typical morphological changes in RBC precursors. Basic underlying pathogenetic mechanism in MA is deficiency of folic acid (FA) and/or Vit. B_{12} at the cellular level with resultant impairment of DNA synthesis. MA is a common feature between 6 months-2 years child and rarely occurs after 5 years of age, especially in a child consuming non-vegetarian diet. The common age group involved in our study was 2 month to 24 months which shows that it's the most vulnerable age for the development of nutritional anemia. Vit. B_{12} deficiency tends to develop in the underprivileged infants who are exclusively/ predominantly breastfed for prolonged period.[3,4] Vit. B_{12} deficiency may occur after 5 years of age because of chronic

diarrhea, malabsorption syndrome, or intestinal surgical causes. Children often present with nonspecific manifestations such as weakness, fatigue, failure to thrive, or irritability. Other common findings include pallor, glossitis, vomiting, diarrhea, and icterus[6-9]. A diagnosis of Vit. B_{12} deficiency is often overlooked in its early stages because these signs are not specific to Vit. B_{12} deficiency alone.

The characteristic dermatological sign of Vit. B_{12} deficiency is cutaneous pigmentation. It may be generalized but is most pronounced over inter-phalangeal joints, terminal phalanges, dorsa of the wrists, palmar creases and flexures, and over the face and neck.. Increased cutaneous pigmentation is especially accentuated in palmar creases, on the dorsa of hands and feet, in knuckles, on oral mucosa and in recent scars. Irregular pigmentation may also be seen on the extensor aspect of arms and thighs, shins and on the trunk. There may be an associated darkening of the buccal mucosa. The nails and nail beds are usually spared. The mechanism of hyperpigmentation is unexplained and remains obscure. Mori K et al[10] consider that the dominant mechanism of hyperpigmentation due to Vit. B_{12} deficiency is not a defect in melanin transport but is rather an increase in melanin synthesis. The children with Vit. B_{12} deficiency was best identified by the presence of hyperpigmentation of knuckle as indicated by the high sensitivity (Pediatric resident :94% and Pediatric Nurse 82%) and satisfactory specificity (Pediatric resident :66% and Pediatric Nurse 33%), compared with hyperpigmentation of terminal phalanges (Pediatric resident: Sn=52%, Sp=66% & Pediatric Nurse: Sn=29%, Sp=66%). Baker et al[8] reported a series of 21 patients with Vit. B_{12} deficiency who had hyperpigmentation of the skin. Aaron et al[9] reported a series of 63 patients with Vit. B_{12} deficiency, in which 41% patients had skin and mucosal changes. Glossitis was the most common mucocutaneous manifestation, followed by skin hyperpigmentation, hair changes, angular stomatitis, and vitiligo. Khanduri U et al[11] conclude that MA was diagnosed from complete blood counts, red cell indices, blood film examination and assays of the two vitamins. Bone marrow examination was not essential for diagnosis. Peripheral smear revealed macrocytic normochromic RBCs. On the electronic cell counter, MCV was increased and RBC count was decreased proportionate to degree of anemia. Nucleated red cell precursors may be seen and they show megaloblastic changes. Serum Vit. B_{12} assay used to be cumbersome dependent upon biological methods , hence they were not performed widely[12]. From this study, it may be concluded that the presence of hyperpigmentation in the anemic children can moderately raise the probability of Vit. B_{12} deficiency. A patient presenting with cutaneous lesions not responding to conventional therapy could very likely be an indication of Vit. B_{12} deficiency.

References

1. SmolkaV, Bekarek V, Hlidkova E. et al. Metabolic complications and neurologic manifestations of Vit. B12deficiency in children of vegetarian mothers. Cas Lek Cesk 2001; 140: 732-735.
2. Casterline JE, Allen LH, Ruel MT. Vit. B12 deficiency is very prevalent in lactating Guatemalan women and their infants at three months postpartum. J Nutr1997, 127:1966-1972.
3. Gomber S, Kela K, Dhingra N. Clinico-hematological profile of MA Indian Pediatr 1998;35:54-57.
4. Gomber S,Kumar S, Rusia U et al. Prevalence and etiology of nutritional anemia in early childhood in an urban slum. Indian J Med Research 1998; 107: 269-273.
5. Chandra J, Jain V, Narain S et al. Folate and cobalamin deficiency in MA in children. Indian pediatr 2002; 39: 453-457.
6. Incecik F, Hergüner MO, Altunba°ak S, Leblebisatan G. Neurologic findings of nutritional Vit. B12deficiency in children. Turk J Pediatr. 2010 Jan-Feb;52(1):17-21.
7. Baker SJ, Ignatius M, Johnson S, Vaish SK. Hyperpigmentation of skin. A sign of vitamin-B12 deficiency. Br Med J 1963;1(5347):1713-5.
8. Baker SJ, Ignatius M, Johnson S, Vaish SK. Pigmentation and Vit. B12deficiency . Br Med J 1963;2(5366):1205.
9. Aaron S, Kumar S, Vijayan J, Jacob J, Alexander M, Gnanamuthu C. Clinical and laboratory features and response to treatment in patients presenting with Vit. B12deficiency–related neurological syndromes. Neurol India 2005;53(1):55-8.
10. Mori K, Ando I, Kukita A. Generalized hyperpigmentation of the skin due to Vit. B12deficiency. J Dermatol. 2001 May;28(5):282-5.
11. Khanduri U, Sharma A. Megaloblastic anemia: prevalence and causative factors. Natl Med J India. 2007 Jul-Aug;20(4):172-5.
12. Naeem MA, Uttra GM. Etiology of increased incidence of MA in district Gilgit. Pak J Pathol 2007; 18: 15-6.