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Prevalence and Clinical Profile of Megaloblastic Anemia in Children

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Abstract: ***Introduction: Megaloblastic anemia is an underestimated disease of nutritional origin in children. Contrary to earlier times, this entity has become much more frequent today. Veganism is one of the common reasons for an increase in the prevalence of nutritional megaloblastic anemia. Deficient mothers often have children with vitamin B12 deficiency with megaloblastic anemia and various neurologic manifestations. It presents with varied clinical features in childhood, sometimes mimicking a hematological malignancy like leukemia. Diagnosing this disease assumes great clinical importance since it responds exceedingly well to treatment. Objective of the study: 1) To study the prevalence and clinical profile of megaloblastic anemia in children referred for anemia, 2) To determine the high risk factors for occurrence of megaloblastic anemia in children and 3) To find out the effectiveness of treatment in these children. Material and Methods: This study was a retrospective analysis of children referred for anemia to the Pediatric Hematology - Oncology Division of a tertiary care centre over the last 3 years from January 2020 to July 2023. Clinical data was charted in a proforma and all patients underwent a complete hemogram, corrected reticulocyte count and peripheral blood smear examination, biochemical investigations including serum bilirubin levels, lactate dehydrogenase levels, serum vitamin B12 levels (NR: 200 – 950 pg/ml) and red cell folate levels (NR: 175 – 700 ng/ml). Bone marrow was done to confirm the diagnosis in those children who could not afford B12 and folate levels. The diagnosis of megaloblastic anemia was established on the basis of serum Vitamin B12 levels below 200 pg/ml. and /or RBC folate levels below 175 ng/ml or bone marrow suggestive of megaloblastic changes along with the clinical findings and smear picture suggestive of megaloblastic anemia. All diagnosed cases were treated as per standard treatment guidelines for Megaloblastic anemia of Indian Academy of pediatrics. Results: A total of 1365 patients were referred to for anemia during the study period. Of these 56 (4.1%) children were diagnosed as per the predefined criteria as megaloblastic anemia. Among these children, the age and sex distribution was as follows: 25 (44.64%) were males 31 (55.35%) were females with male to female ratio of 0.8: 1. The youngest was 3 month old and the oldest was 12years old.22 (39.28%) of them were in age group of 0 to 12 months, 17 (30.3%) each belonged to age group of 1 to 6 years and 6 to 12 years group. When evaluating diet in these children, history of milk based diet was obtained in 24 (42.85%) children, 15 (26.78%) were lacto - vegetarian and17 (30.35%) consumed a mixed (non - vegetarian) diet. Clinical presentations varied from recurrent infections to various hematological manifestations including mucosal or skin bleeds.29 (51.78%) patients were incidentally found to have megaloblastic anemia on routine blood counts when they were seen for acute infections.12 (21.42%) had pallor as presenting complaint.5 (8.92%) children presented with skin and mucosal bleeds.10 (17.8%) of them presented with neurological complications; 4 (7.14%) of these had infantile tremor syndrome and the remaining 6 had developmental delay. On examination, pallor was present in all, hyperpigmented knuckles were seen in 37 (66.07%) children, whereas sallow complexion was found in 30 (53.57%) children.8 (14.2%) had icteris, 18 (32.1%) children had mild hepatosplenomegaly.20 (35.7%) patients had Severe Acute malnutrition, while 26 (46.42%) of them had moderate acute malnutrition. Only 10 (17.85%) children had a normal nutritional status. On investigations, hemoglobin ranged from 1.6gm% to 7.5gm% (mean Hb 5.7±1.02gm%). MCV ranged from 90fL to 123 fL (Mean MCV was 102.43±6.94 fL).14 (25.00%) children had pancytopenia and 18 (32.14%) had bicytopenia (anemia with leucopenia).6 (10.71%) patients who presented with mucosal and skin bleeds had thrombocytopenia (platelet counts ranged from 30, 000 to 50, 000 per c. mm). Peripheral blood smear showed macrocytes, macroovalocytes and pear shaped poikilocytes in all of them. Hypersegmentation and large sized neutrophils were seen in 21 (37.5%) cases. Serum bilirubin levels ranged from 0.4mg/dl to4.7 mg/dl (with high indirect bilirubin in those with elevated levels). Serum LDH levels>1000 IU/L was seen in as many as 34 (60.71%) children. Serum vitaminB12 and red cell folate levels could be done in 45 (80.35%) patients. Of these, 24/45 (53.33%) had low serum vitamin B12 levels, 8/45 (17.7 %) had low folate levels and 13/45 (28.8%) patients had normal levels.11 (19.64%) children were diagnosed on the basis of bone marrow aspirate findings of megaloblastic anemia. Treatment was effective in a short duration with a mean rise in hemoglobin of 1 to 2 gm% in the 1st week and by 4 to 4.3 gm% in 2nd week. Thrombocytopenia and other morphological parameters also showed improvement on treatment within 4 weeks.***

Keywords: megaloblastic anemia, pediatric nutrition, vitamin B12 deficiency, neurological symptoms, treatment response

1. Introduction

The prevalence of megaloblastic anemia (MA) reported by various Indian studies ranges from 02% to 40%. [1–6] Most of these studies were carried out in children and in hospitalized patients. MA remains the commonest cause of macrocytic anemia [7] and pancytopenia. [8–12] It can have a varied clinical and hematological presentation. [13–15] While overt neurological syndromes associated with MA are well documented, there is paucity of data on the existence of subclinical neurological manifestations in MA with one study published in British Journal in 1980 having shown a prevalence of 25%. [16] In the current study, we calculated the prevalence of MA in patients of anemia, studied its clinico - hematological profile and the existence of overt and subclinical neuropathy in patients of MA.

2. Material and Methods

This study constituted a retrospective analysis of pediatric patients referred for anemia to the Pediatric Hematology - Oncology Division of a tertiary care hospital situated in an urban area of the western zone of India, spanning a period of three years from January 2020 to July 2023. Clinical data were meticulously documented in a structured proforma.

Hemogram was measured using 2 ml of ethylene diamine tetraacetic acid anticoagulated blood in a 5 part Sysmex Coulter. Anemia was defined as hemoglobin (Hb) < 13 g/dL in males and Hb < 12 g/dL in females, as per WHO definition of anemia. Severe anemia was defined as Hb < 8 g/dL. All patients of anemia with mean corpuscular volume (MCV) > 100 fL were evaluated with peripheral blood smear (PBS), bone marrow studies, Vit B12 and folic acid levels. Peripheral blood smear suggestive of MA was defined by presence of macro - ovalocytosis, anisocytosis, poikilocytosis, hypersegmented neutrophils and pancytopenia. The diagnosis of MA was confirmed with bone marrow aspiration studies where presence of hypercellular marrow with increased erythroid/myeloid ratio, megaloblasts, giant bands and metamyelocytes and decreased megakariocytes favor the diagnosis of MA. Vit B12 and folic acid levels were measured using chemiluminescence method. Normal levels of Vit B12 and folic acid were defined as 211–911 pg/ml and >175 ng/ml respectively. A detailed dietary history was taken. Non vegetarian diet was defined as diet comprising predominantly of animal food, mixed diet as one containing food of both plant and animal origin, vegetarian diet comprised of food of plant origin and milk, whereas pure vegan diet was defined as vegetarian diet less the milk. History of intake of drugs including proton pump inhibitor (PPIs) was taken along with history of previous surgery if any. History of neurological symptoms if any was noted. All patients were subjected to a detailed clinical examination. Further evaluation of patients with MA included Liver Function Tests (LFTs) and, Lactate Dehydrogenase (LDH). All diagnosed cases were treated as per standard treatment guidelines for Megaloblastic anemia of Indian Academy of pediatrics.

3. Statistical Analysis

The continuous variables were analyzed using unpaired t test, while proportions and qualitative variables were analyzed using chi - square and Fisher's exact test. A 'p' value of less than or equal to 0.05 was considered statistically significant.

4. Results

A total of 1365 patients were referred to for anemia during the study period. Of these 56 (4.1%) children were diagnosed as per the predefined criteria as megaloblastic anemia. Among these children, the age and sex distribution was as follows: 25 (44.64%) were males 31 (55.35%) were females with male to female ratio of 0.8: 1. The youngest was 3 month old and the oldest was 12years old.22 (39.28%) of them were in age group of 0 to 12 months, 17 (30.3%) each belonged to age group of 1 to 6 years and 6 to 12 years group. (As shown in Table 1.)

Diet and Nutrition in Younger Children: When assessing the dietary habits of these children, it was found that a history of a milk - based diet was reported in 24 (42.85%) of the participants, while 15 (26.78%) identified as lactovegetarians, and 17 (30.35%) adhered to a mixed (non - vegetarian) diet.

Clinical presentation: - signs and Symptoms varied from recurrent infections to various hematological manifestations including mucosal or skin bleeds.29 (51.78%) patients were incidentally found to have megaloblastic anemia on routine blood counts when they were seen for acute infections.12 (21.42%) had pallor as presenting complaint.5 (8.92%) children presented with skin and mucosal bleeds.10 (17.8%) of them presented with neurological complications; 4 (7.14%) of these had infantile tremor syndrome and the remaining 6 had mild developmental delay.

On examination, pallor was present in all, hyperpigmented knuckles were seen in 37 (66.07%) children, where as sallow complexion was found in 30 (53.57%) children.8 (14.2%) had icteris, 18 (32.1%) children had mild hepatosplenomegaly.20 (35.7%) patients had Severe Acute malnutrition, while 26 (46.42%) of them had moderate acute malnutrition. Only 10 (17.85%) children had a normal nutritional status.

Investigations: - On investigations, hemoglobin ranged from 1.6gm% to 7.5gm% (mean Hb 5.7±1.02gm%). MCV ranged from 90fL to 123 fL (Mean MCV was 102.43±6.94 fL).14 (25.00%) children had pancytopenia and 18 (32.14%) had bicytopenia (anemia with leucopenia).6 (10.71%) patients who presented with mucosal and skin bleeds had thrombocytopenia (platelet counts ranged from 30, 000 to 50, 000 per c. mm). Peripheral blood smear showed macrocytes, macroovalocytes and pear shaped poikilocytes in all of them. Hypersegmentation and large sized neutrophils were seen in 21 (37.5%) cases. Serum bilirubin levels ranged from 0.4mg/dl to 4.7 mg/dl (with high indirect bilirubin in those with elevated levels). Serum LDH levels>1000 IU/L was seen in as many as 34 (60.71%) children. Serum vitaminB12 and red cell folate levels could

be done in 45 (80.35%) patients. Of these, 24/45 (53.33%) had low serum vitamin B12 levels, 8/45 (17.7 %) had low folate levels and 13/45 (28.8%) patients had normal levels.11 (19.64%) children were diagnosed on the basis of bone marrow aspirate findings of megaloblastic anemia.

Treatment: Treatment was effective in a short duration with a mean rise in hemoglobin of 1 to 2 gm% in the 1st week and by 4 to 4.3 gm% in 2nd week. Thrombocytopenia and other morphological parameters also showed improvement on treatment within 4 weeks. (figure 1 to 3)

5. Discussion

Most of the studies on prevalence of MA have been done in children and the prevalence of MA in these studies have been documented anywhere between 2% and 42%. [1 - 5, 17]. The prevalence of MA in our patients of anemia was 4.1%. Most of our patients of MA were females. This observation may be due to the fact that females are often neglected in indian culture for proper nutrition and tend to be more iron deficient as well. In presence of iron deficiency, the MCV won't rise above 100 fL even with co - existent Vit B12 or folic acid deficiency. We could not do the iron profile of our whole anemia cohort because of financial constraints and also as it was beyond the scope of our study. The female preponderance for MA has been noted in another study by jadhav et al. [18]. While studies have shown an increased prevalence of MA in vegetarians [19, 20], majority of our patients consumed milk based mixed diet (42.85%) and none of them was a pure vegan. Though the limitation of our finding was that the number of MA patients was small; but still we would like to point out an important observation that diet does seem to play a role, as the etiological work up was more likely to be negative in vegetarian group (Fischer's exact test value: 0.04). There was no significant association between diet and type of vitamin deficiency (Chisquare test: 0.3137). Vitamin B12 deficiency was found in 53 % of our patients, folic acid deficiency was seen in 17.7 % while combined deficiency was recorded in 35% patients. The Indian series from 1960s documented folate deficiency to be more common cause of MA. [21, 22] Subsequent studies done in 1980s and 1990s highlighted that Vit B12 deficiency is far more common than folate deficiency.5, [23–24] Increased prevalence of Vit B12 deficiency as compared to folic acid deficiency has been reported from countries outside India also. [25]. Indirect hyperbilirubinemia and raised LDH are commonly found in MA which occur due to ineffective erythropoeisis. Lower Hb level was associated with higher values of LDH as has also been noticed by Emerson et al. [26] In our study, MA accounted for 28.30% of all cases of severe anemia. This has also been shown in another study where MA accounted for 42.5% of all cases of severe anemia. In our study, As many as 14 (25.00%) children had pancytopenia and 18 (32.14%) had bicytopenia (anemia with leucopenia).6 (10.71%) patients who presented with mucosal and skin bleeds had thrombocytopenia (platelet counts ranged from 30, 000 to 50, 000 per c. mm). Such varied presentations of MA have been documented in earlier studies also. [27 - 28.] MA can mimic aplastic anemia, leukemia and myelodysplastic syndrome. Even an expert hematopathologist may find it difficult to differentiate between myelodysplastic syndrome and megaloblastosis on bone marrow without the support of cytogenetics. [29] Overt neurological manifestations were found in 30% patients as has been documented in the literature earlier. [16] The sub - clinical neurological manifestations were documented only in 10 (17.8%) patients unlike the previous report where a prevalence of 25% was reported. There was no relation between the neurological manifestations and the Hb levels as was demonstrated in other studies also. [30]

Treatment was effective in a short duration with a mean rise in hemoglobin of 1 to 2 gm% in the 1st week and by 4 to 4.3 gm% in 2nd week. Thrombocytopenia and other morphological parameters also showed improvement on treatment within 4 weeks.

Conclusion

We conclude that an appropriate diet could avert the onset of megaloblastic anemia in children, which is predominantly attributable to nutritional deficiencies. This proactive approach can mitigate overt hematological manifestations and diminish neurological complications. Early detection and enhanced nutritional support for mothers of childbearing age can significantly reduce the morbidity associated with megaloblastic anemia.

Table 1: Demographic and Clinical Parameters

Demographic Variables	Value (n=56)	Percentage (%)
Age of presentation		
1. Less than 1 year	22	39.3
2. 1 - 6 years	17	30.3
3. 6 - 12 years	17	30.3
Sex		
1. 1. male	25	44.6
2. 2. female	31	55.3
Nutritional Status		
1. Normal Nutrition	10	17.8
2. Moderate Acute Malnutrition	26	46.2
3. Severe Acute Malnutrition	20	35.7
Diatery Habits		
1. Vegetarian /Milk based	39	69.6
2. Mixed Diet	17	30.3
Clinical presentation		
1. Anaemia	12	21.4
2. Acute infections	29	51.7
3. Development Delay	6	10.7
4. Infantile Tremors	4	07.1
5. Mucosal Bleed	5	08.9
Examination Findings		
1. Pallor	56	100
2. Hyperpigmented Nuckles	37	66
3. Sallow complexion	30	53.5
4. Hepatospleenomegaly	18	32
5. Icteris	08	14.2
Levels done in 45 patients	45	80.3
1. Low Serum Vit. B12 Levels	24/45	53.3
2. Low RBC Folate Levels	8/45	17.7
3. Normal B12 & RBC Folate levels	13/45	28.8

References

[1] Ghai OP. Aetiology of anemias in infancy and childhood (in New Delhi). Indian J Child Health.1956; 95–100.

[2] Dalal RJ, Udani PM, Parekh JG. Megaloblastic anemia in infancy and childhood. Indian J Pediatr.1969; 6: 255–262.
[3] Ghai OP, Choudhry VP, Singla PN, Saraya AK. Nutritional macrocytic anemia in infancy and childhood. In: Ghai OP, ed. New Developments in Pediatric Research. New Delhi: Interprint; 1977: 121.
[4] Sharma A, Sharma SK, Grover AK, Tewari AD, Abrol P. Anemia in protein energy malnutrition. Indian Pediatr.1985; 22: 841–844.
[5] Gomber S, Kumar S, Rusia U, Gupta P, Agarwal KN, Sharma S. Prevalence and etiology of nutritional anemias in early childhood in an urban slum. Indian J Med Res.1998; 107: 269–273.
[6] Gera R, Singh ZN, Chaudhury P. Profile of nutritional anemia in hospitalized children over a decade. In: Conference Abstracts, 38th National conference of Indian Academy of Pediatrics Patna, HO - 09.2001; 60.
[7] Unnikrishnan V, Kumar Dutta T, Badhe BA, Bobby Z, Panigrahi AK. Clinico - aetiologic profile of macrocytic anemias with special reference to megaloblastic anemia. Indian J Hematol Blood Transfus.2008; 24 (4): 155–165.
[8] Santra G, Das BK. A cross - sectional study of the clinical profile and aetiological spectrum of pancytopenia in a tertiary care centre. Singapore Med J.2010; 51 (10): 806–812.
[9] Premkumar M, Gupta N, Singh T, Velpandian T. Cobalamin and Folic Acid status in relation to the etiopathogenesis of pancytopenia in adults at a tertiary care centre in North India. Anemia.2011; 2012: 1–12.
[10] Bhatnagar SK, Chandra J, Narayan S, Sharma S, Singh V, Dutta AK. Pancytopenia in children – etiological profile. J Trop Pediatr.2005; 51: 296–299.
[11] Khunger JM, Arulselvi S, Sharma U, Ranga S, Talib VH. Pancytopenia – a clinicohematologicalstudy of 200 cases. Indian J Pathol Microbiol.2002; 45: 375–379.
[12] Kumar R, Kalra SP, Kumar H, Anand AC, Madan H. Pancytopenia – a six year study. J Assoc Physicians India.2001; 49: 1078–1081.
[13] Zengin E, Sarper N, CakiKilic S. Clinical manifestations of infants with nutritional vitamin B12 deficiency due to maternal dietary deficiency. Acta Pediatr.2009; 98: 98–102.
[14] Chandra J. Megaloblastic anemia: back in focus. Indian J Pediatr.2010; 77: 795–799.
[15] Marwaha RK, Singh S, Garewal G, Marwaha N, Walia BNS, Kumar L. Bleeding manifestations in megaloblastic anemia. Indian J Pediatr.1989; 56: 243–247.
[16] Shorvon SD, Carney MWP, Chanarin I, Reynolds EH. The neuropsychiatry of megaloblastic anaemia. BMJ.1980; 281: 1036–1038.
[17] Khanduri U, Sharma A. Megaloblastic anemia: prevalence and causative factors. Natl Med J India.2007; 20 (4): 172–175.
[18] Jadhav M, Webb JKB, Vaishnava S, Baker SJ. Vitamin B12 deficiency in Indian infants: a clinical syndrome. Lancet 1962; 2 (7262): 903 - 907.
[19] Chanarin I, Malkowska V, O'Hea AM, Rinsler MG, Price AB. Megaloblastic anemia in vegetarian Hindu community. Lancet.1985; 42: 1168–1172.
[20] Carmel R. Nutritional vitamin B12 deficiency: possible contributory role of subtle vitamin B12 malabsorption. Ann Intern Med.1978; 88: 647–649.
[21] Bhende YM. Some experience with nutritional megaloblastic anemia. J Postgrad Med.1965; 11: 145–155.
[22] Mittal VS, Agarwal KN. Observations on nutritional megaloblastic anemia in early childhood. Ind J Med Res.1969; 57: 730–738.
[23] Sarode R, Garewal G, Marwaha N, et al. Pancytopenia in nutritional megaloblastic anemia: a study from north - west India. Trop Geogr Med.1989; 41: 331–336
[24] Gomber S, Kela K, Dhingra N. Clinico - hematological profile of megaloblastic anemia. Indian Pediatr.1998; 35: 54–57.
[25] Chandra J, Jain V, Narayan S, et al. Folate and cobalamin deficiency in megaloblastic anemia in children. Indian Pediatr.2002; 39: 453–457.
[26] Emerson PN, Wilkinson JH. Lactate dehydrogenase in the diagnosis and assessment of response to treatment of megaloblastic anemia. Br J Haematol.1966; 12: 678–688.
[27] Khanduri U, Sharma A, Joshi A. Occult cobalamin and folate deficiency in Indians. Natl Med J India.2005; 18: 182–183.
[28] Mukibi JM, Makumbi FA, Gwanzura C. Megaloblastic anemia in Zimbabwe: spectrum of clinical and hematological manifestations. East Afr Med J.1992; 9: 83–87.
[29] Madood - ul - Mannan. Anwar M, Saleem M. Study of serum vitamin B12 and folate levels in patients of megaloblastic anemia in northern Pakistan. J Pak Med Assoc.1995; 45: 187–188.
[30] Briani C, Dalla Torre C, Citton V, et al. Cobalamin deficiency: clinical picture and radiological findings. Nutrients.2013; 5 (11): 4521–4539.

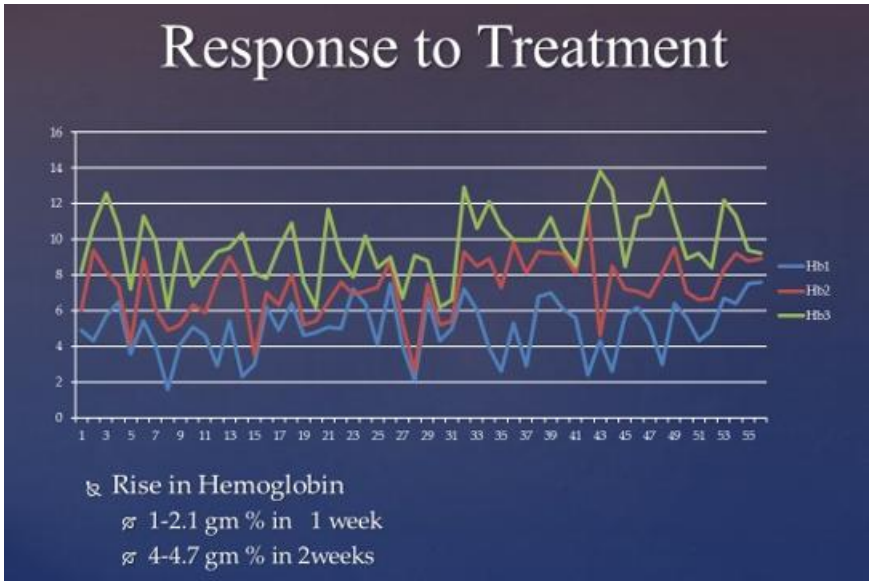

Figure 1

Treatment was effective in a short duration with a mean rise in hemoglobin of 1 to 2 gm% in the 1st week and by 4 to 4.3 gm% in 2nd week. Thrombocytopenia and other morphological parameters also showed improvement on treatment within 4 weeks

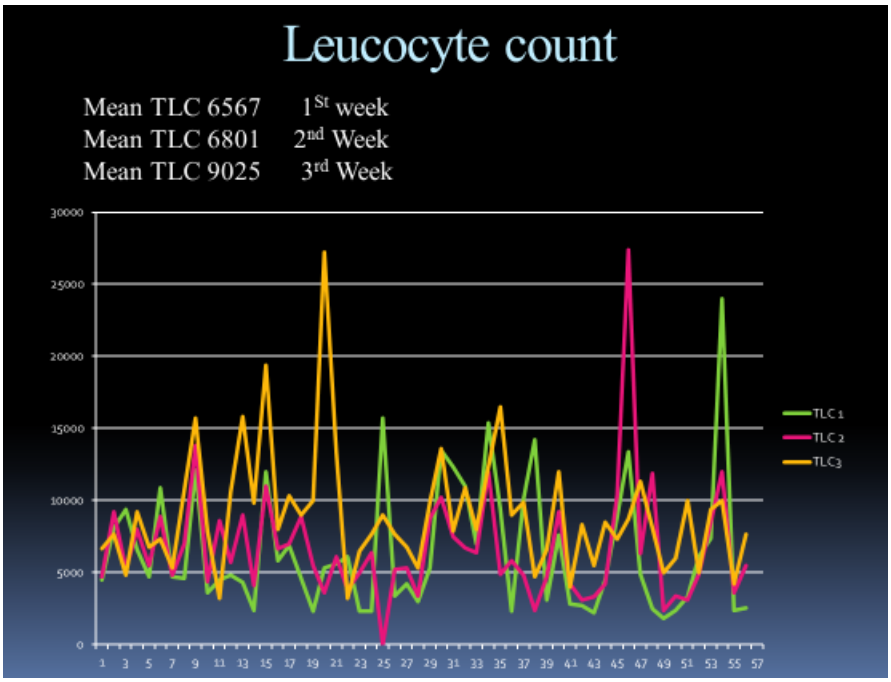

Figure 2

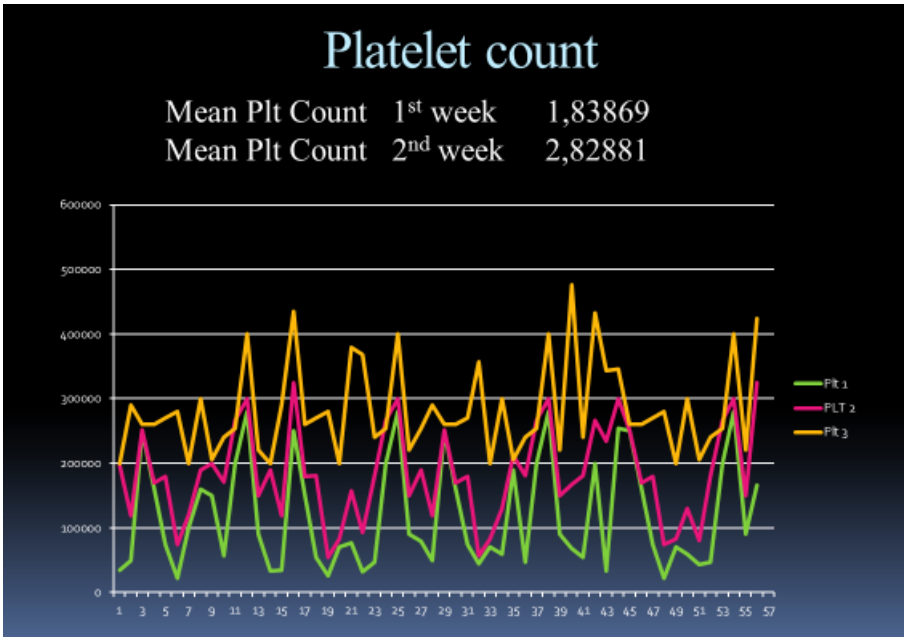
Platelet count
Mean Plt Count 1st week 1,83869
Mean Plt Count 2nd week 2,82881
600000
500000
400000
300000
200000
100000
0
1 3 5 7 9 11 13 15 17 19 21 23 25 27 29 31 33 35 37 39 41 43 45 47 49 51 53 55 57
Plt 1
PLT 2
Plt 3

Figure 3