Vitamin B12 and/or Folate Deficiency is a Cause of Macro Thrombocytopenia

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Abstract: This retrospective study reveals that it is likely that vitamin B12 and / or folate deficiency is an important cause for isolated thrombocytopenia with larger than normal sized platelets. Data collection and interpretation from the laboratory has revealed this and as this can have further therapeutic utility, more studies on the subject are indicated. Hypothyroidism may also be another cause for the findings.

Keywords: Vitamin B12 deficiency, Large platelets, Isolated thrombocytopenia, Macro thrombocytopenia.

INTRODUCTION

Vitamin B12 deficiency has profound effects on the bone marrow, resulting in characteristic changes on the blood film. Not all of these features are always present.

Thrombocytopenia is a documented feature of vitamin B12 deficiency. This may or may not be accompanied with macrocytic anaemia and a low reticulocyte count [1].

Vitamin B12 is an essential part of methylation reactions in the body. It is essential along with folate for the formation of methionine from homocysteine [2] and this is very much an essential part of the formation of the formed elements of blood in the bone marrow. Hence, deficiency of vitamin B12 and/or folate can lead to megaloblastic anaemia, thrombocytopenia, leucopenia, cardiovascular and neurological complications.

Some rare haematological presentations have also been noted with vitamin B12 deficiency. Interestingly, pseudo-microangiopathic haemolysis is one of them [3].

MDS affects predominantly the elderly population with a median age of 69 years [2].

Some studies have reported 28% incidence of thrombocytopenia in vitamin B12 deficient cohorts [4]. However, most of these studies have looked at patients who have presented with macrocytic anaemia and this has only been a corroborative finding.

Rarely, isolated thrombocytopenia has been reported with vitamin B12 deficiency and this has been documented to have improved with supplementation [5]. This has been noted in the paediatric population, and hence, our attempt to study if this is prevalent in the adult population as well.

Interestingly, measurements of metabolites such as methylmalonic acid and homocysteine have been shown to be more sensitive in the diagnosis of vitamin B_{12} deficiency in comparison to vitamin B12 levels tested biochemically [6]. If only vitamin B12 levels are used in comparison to using all 3 of the above mentioned, it has been reported in different studies that 10% to 26% of patients with vitamin B12 deficiency may be missed [7].

OBJECTIVES / AIMS OF THE STUDY

1. To determine if isolated thrombocytopenia can be a manifestation of vitamin B12 deficiency
2. To determine if platelet size in vitamin B12 deficient patients is different from normal
3. To determine if low normal vitamin B12 levels may also be reflective haematologically of vitamin B12 deficiency

PATIENTS/METHODS

This is a retrospective study from 7th February 2014 to 31st March 2014.

The nodal point of identifying cases is the Haematology laboratory.

Over this period of 7 weeks, all thrombocytopenia patients presenting to the Haematology laboratory were added to our data and the following investigation results were further traced and recorded for them

1. Thrombocytopenia patient flagged up in

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Haematology laboratory (Thrombocytopenia for the purpose of this study was defined as a platelet count of less than 100 x 10^9/ml.

2. Confirmed that blood film also showed true thrombocytopenia

3. Once confirmed, the MPV (mean platelet volume) measured by the automated analyser noted.

4. If MPV above 11fl, the patient was noted as a patient with thrombocytopenia having large platelets.

5. History and other investigations of the patient were evaluated to rule out disseminated intravascular coagulation, sepsis and other obvious causes of thrombocytopenia.

6. If no overt cause is found, a recent vitamin B12 level if done on the patient noted.

7. Data then analysed accordingly.

ETHICAL CONSIDERATIONS

The PT and APTT are investigations that would be routinely performed in the workup of thrombocytopenia. The vitamin B12 level is performed at our centre as part of haematinic workup for most blood dyscrasias. Hence, data was collected with regards to this in retrospect for the thrombocytopenic patients.

RESULTS

Over this period of 7 weeks, 26 patients with thrombocytopenia were noted by the Haematology department. (These 26 patients were noted to have a platelet count below 100).

INTERPRETATION OF RESULTS

Of the 26 patients with true thrombocytopenia, 14 were noted to have a raised MPV (MPV above the higher limit of normal for our analyser that is 11fl). Of these 14 patients, 7 patients (that is 50% of those with thrombocytopenia and raised MPV) had a large rise in MPV (that is, MPV was documented to be above 13fl).

8 out of 14 patients with thrombocytopenia + large MPV had documented evidence of one of the following:

1. Low normal vitamin B12 level

2. Macrocytic anaemia

3. History of vitamin B12 deficiency documented in past

4. Clinical suspicion of vitamin B12 deficiency

2 out of these 14 patients (that is, patients in the study with thrombocytopenia + large MPV) had documented evidence of folate deificiency +/- alcoholic liver disease.

3 out of 14 patients with thrombocytopenia + large MPV were also co-incidentally noted to be hypothyroid.

Interestingly, the remaining 12 patients with thrombocytopenia who had normal MPV had no evidence of biochemical or clinical features of vitamin B12 and/or folate deficiency. Also, none of these patients were noted to be hypothyroid.

As this is a retrospective study, not all patients had biochemical evaluation for vitamin B12 and folate deficiency. However, clinical features and history were relied upon in many patients.

Co-existent macrocytic anaemia was only noted in 1 patient with thrombocytopenia and large MPV.

Hence, it was significantly observed that:

1. Thrombocytopenia and large platelet size correlated with vitamin B12 deficiency, irrespective of other features of the deficiency being observed in blood or not

2. Hypothyroidism is another feature that correlated with thrombocytopenia and large platelet size

3. Vitamin B12 deficiency features are also observed when the biochemical levels of the vitamin are low normal.

4. Folate deficiency was also noted to correlate with thrombocytopenia and larger than normal sized platelets, but in a far smaller number of patients.

DISCUSSION

This study clearly demonstrates that vitamin B12 deficiency correlates with the presence of platelet abnormalities – quantitatively decreased in number and morphologically of larger size in a significant number of patients. However, only 1 of the 8 patients noted here

Table 1: Observation Chart

Serial No.	Platelet Count	MPV	Serum Vitamin B12 Level in pg/ml	Serum Folate Level in ug/l	Etiology Suspected on Basis of Case Review	Clinical History
1.	98	NORMAL	624	10.1	Sepsis	Intestinal obstruction
2.	94	NORMAL	Not checked	Not checked	Proven AML	
3.	82	NORMAL	1092	Not checked	Liver disease + Hypersplenism	Cirrhosis of liver
4.	100	11.1	Not checked	Not checked	Chemotherapy	Carcinoma Ovary
5.	73	13.2	270	7.1	B12 deficiency – no other feature	Incidental finding
6.	68	13.1	1651	4.3 (low)	Folate deficiency	Alcoholic liver disease
7.	22	NORMAL	987	11	ITP	Bleeding
8.	44	NORMAL	Not checked	Not checked	Chemotherapy	AML
9.	14	12.5	274	Not checked	Not clear	Dementia
10.	93	11.5	Not checked	Not checked	Not clear	Hypothyroid
11.	83	13.2	227	Not checked	B12 deficiency	Incidental finding
12.	72	12.8	Not checked	Not checked	B12 deficiency	Macrocytic anaemia
13.	63	13.1	Not checked	Not checked	Suspected vitamin deficiency	Suspected coeliac
14.	79	12.4	630	12.4	ITP attributed/ B12 deficiency features on blood film	Incidental finding
18.	78	13.1	227	Above 20	ITP suspected/ B12 deficiency	Incidental finding
19.	66	NORMAL	Not checked	Not checked	Chemotherapy	Carcinoma ovary
20.	41	11.5	Not checked	Not checked	Not clear	Hypothyroid
21.	83	NORMAL	603	18.8	Infection	Fever
22.	33	NORMAL	960	Not checked	MPD	High white cell count
23.	91	NORMAL	Not checked	Not checked	DIC	Fracture limb
24.	33	13.2	214	Not checked	Infection	Pneumonia
25.	22	13.1	212	8	ITP labelled but no response to steroids (B12 deficiency also)	Bleeding
26.	73	12.5	Not checked	Not checked	Not clear	Hypothyroid patient with Incidental finding

Normal Vitamin B12 level for our laboratory: More than 150ng/l
Normal serum folate level for our laboratory: 4.6 - 18.7 ug/L

demonstrating this fact had accompanying macrocytic anaemia. Hence, it seems that this can be attributed to be an independent finding in vitamin B12 deficiency.

Hypothyroidism also is another condition which has shown a correlation with thrombocytopenia with morphologically large platelets in our small cohort of patients. Macrocytic anaemia is a recognised complication of hypothyroidism, but this is the first time that it has been postulated as a cause for thrombocytopenia with larger than normal sized platelets.

Also, it is interesting that in the patient who were detected to be thrombocytopenic but had normal MPV neither vitamin B12 deficiency nor hypothyroidism were noted.

The vitamin B12 levels in our patients with thrombocytopenia and large platelets have been in the low normal end of the range. This is well reflective of the deficiency as noted by other findings. Unfortunately we were unable to perform the diagnostic total homocysteine and serum methylmalonic acid testing to further confirm the diagnosis. These tests even though

ideal have limited availability. However, the serum holotranscobalamin level is easily available and has better sensitivity and specificity in diagnosing vitamin B12 deficiency, including the subclinical state or where the vitamin B12 levels are in the indeterminate area. This test though is not 100% accurate, and so cannot be considered a goldstandard investigation.

Our study has certain draw backs:

1. The number of patients is rather small

2. It is a retrospective study and so it is difficult for all the appropriate testing to have been performed on all the patients. For instance, there are some patients in whom vitamin B12 levels could not be assessed and clinical markers for the deficiency had to be relied upon.

3. Vitamin B12 levels are not always truly reflective of the deficiency state. Plasma total homocysteines level and serum methylmalonic acid level have been suggested in the recent BCSH guidelines to be more accurately responsible for the diagnosis of vitamin B12 deficiency when the clinical suspicion exists but the serum vitamin B12 levels are indeterminate (8).

4. Ideally, bone marrow examination should have also been included in the workup of the patients.

However, despite these drawbacks it is a pilot retrospective study which has produced results that, hopefully, can be further confirmed in larger trials.

There is a possibility that these patients may have acquired thrombocytopenia due to an immune or other consumptive pathology and as the bone marrow would have tried to regenerate more platelets to compensate, the vitamin B12 stores have fallen. In these patients this has given rise to low normal levels of the vitamin. However, clinically there is no other feature in these patients to support this hypothesis.

Folate deficiency has also been documented in 1 patient and in the same way happens to have contributed to the thrombocytopenia with larger than normal sized platelets.

CONCLUSION

It appears likely that vitamin B12 and / or folate deficiency is an important cause for isolated thrombocytopenia with larger than normal sized platelets. Hypothyroidism may also be another cause. Further studies focussing on this area may yield more evidence to support this.

FUTURE SUGGESTIONS

A prospective study on patients with thrombocytopenia and large platelets on a larger number of patients should be planned. The study should also include testing for total homocysteine and serum methylmalonic acid levels on these patients. Bone marrow examination and documentation of reversal of the findings to a normal platelet count with normal platelet size following vitamin B12 and/or folate supplementation will further add significance to the results.

It will be interesting to confirm vitamin B12 deficiency in patients with low normal levels on biochemical assay for vitamin B12 by testing for the more definitive total homocysteine and serum methylmalonic acid levels, coupled with bone marrow examination. Then reversal of the thrombocytopenia with appearance of normal sized platelets on blood film examination following vitamin B12 and/or folate administration will be the gold standard test for proving our hypothesis. If not possible to perform these tests due to limited availability, it will be worth testing the serum holotranscobalamin levels to aim for better sensitivity and specificity in diagnosing vitamin B12 deficiency, including in the subclinical cases.

Studies on the platelet count and blood films of patients with hypothyroidism may also reflect more light upon the findings gathered in this study.

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