



## VITAMIN B<sub>12</sub> DEFICIENCY; FREQUENCY OF NEUROLOGICAL MANIFESTATIONS IN QUETTA.

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**ABSTRACT... Objectives:** To determine the frequency of neurological manifestations of vitamin B<sub>12</sub> deficiency and to observe the reversibility of the symptoms after the therapy. **Study Design:** Descriptive study. **Study Design:** Descriptive study. **Setting:** Medicine Department of Bolan Medical Complex Hospital Quetta. **Period:** One year that is from January 2012 to December 2012. **Methodology:** 46 patients presented to various OPDS of B.M.C.H.. The inclusion criteria for the patients to be studied were: Anemia, Neurological complaints. **Results:** Out of 46 patients 26(56%) were males and 20(43%) were the females with a mean age of (40) years. 32 (69%) belonged to the rural areas. 45(97%) had mixed diets whereas only one 1(2.1%) young non Muslim was found to be pure vegetarian. 32 (69%) patients presented with hematological as well as neurological complaints. 23(30%) had pancytopenia and 9(19.5%) had bicytopenia. 14(30%) presented with neurological complaints only as sacd 6 (13%), ataxia 8 (17%), sensorimotor neuropathies 36 (78%) and dementia 2 (4.3%). In signs glossitis was found in 6(13%), jaundice in 22 (47%), pallor in 32 (69%) proximal myopathy in 12 (26%) out of which 6 (13%) had shoulder girdle and 8 (17%) pelvic girdle myopathy. Impaired position sense was found in 18 (39%) patients and vibration sense in 21 (45%) patients. other signs were pigmentation 2(4.3%) hypotonia in 6(13%) Spasticity in 2(4.3%) and Upgoing plantars in 6(13%) patients. Lhermittes sign could be elicited in only 2(4.3%) patients Optic neuritis and optic atrophy was found in 4(8.6%) patients who came with paraplegia and marked anemia. Rhomberts sign was positive in 8(17.3%) who came with clumsiness of gait. Hemoglobin (Hb %) was found to be low in 32(69%) with a mean of 7.2gm%. pancytopenia (anemia+leucopenia+thrombocytopenia) was found in 23(50%) of patients whereas bicytopenia was found only in 9(19.5%) of patients. Hypersegmented W.B.C were very carefully looked for and were found in 20(43%) of cases. ovalomegaloblasts were found in 32 (69%) of cases .both findings of ovalomegaloblasts and hypersegmented w.b.cs were found in 20 (43%). in the rest 14 (30%) the blood investigations were found to be normal. The next investigation in all patients was serum B<sub>12</sub> estimation, It was found that levels below 200pg/ml were found in 95% cases where only 2(4.3%) patients came with levels slightly above 205pg/ml and 210pg/ml. the response to therapy was recorded as reversible and irreversible. the irreversible features were sacd in 6 (13%), optic atrophy in 2 (4.3%), and dementia in 2 (4.3%) patients. the partially reversible features were myelopathy 10 (21%) numbness and paraesthesias 30 (65%) optic neuritis inn 2 (4.3%) patients were assessed on a duration of 24 weeks. partially reversible features were ataxia, in 6 (13%) patients myelopathy in 2 (4.3%) patients dementia in 2 (4.3%) patients and paraesthesias and numbness in 6 (13%) patients over a period of 24 weeks. **Conclusion:** It is concluded from my study that the neuropsychiatric manifestations of vitamin B<sub>12</sub> deficiency are common among the elderly age group, either with or with out the evidence of anemia.

**Key words:** Megaloblastic Anemia, Serum B<sub>12</sub>, Dementia, Mcv.

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## INTRODUCTION

Nutrition influences the clinical practice in all branches of medicine particularly in the developing countries. In our setup nutrition is compromised due to Prevalence of many chronic inflammatory conditions, poverty. Poor sanitation, and low health status of females in particular.

Under these conditions of deprivation deficiency of nutrients especially of vitamins occurs. Vitamins are the organic nutrients that are required in small

quantities for a variety of biochemical functions. These must be therefore supplied by diet.<sup>1</sup>

Vitamin B<sub>12</sub> has a complex ring structure. Intrinsic factor is necessary for its absorption. Vitamin B<sub>12</sub> is a coenzyme for two biochemical reactions in body. First as methyl B<sub>12</sub>.

It is a cofactor for methionine synthetase. The enzymeresponsibleformethylationofhomocystein to methionine using methyl tetrahydrofolate as a

donor. Second as deoxyadenosyle B<sub>12</sub> (adeno b12) it assists in conversion of methylmalonyl coenzyme A (CoA) to succinyl co A.<sup>1</sup>

The animal products are the primary dietary source of vit. B<sub>12</sub>, its recommended daily allowance is 2 µgrams/day. It is stored mainly in liver.<sup>2</sup> Cobalamin deficiency can result from decreased ingestion, impaired absorption, and congenital enzyme deficiency pernicious anaemia is the most common cause of B<sub>12</sub> deficiency associated with atrophic gastritis.<sup>3</sup>

But its deficiency is not always due to pernicious anaemia, deficiency due to uncommon causes can manifest at any age resulting in severe morbidity.<sup>4</sup>

Fish tape worm absorbs large quantities of B<sub>12</sub> and interferes with the ileal absorption particularly in elderly, who present with megaloblastic anaemia exhibit severe neurological sequelae of B<sub>12</sub> deficiency<sup>5</sup>, which produces neuropsychiatric disturbances in CNS.

These affect mainly the myelin sheath and the spongy degeneration and diffuse demyelination of the posterior and lateral columns of the cord. Similar changes in cerebral hemisphere can occur. And it is suggested that pernicious anaemia is a differential diagnosis to consider in central demyelinating lesions at MRI.<sup>6</sup>

But still some of these lesions are very specific as subacute combined degeneration of cord in case of B<sub>12</sub> deficiency.<sup>7</sup>

This cobalamin associated neuropathy is particularly common in elderly the potential danger today is that with supplementation with folic acid of dietary staples as flour that the incidence of this disease could rise because artificial folic acid as apposed to natural folate enters the cell and the metabolic pathway by a cobalamin independent path way.<sup>8</sup> Cobalamin deficiency produces megaloblastic anaemia and unlike the other causes of this anemia it produces a wide variety of neuropsychiatric manifestations,

absence of one or other does not exclude its deficiency.<sup>9</sup>

And at this stage the administration of folic Acid can mask the megaloblastic anaemia caused by cobalamin deficiency more critically this masking although neither complete nor permanent can permit neurology dysfunction to develop and sometimes become irreversible.<sup>10</sup>

Neurological damage may become permanent when the disorder is mistaken for multiple sclerosis or diabetic neuropathy.<sup>11</sup>the psychiatric manifestations may be the first symptom of the deficiency and thus antedate anemia and spinal cord involvement.<sup>12</sup>

Although previously considered rare the neurological manifestations of gastrointestinal diseases, are increasingly recognized so these conditions are becoming the province of neurologists.<sup>13</sup>

Over the past three decades the association between elevated plasma levels of homocystein and risk factor of cardiovascular disease has grown from an obscure hypothesis to a major current topic in preventive cardiology. An elevated homocystein level induces pathogenic changes in arterial walls and is strongly associated with an increased risk of cardiovascular, cerebrovasclar and peripheral vascular events.<sup>14</sup> increased plasma homocystein is a risk factor for dementia and Alzheimer's disease.<sup>15</sup>

So it is concluded from the above discussion that vitamin B<sub>12</sub> deficiency is not merely the deficiency of a micronutrient but the beginning of a terrible yet treatable disease spell.

## METHODOLOGY

It was a DESCRIPTIVE study conducted on 46 patients presented to various OPDS of B.M.C.H .during a period of one year that is from January 2012 to December 2012.

The inclusion criteria for the patients to be studied were:

- Anemia
- Neurological complaints

All those patients not presenting with the neurological complaints mentioned in inclusion criteria.

- Patients with other causes of anemia
- Patients with other causes of neurological deficits.

A detailed clinical history, dietary history as well as socioeconomic history was given due weight.

Examination including both the general physical as well as systemic was carefully done and, Neurological examination was given much consideration.

The baseline or presentation day findings were recorded so as to keep a record of before therapy and after therapy findings.

As a next step was the care full and accurate selection of investigations for each patient as all the patients did not present with anemia so the bone marrow as well as L.F.Ts were not performed for each patient

A complete blood picture was performed for each patient including

- c b c (complete blood count )
- peripheral smear
- stool d/r.
- l.f.ts
- bone marrow
- serum b<sub>12</sub>

The other investigations were done only on a restricted number of patients. The two novel investigations tHcy and MMA levels are not available in QUETTA as is the case with MRI and the nerve conduction studies so no patient could be subjected to these investigations.

Once the B<sub>12</sub> levels were confirmed to be low that is below 210pg/dl no further investigation was done for the etiology of the deficiency keeping in view the financial burden on the patient as well as

non-availability of these tests the center of study.

All the statistical analysis of the results is done in descriptive and inferential manner. The confidence intervals are calculated manually with the help of estimation formulas with 95% confidence interval or the significance level of 0.05 is used to calculate the critical value from the table .p values (probability of obtaining a test statistic )is calculated by the

$$\text{FORMULA } \quad X \pm \frac{S}{\sqrt{n}}$$

The chi square test is also calculated manually. The table values for chi square test and distributions are adapted from (Statistics Allen G Bluman).

## RESULTS

The patients were selected strictly in accordance with inclusion and exclusion criteria by the history, physical examination and finally by the investigation out of which serum B<sub>12</sub> was the one important investigation.

Out of a total of 1000 patients presenting with anemia and neurological complaints during one year (jan2003-dece2003), 60(6%) patients were selected following the inclusion criteria. Fourteen patients were later excluded from the study after the initial work up as they proved to have other diagnosis. Remaining 46 patients 26 (56%) males and 20(43%) females were finally selected for the study.

Out of 46 patients 26(56%) were males and 20(43%) were the females with a mean age of (40) years. 32 (69%) belonged to the rural areas.

45(97%) had mixed diets whereas only one 1(2.1%) young non Muslim was found to be pure vegetarian.32 (69%) patients presented with hematological as well as neurological complaints. 23(30%) had pancytopenia and 9(19.5%) had bicytopenia.

14(30%) presented with neurological complaints only as sacd 6 (13%), ataxia 8 (17%), sensorimotor neuropathies 36 (78%) and dementia 2 (4.3%).

12(26%) patients had other comorbid conditions as 2 (4.3%) with diabetes mellitus, 2(4.3%) with sickle cell anemia, 4(8.6%) with mixed deficiency anemia, 2(4.3%) with malabsorption, 1(2.1%) with pulmonary tuberculosis and 1(2.1%) of epilepsy.

The most common complaint among both age groups was 36(78%) was generalized weakness and paraesthesias.

In signs glossitis was found in 6(13%), jaundice in 22 (47%), pallor in 32 (69%) proximal myopathy in 12 (26%) out of which 6 (13%) had shoulder girdle and 8 (17%) pelvic girdle myopathy. Impaired position sense was found in 18 (39%) patients and vibration sense in 21(45%) patients. other signs were pigmentation 2(4.3%) hypotonia in 6(13%) Spasticity in 2(4.3%) and Upgoing plantars in 6(13%) patients.

Rhombergs sign though uncommon could be elicited in only 2(4.3%) patients Optic neuritis and optic atrophy was found in 4(8.6%) patients who came with paraplegia and marked anemia. Rhombergs sign was positive in 8(17.3%) who came with clumsiness of gait.

Regarding the investigations a complete blood count including Hb%. rbc count, wbc patelets pcv, mcv, mch, and reticulocyte count and peripheral smear for ovalomegaloblasts and hypersegmented w.b.c was the initial step in all 46 patients .

Hemoglobin (Hb %) was found to be low in 32(69%) with a mean of 7.2gm%.pancytopenia (anemia+leucopenia+thrombocytopenia) was found in 23(50%) of patients whereas bicytopenia was found only in 9(19.5%) of patients.

Hypersegmented W.B.C were very carefully looked for and were found in 20(43%) of cases. ovalomegaloblasts were found in 32 (69%) of cases .both findings of ovalomegaloblasts and hypersegmented w.b.cs were found in 20 (43%). in the rest 14 (30%) the blood investigations were found to be normal.

Only 32(69%) patients were subjected to bone

marrow where 28(60%) showed megaloblastic changes and the 4(8.6%) showed mixed deficiency changes.

The rest 14 patients were exempt from bone marrow examination as the CBC was found to be normal. The stool D/R was done on every patient but it was found to be very little help as only 1(2.1%) patient showed the ova of fish tape worm.

The next investigation in all patients was serum B<sub>12</sub> examination because MMA and tHcy levels are not available in even the highly sophisticated lab of Quetta, but the b12 is still the considered as gold standard in diagnosing the deficiency.

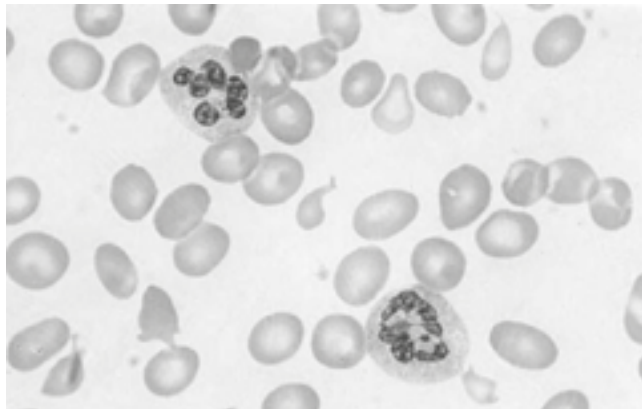
The values were expressed in pg/ml. The cut off point was set below 200pg/ml and the serum levels above 200pg/ml were set in gray zone. It was found that levels below 200pg/ml were found in 95% cases where only 2(4.3%) patients came with levels slightly above 205pg/ml and 210pg/ml but were included in study because history revealed that they were on I/V B<sub>12</sub> injections during the past few months.

The other investigations as nerve conduction study, MRI, were not available in Quetta so only one patient could go out side Quetta for NCS and it proved to be of great help in excluding any gross anatomical abnormalities.

The therapy in each patient was started as soon as the diagnosis was confirmed and the response was assessed on both the subjective and the objective grounds, after an average duration of 24 weeks that is 6 months. It was explained as reversible and irreversible .The reversible features were again classified as partial and complete.

The irreversible features were sacd in 6 (13%), optic atrophy in 2 (4.3%), and dementia in 2 (4.3%) patients. the partially reversible features were myelopathy 10 (21%) numbness and paraesthesias 30 (65%) optic neuritis inn 2 (4.3%) patients were assessed on a duration of 24 weeks. Partially reversible features were ataxia, in 6 (13%) patients myelopathy in 2 (4.3%) patients

dementia in 2 (4.3%) patients and paraesthesias and numbness in 6 (13%) patients over a period of 24 weeks.



Peripheral Film of A Patient With Pernicious Anemia Neurological Response to Therapy

Improvement was assessed with the examination of patient after therapy compared to the one done before therapy

$\chi^2$  TEST

Critical value (table value) = 3.842

Chi square test value is

(from given contingency table) 1.66

Effectiveness of increase in mcv with vitamin b12 deficiency

Test value is (1.66) Is < than the critical value (3.842)

So we accept hypothesis and the rejection of hypothesis.

	High	Normal	Total Patients
Males	16	10	26
Females	16	4	20
Total	32	14	46

DISCUSSION

Anemia is a prevalent condition with diverse causes. An expensive scattershot approach to evaluation can be avoided by combining information from history, physical examination and complete blood count with a review of peripheral blood smear and reticulocyte count. This information can simplify the differential diagnosis allowing the clinician to select the precise therapy for underlying condition or when necessary seek sharply focused second line treatment.<sup>16</sup>

Anemia is a complex of signs and symptoms rather than a disease, and is an extremely common manifestation of illness<sup>17</sup> as many as 1/3 of the patients admitted to hospital have low haematocrit.<sup>18</sup> Its apparent severity indicates neither its clinical significance nor its cause. Failure to establish the cause of even mild anemia is a frequent and potentially dangerous oversight.<sup>19</sup>

This study was conducted keeping in view the same points about the importance of anemia.

46 patients were finally selected for study .Out of these 26 were males and 20 were females. The greater risk of male patients having cognitive impairment when they are anemic in comparison with females has been reported in another study<sup>20</sup> The mean age of presentation was (40 years). That is the elderly age group as is supported by other studies. It is widely accepted that anemia is a common health problem among the elderly people, and cobalamin deficiency increase with advancing age, there are several studies which reflect an association between cobalamin deficiency and the cognitive impairment with the advancing age.<sup>18,19</sup>

No. of Patient	Duration	Complaint	Response		Percentage
			Subjective	Objective	
30	22Weeks	Neuropathies (Sensorimotor)	Satisfactory	Improved	65.2%
30	24Weeks	Numbness (Only Digital)	V good	Improved	65.2%
4	24Weeks	Ataxia	Good	Improved	8.6%
4	24 Weeks	Myopath`y (pelvic+ pectoral girdle)	Average	Improved	8.6%
22	24Weeks	Dementia	Average	Too short duration to asses the response	4.3%
1	24Weeks	Psychoses (functional)	Average	Improved	2.1%

As the number of females were less than the males this factor can be attributed to the fact that iron deficiency anemia is more common in females related to many factors as menstrual loss, multiple pregnancies, prevailing PIDs leading to undue loss, helminthic infestations and poverty and negligence regarding the provision of balanced diets.<sup>21,22</sup>

The fact that 32 of the patients in the study belonged to the rural areas where there is paucity of the basic life facilities and large family sizes.

The racial differences were as such not given so weight as the two most prevailing groups were Pathans and Baloch and most patients belonged to the same two groups. Religion was asked for the evaluation of the dietary habits<sup>37,38</sup> and one young non Muslim was found to be pure vegetarian who had both the anemia as well as the neurological complaints of paraesthesias and depression as well.

Drug history was taken from every patient and it was found that 43(93%) out of 46 patients had either used or were at that time using ppi, antacids and / or h<sub>2</sub> receptor blockers<sup>23</sup> this itself added to the deficiency of vitamin b12 as it is absorbed in the acidic medium of stomach.

The symptomatology of the patients varied greatly among different age groups, as well as among the same age group and the two genders. About 42 presented with multiples complaints. It is accepted that cobalamin deficiency may result in a variety of symptoms which are atypical, and hematological changes typical of megaloblastic anemia are frequently absent in the majority of patients with neurological disorders.<sup>24,25</sup>

Out of 46 patients 24(52%) were above 40 years, 20(43%) were below 40 years but above 24 years, and two (4.3%) were below 12 years. The most common complaint among the young age group (mean age 24±4years) was generalized weakness and fatigue in 22 (47%) patients followed by complications of anemia as dispend 18(39%), high out put cardiac failure 4(8.6%)

and than followed by the clumsiness of gait and movements in 8 (17%) patients. The rare complaint in this age group was dementia in 0 (0%) patients.

The most common complaint in elderly (age 40 years and above) was paraesthesias in 36(78%) patients followed by generalized weakness in 22(47%) patients memory impairment in 8(17%) and ataxia in 2(4.3%) was found.

Among 20 females 18(39%) had weakness and /or paraesthesias followed by the constitutional symptoms in 17(36%) and among 26 males 18(39%) had fatigue /generalized weakness and or paraesthesias followed by abnormal gait.

Almost the same findings are reported by an international study of Heaton et al it shows that no very big differences occur among the presentation of patients with neurological complaints of vitamin B<sub>12</sub> deficiency.

Out of 46 patients 28(60%) had impaired joint position and vibration sense in lower limbs and 4(14%) had in upper limbs as well lower limbs were spastic in 6 (13%) and upper limbs in only 1(2.1%) as it is in accordance with the study of UK Misra and J Kalita that loss of the dorsal column sensations is more common in lower limbs than in upper limbs also the most prominent clinical finding in the patients were dysfunction of posterior column as is illustrated by Hemmer B study of SADC carried out in Germany.

Hb% was found to be low in 32 with a mean of 7.2gm%.<sup>26,27</sup> pancytopenia (anemia+leucopenia+thrombocytopenia) was found in 23 of patients whereas bicytopenia was found only in 9 of patients. these findings of both the pancytopenia and bicytopenia is in accordance with the three different studies carried out in Pakistan two in Rawalpindi and one in islamabad where it was found that megaloblastic anemia is the most common cause of pancytopenia and bicytopenia seen in the peripheral film which were later confirmed by bone marrow examination<sup>28,29,30</sup> hypersegmented

w.b.c were very carefully looked for and were found in 20 of cases which is basically a low percentage as compared to other studies or as mentioned in books<sup>39</sup> but here is one explanation that over whelming bacterial infections in a few cases and paucity of technical expertise may be a contributing factor.

ovalomegaloblasts were found in 32 of cases with substantial ease as is mentioned. both findings of ovalomegaloblasts and hypersegmented w.b.cs were found in 20 patients .mixed deficiency changes (microcytic and macrocytic) were seen in 4 female patients as it may occur in females, supported by a local study carried in rawalpindi where 9 out of 40 patients of megaloblastic anemia had mixed deficiency changes.<sup>28</sup>

In the rest 14 the blood investigations were found to be normal, as is supported by other studies<sup>31</sup> where the majority of the patients with low serum vitamin b12 levels had normal Hb and MCV values<sup>32</sup> Studies also show that only about 60% of the patients with vitamin B<sub>12</sub> deficiency are anemic in addition the neurologic symptoms of deficiency can develop long before the patient can become anemic.<sup>33</sup>

The other investigations as nerve conduction study, MRI, are not available in Quetta so only one patient could go out side QUETTA for NCS and was proved to have sensorimotor deficit with a low (78pg/ml) of serum B<sub>12</sub> levels.

The other investigation done in patients with ataxia was CT scan where it proved to be of great help in excluding any gross anatomical abnormalities.

Regarding the treatment of vitamin b<sub>12</sub> deficiency majority of the patients were prescribed i/v injections of hydroxycobalamin, and only few were given oral preparations of hydroxycobalamin but regarding the response no significant difference was noticed in both the age groups as is supported by another study<sup>34</sup> that oral vitamin b<sub>12</sub> therapy might be as effective as conventional injectible therapy and it might be suitable for long term treatment.

The earliest that is with in 48 hours hematological response was in increased reticulocyte count that is increasing to 1-2 fold or more from base line recording and hypokalemia in (<3.2 mEq/L) which was corrected by potassium oral because if neglected severe hypokalemia can even lead to serious complications.

The H b% raised in within a duration of 8 weeks to 8 gm from the base line recording that is approximately 1gm/week,<sup>39</sup> MCV returned to normal (98fl) with in a duration of 8 weeks<sup>39</sup> this response is in accordance with an other study where the hematological parameters almost came to normal in all the patients included in study with effective treatment and good compliance.<sup>34</sup>

The neurological response in all presenting with both neurological +hematological and presenting with neurological only was assessed on subjective and objective grounds and was categorized as reversible and irreversible features, with a sub classification of reversible features as partially reversible or completely reversible.

Dementia and functional psychoses were another two features in of patients with no response confirmed by the objective assessment, over a period of 24 weeks duration this may correlate to the long duration of symptoms as well as the short duration of therapy the reversible features were categorized as partial and complete.

The complete reversal of myelopathy 35numbness and paraesthesias 35optic neuritis and ataxia in 36were assessed over a duration of 24 weeks (6 months) during follow up.

These observations in my study are in accordance to the other studies where all above mentioned features were completely reversible with adequate treatment.

Partially reversible features were ataxia in myelopathy in paraesthesias and numbness over a period of 24 weeks as assessment confirmed the response.

## CONCLUSION

It is concluded from my study that the neuropsychiatric manifestations of vitamin B<sub>12</sub> deficiency are common among the elderly age group, either with or without the evidence of anemia. Most of the patients in our set up do not get balanced diet, and the prices of the supplements are beyond their reach.

Serious complications of vitamin B<sub>12</sub> are observed in the young age group, as optic atrophy and SADC in this study particularly the females so taking into consideration the minor neurological deficits in the patients, can prevent them from serious irreversible complications.

## RECOMMENDATIONS

This study was conducted on a very small number of patients in very limited resources where all the facilities of highly sophisticated investigations are not present. Patients weak financial background was also a limiting factor, yet a small step was taken largely contributed by the clinical experience of the seniors in order to give the problem the due consideration, that a simple and timely treatment can prevent the life long complications of a micro nutrient.

There is an increasing trend of prescribing the anti depressant for the patients, but it is suggested that if a due thought is given for assessing the levels of vitamin B<sub>12</sub> in these patients a simple treatment regardless of the etiology can be instituted.

## CONCLUSION

Is the association with b12 deficiency increase of mcv does not depend on gender.

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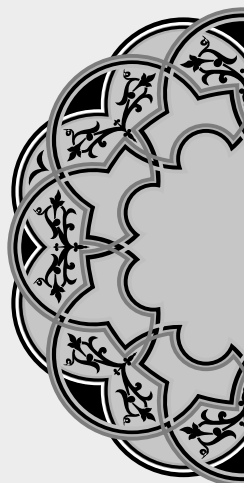
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*“It is very easy to defeat someone,  
But its is very hard to win someone.”*

**APJ Abdul Kalam**

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