Original Article

Does anemia affects cognitive functions in neurologically intact adult patients: Two year cross sectional study at rural tertiary care hospital

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Abstract

Background: The anemia not only negatively affects physical function but also the cognition, mood, and quality of life in adult patients due to hypoxic condition as per its severity. This study has been planned to investigate the cross-section association of anemia with cognitive function in neurologically intact patients. **Methods:** In this study, a total 200 subjects were enrolled out of which 100 were cases and 100 age and sex matched controls. Mini-mental status examination (MMSE) and short portable mental status questionnaire (SPMSQ) scales were used to assess cognition in all the subjects. **Results:** This study showed that there was a significant correlation between the anemia and the cognitive skills in the neurologically intact patients. **Conclusion:** The cognitive functions were strongly related to hemoglobin levels as seen by low MMSE score and higher SPMSQ error in those with low hemoglobin levels compared with those with higher hemoglobin levels.

Keywords: Adult, anemia, cognition, neurologically intact

Relevance to the practice

- Anemia is a widespread disorder in the community and it is strongly associated with poor cognitive performance irrespective of etiology of anemia
- As most of the patients of anemia had cognitive impairment, all the patients of anemia should be screened for cognitive functions
- Early detection and prompt treatment may help to reduce the effect of anemia on cognition.

Introduction

Anemia is defined according to World Health Organization (WHO) as a hemoglobin concentration less than 12 g/dL in women and less than 13 g/dL in men.[1] An estimated two billion of the world's population is suffering from anemia and most of this population lies in developing countries. The prevalence of anemia is 5% below age of less than 5 years, 48% in age group of 5--14, 42% in women between 15 and 59 years age, 30% in men between 15 and 59 years of age, and 45% above age of 60 years.[1]

In anemia there is decreased in number of RBCs or their oxygen carrying capacity which becomes insufficient to meet body's physical needs, depending on age, sex, and pregnancy status. Studies which have been done on Indian children have shown that iron deficiency anemia causes lower levels of attention and concentration.[2-4] Anemia is associated with poor cognitive performance as shown by the effect of anemia on age-related cognitive decline or it may also be independent risk factor for poor cognition.[5] In the general population, anemia is associated

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with increased risk for cognitive decline and dementia in elderly. In prospective studies, anemia has been associated with a 41–61% increased risk for dementia in elderly.[6-8]

Low hemoglobin levels are associated with tissue hypoxia and decreased oxygen delivery to brain which may lead to cognitive impairment.[8] Some experimental studies in humans have shown that iron deficiency may cause brain mitochondrial damage causing decreased function of the enzyme cytochrome oxidase leading to cognitive impairment.[9,10]

Very few studies and all in elderly have been conducted to study the impact of anemia on cognitive performance and having incontinent results.[9,10] No information is available regarding the prevalence of cognitive impairment in anemic adult population of India. Considering this fact, there is need to study the impact of anemia on cognitive functions in neurologically intact adult anemic patients in rural population from a tertiary care hospital.

Methods

This cross-sectional study was done in patients of anemia who were neurologically intact on clinical examination from 2016 to 2018, after approval of institutional ethics committee, DMIMS (DU) (Reference no –DMIMS(DU)/IEC/2016-17/407 dated 30.09.16), Wardha. Patients with history of any neurological injury or stroke, abnormal neurological finding on clinical examination, history of any psychiatric illness in the past or patients who are on any antipsychiatric medications, chronic disorders like chronic lung disease, renal or liver disease that could affect cognitive functions. The nature of study was explained to the participants and written informed consent was taken from the participants in English and Marathi language. The participants were investigated for anemia and those with anemia were enrolled in case group and those without anemia were enrolled in control group. All the participants were subjected to baseline investigation to rule out chronic diseases like renal failure, chronic liver or chronic lung disease which might affect the cognition. All the enrolled subjects were investigated with complete hemogram, serum creatinine, liver function test, serum ferritin, serum B12 levels, and reticulocyte count. All these tests were carried out by standard laboratory technique. After all these investigations, both cases and control groups were subjected to cognitive function testing with the help of two scales, mini-mental status examination (MMSE) and short portable mental status questionnaire (SPMSQ).

Folstein's MMSE scale is used for cognition testing. The interpretation of the test is based on MMSE score with maximum score of 30.

No cognitive impairment - MMSE score of 24–30, mild cognitive impairment - MMSE score of 23–18, severe cognitive impairment - MMSE score of less than 18. The MMSE includes 11 items covering a person's orientation to time, place, recall ability, short-term memory, and arithmetic ability. The test can be used as a screening tool for cognitive loss. The time administered to complete a questionnaire is 15--30 min. SPMSQ is a 10 question questionnaire to assess cognitive function. This test checks for orientation, remote memory, recent memory, practical and mathematical skills. ["0--2 errors = normal intellectual function, 3--4 errors = mild cognitive decline, 5--7 errors = moderate cognitive decline, 8--10 errors = severe cognitive decline."]

SPMSQ is a modification of mental status questionnaire. It provides a brief, quantitative measurement of cognitive function in elderly. The questions cover orientation in time and place, remote memory, and general knowledge and serial subtractions. Time administered to complete the questionnaire is 5 min.

Statistical analysis

Statistical analysis was done by using descriptive and inferential statistics using Chi-square test and student's unpaired *t*-test, ANOVA test and software used in the analysis were SPSS 22.0 version and Graph Pad Prism 6.0 version and $P < 0.05$ is considered as level of significance.

Results

Of the 200 participants (100 case and 100 control) enrolled in this study 61% were male and 39% were female with the mean age of 36.62 ± 13.03 years. The baseline characteristics of both cases and controls are shown in Table 1. Table 2 shows comparison of cognitive impairment in cases and controls based on MMSE scale. 52% of the cases had mild cognitive impairment compared with 18% in controls ($P = 0.0001$). Table 3 shows comparison of cognitive impairment in cases and controls

Table 1: Base line characteristics of the patients

Variables	Cases	Controls
Mean age (years)	36.62±13.03	35.84±13.41
Gender		
Male	61 (61%)	61 (61%)
Female	39 (39%)	39 (39%)
Hemoglobin	8.69±1.90	14.10±1.06
MCV	79.57±18.27	84.67±3.86
MCH	26.78±3.01	30.18±1.61
MCHC	31.96±1.73	33.57±1.57
RBC	4.15±0.56	4.79±0.37
HCT	40.45±3.83	44.57±2.19
Serum ferritin	41.61±50.42	109.78±5.93
Serum B12	433.57±198.79	556.48±125.24
Reticulocyte count	0.99±0.21	1.13±0.17
MMSE Score	24.17±3.12	26.62±2.69
SPMSQ Errors	2.90±1.36	1.75±0.82
Serum Creatinine	0.98±0.18	1.02±0.18
Serum Bilirubin	0.88±0.15	0.91±0.12
Serum albumin	3.98±0.30	4.03±0.39
SGPT	26.54±6.30	26.32±6.78
SGOT	26.99±5.88	27.66±6.76

based on SPMSQ scale. 41% of the cases had mild cognitive impairment and 14% cases had moderate cognitive impairment. In controls only, 15% had mild cognitive impairment and 1% had moderate cognitive impairment ($P = 0.0001$). Table 4 shows comparison of cognitive impairment in various age groups of anemia. Using ANOVA test F value was calculated and it was $F = 0.50$, $P = 0.60$, which was not significant. Thus, age is not a detrimental factor in cognitive impairment in cases of anemia. Table 5 shows age wise comparison of cognitive impairment in cases based on SPMSQ scale. Using ANOVA test, F value was calculated and it was $F = 1.30$ with P of 0.27 which was statistically nonsignificant. Table 6 shows cognitive impairment in cases based on severity of anemia. The above observations suggest that patients with severe anemia had low mean MMSE score and had mean SPMSQ errors of 4.06 ± 1.17 compared with normal mean MMSE scores and less mean SPMSQ errors in patients of mild and severe anemia. Using one-way ANOVA test of variance, P value was found to be significant ($P = 0.0001$), suggestive of significant cognitive impairment compared with patients of severe anemia compared to mild and moderate anemia.

Table 2: Cognitive impairment in patients of anemia compared to controls based on mmse scale

MMSE Scale	No Cognitive Impairment 24-30	Mild Cognitive Impairment 18-23	Severe Cognitive Impairment <18
Cases n=100	48 (48%)	52 (52%)	0 (0%)
Controls n=100	82 (82%)	18 (18%)	0 (0%)
χ^2	25.41, P=0.0001, significant		

Discussion

In this study, we had observed that severity of anemia affects the MMSE score and SPMSQ errors. In the study population, the cases and controls were age and gender matched. Out of 100 cases, 61 were males and 39 were females and equal number of male and female controls. The mean age of the cases was 36.81 ± 13.14 and that of controls was 35.84 ± 13.41. Most of the cases and controls were in the age group of 20--40 years of age. The mean hemoglobin levels in case group was 8.69 ± 1.90 and in controls was 14.10 ± 1.06. Out of 100 cases, 70 were of iron deficiency anemia, 23 were of megaloblastic anemia, and 7 were of hemolytic anemia.

Studies in children had shown that anemia affects cognition by its direct neurochemical effect and by its indirect effect on behavior, where they become less attentive and less responsive. Main pathogenesis may be iron, as it is seen throughout the white matter in the brain being more in basal ganglia. Iron deficiency anemia affects cognition by causing a decrease in the iron concentration in the brain, hence reduction in the neurotransmitter levels leading to hypomyelination and delayed neuromaturation.[4,5]

In a cross-sectional study carried out by Stella Argiriyadou *et al.* studying relationship between anemia and cognitive impairment in elderly population showed anemic population had significant cognitive impairment compared with nonanemic population. The cognitive impairment was more in anemic and nonanemic

Table 3: Cognitive impairment in patients of anemia compared to controls based on SPMSQ scale

SPMSQ Scale	Normal	Mild Cognitive Impairment	Moderate Cognitive Impairment	Severe Cognitive Impairment
Cases n=100	45 (45%)	41 (41%)	14 (14%)	0 (0%)
Controls n=100	84 (84%)	15 (15%)	1 (1%)	0 (0%)
χ^2			23.56, P=0.0001, significant	

Table 4: Cognitive impairment in patients of anemia according to age in years based on MMSE score

Age Group (years)	n	Mean	Std. Deviation	Std. Error	95% Confidence Interval for Mean		Minimum	Maximum
					Lower Bound	Upper Bound		
<20	7	24.00	4.04	1.52	20.26	27.73	20.00	29.00
20-40	58	23.93	3.04	0.39	23.13	24.73	18.00	30.00
>40	35	24.60	3.10	0.52	23.53	25.66	18.00	30.00
Total	100	24.17	3.12	0.31	23.55	24.78	18.00	30.00

F=0.50, P=0.60, NS, P>0.05

Table 5: Cognitive impairment in patients of anemia according to age in years based on SPMSQ score

Age Group (years)	n	Mean	Std. Deviation	Std. Error	95% Confidence Interval for Mean		Minimum	Maximum
					Lower Bound	Upper Bound		
<20	7	2.71	1.38	0.52	1.43	3.99	1.00	5.00
20-40	58	3.08	1.40	0.18	2.71	3.45	1.00	7.00
>40	35	2.62	1.28	0.21	2.18	3.07	1.00	7.00
Total	100	2.90	1.36	0.13	2.62	3.17	1.00	7.00

F=1.30, P=0.27, NS, P>0.05

Table 6: Cognitive impairment in relation to severity of anemia

Anemia	Mild ≥11 (*n*=49)	Moderate 8-10.9 (*n*=33)	Severe <8 (*n*=18)	*F*
Mean MMSE Score	26.26±3.47	24.89±2.91	21.80±1.60	18.19, *P*=0.0001, S
Mean SPMSQ Score	2.20±1.01	2.45±1.15	4.06±1.17	22.76, *P*=0.0001, S

males than females. They also showed megaloblastic patients had MMSE scores below 24.[10-12]

In our study, there was marked difference in MMSE and SPMSQ scores in cases and controls and more number of cases had lower MMSE scores and more SPMSQ errors which was significant. Anemia is associated with low MMSE scores and more SPMSQ errors. There was no gender-wise difference in cognitive functions in cases and controls. In this study, we also found age was not a detrimental factor in cognitive impairment in cases of anemia. In our study, out of 100 cases of anemia, 23 cases had megaloblastic anemia and was associated with significant cognitive impairment.

Conclusion

The cognitive functions were strongly related to hemoglobin levels as seen by low MMSE score and higher SPMSQ error in those with low hemoglobin levels compared to those with higher hemoglobin levels. All types of anemia, irrespective of the etiology were associated with poor cognitive functions. Anemia, irrespective of the etiology was found to cause mild to moderate cognitive impairment. Anemia does not cause severe cognitive impairment.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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