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# Relationship between serum Cobalamin levels and Neuropsychiatric Syndromes in individuals at Ahmadu Bello University Teaching Hospital Zaria, Nigeria

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## Abstract

*Background: Cobalamin deficiency causes defective methylation of myelin resulting in progressive neuropathy. This affects the spinal cord's peripheral sensory nerves and posterior and lateral columns. Inadequate methylation of myelin affects its quality and sufficiency with resultant interference of neuronal signal transmission. Objectives: To determine the relationship between Cobalamin deficiency and neuropsychiatric syndromes in patients attending neurology and psychiatric units of Ahmadu Bello University Teaching Hospital (ABUTH), Zaria. Methods: We conducted a cross-sectional study involving 68 patients with neuropsychiatric symptoms and signs. A semi-structured interviewer-administered questionnaire was used to collect information from the study participants. Tables were used to show the frequencies and proportions of the neuropsychiatric syndromes. Serum cobalamin levels were estimated using Human Transcobalamin 2 (TCN2) ELISA Kit, WKEA MED SUPPLIES CORP Changchun 130012 China. Results: 68 participants were enrolled in this study, with males being 45 (66.2%). The mean (±Standard Deviation) age and the median with interquartile range (IQR) of cobalamin level of the study participants were 34.37±13.70 years and 140 (30) pmol/L respectively. Some neuropsychiatric syndromes of statistical significance were icteric 17 (25.0%), abnormal light touch sensation 13 (19.1%), abnormal vibration sense 23 (33.8%), abnormal joint position sense 24 (35.3%) and hyperpigmentation of palms and soles 13 (19.1%). Conclusion: This study showed a high cobalamin deficiency among the patients attending neuropsychiatric units. It also showed a statistically significant relationship between serum cobalamin and clinical signs, signifying proficiency in eliciting clinical signs is paramount in detecting people with suspected cobalamin deficiency. Therefore, vitamin $B_{12}$ deficiency is a frequently ignored cause of neuropathy and psychiatric disorders.*

***Keywords:*** *Vitamin $B_{12}$ deficiency, Cobalamin deficiency, Neurology unit, Neuropsychiatric syndromes, Psychiatric unit.*

## Introduction

Neuropsychiatric syndromes associated with cobalamin (Vitamin $B_{12}$) deficiency include dementia, depression, mania, psychosis, impaired memory, disorientation, irritability, hallucinations, personality changes and obsessive-convulsive disorder. Foods that contain Vitamin $B_{12}$ are those of animal origin like meat, liver, seafood and dairy products.[1]The neurologic manifestation of cobalamin deficiency is less understood, however, central nervous system demyelination may play a role.[2] Cobalamin deficiency characteristically causes defective methylation of myelin and other substrates resulting in progressive neuropathy affecting the peripheral sensory nerves, and posterior and lateral columns of the spinal cord.[3] Inadequate methylation of myelin affects its quality and sufficiency with resultant interference of neuronal signal transmission. Therefore, cobalamin deficiency is essentially a demyelination disorder[3.] S-adenosyl methionine (SAM) which is useful in polyamine synthesis and transmethylation reactions.[4] S-adenosyl methionine is required for the production of phosphatidyl choline which is an essential part of myelin- a fatty material that insulates many nerves. Therefore, low levels of SAM as found in cobalamin deficiency may compromise neurological repair mechanisms, relevant to encephalopathy and myelopathy and

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synthesis of the neurotransmitters, which may result in mental status changes.[5] Another explanation of neuronal damage is that cobalamin deficiency attracts activated macrophages to the poorly myelinated nerve with the subsequent elaboration of inflammatory cytokines such as Tumour necrosis factor alpha (TNF-α) and Interleukin-6 (IL-6) which aggravate myelin damage.[6] Removal of damaged myelin by macrophages leads to characteristic vacuoles in all classes of nervous tissue, manifesting with motor, sensory and autonomic features hence subacute combined degeneration of the nerves.[6]

Prolonged Vitamin $B_{12}$ deficiency with its attendant effects on the nervous system may lead to neuropsychiatric syndromes. Therefore, there is a need for those concerned to increase Vitamin $B_{12}$ intake through improved earnings and awareness. This study, therefore, aimed at studying the relationship between serum cobalamin and neuropsychiatric syndromes in patients attending neurology and psychiatric units of Ahmadu Bello University Teaching Hospital Zaria, Nigeria.

## Materials and Methods

**Study settings:** This study was carried out at the departments of neurology and internal medicine of Ahmadu Bello University Teaching Hospital Zaria, Nigeria.

**Study design:** This was a cross-sectional study among 68 patients attending neuropsychiatric clinics of ABUTH, Zaria. A semi-structured questionnaire was used to collect information on clinical symptoms and signs, and some laboratory tests were carried out on the study participants.

**Study population:** This study was carried out on subjects with Neurological and/or psychiatric problems aged between 18 to 80 years.

**Sampling technique:** The participants were conveniently recruited as they presented to the units using a simple random sampling technique.

**Study instrument:** Semi-structured interviewer-administered questionnaires were used to collate information on socio-demographic variables (Table 1), clinical symptoms and signs. Venipuncture was carried out on the subjects to obtain samples for serum cobalamin levels. Serum cobalamin was spectrophotometrically measured at a wavelength of 450nm using Human Transcobalamin 2 (TCN2) ELISA Kit, WKEA MED SUPPLIES CORP Changchun 130012 China. Cobalamin deficiency was defined as a serum cobalamin level of <150pmol/L with clinical features and/or haematological anomalies related to cobalamin deficiency.[7]

**Data collection methods:** Each questionnaire was administered by an interviewer who was trained for the purpose after pre-testing. Five millilitres of venous blood were drawn from each participant for the determination of serum cobalamin levels. To ensure biosafety, universal precaution was observed by using latex gloves, spirit swabs for disinfecting the skin before blood collection, and safety boxes for sharps disposal.

**Data management:** The questionnaires were examined for completeness and accuracy by the principal investigator. The information on the questionnaires and the laboratory investigations were subsequently entered into Microsoft Excel version 20.0 for Windows and then imported into and analysed using SPSS version 20.0. Tables were used to show frequencies and proportions of serum cobalamin levels and neuropsychiatric syndromes (Table 2).

**Statistical analysis:** The data was analysed using IBM SPSS (version 20.0). Univariate analysis was used for frequencies and proportions of socio-demographic variables and serum cobalamin levels. The chi-square test was used to determine the relationship between serum cobalamin level and neuropsychiatric syndromes. The level of statistical significance was set at $p<0.05$.

**Ethical approval**

The study protocol was submitted to the Health Research Ethics Committee (HREC) of Ahmadu Bello University Teaching Hospital Zaria, and the research was approved. The approval number for this research is ABUTH/HREC/TRG/36. A written informed consent was obtained from the literate subjects while non-literate subjects thumb-printed the consent form.

## Results

68 participants were enrolled in this study, with males being 45 (66.2%). The mean (±Standard Deviation) age and the median (IQR) of the cobalamin level of the study participants were 34.37±13.70 years and 140 (30) pmol/L respectively. Some clinical signs that had statistically significant associations with cobalamin levels were; icteric 17 (25.0%, p=0.004), abnormal light touch sensation 13 (19.1%, p=0.022), abnormal vibration sense 23 (33.8%, p=0.037), abnormal joint position sense 24 (35.3%, p=0.006) and hyperpigmentation of palms and soles 13 (19.1%, P=0.022) Table 3.

Table 1: Socio-Demographic Characteristics of First and Regular Blood Donors

| Variables | Patient group Frequency (%) | Control group frequency (%) |
|---|---|---|
| **Gender** | | |
| Male | 24 (35.3%) | 45 (66.2%) |
| Female | 44 (64.7%) | 23 (33.8%) |
| **Age** | | |
| <20 years | 4 (5.9%) | 1 (1.5%) |
| 20-29 years | 29 (42.6%) | 21 (30.9%) |
| 30-39 years | 18 (26.5%) | 28 (41.2%) |
| 40-49 years | 7 (10.2%) | 15 (22.1%) |
| 50-59 years | 5 (7.4%) | 3 (4.3%) |
| ≥60 years | 5 (7.4%) | 0 (0%) |
| **Level of education** | | |
| Formal | 61 (89.7%) | 68 (100%) |
| Non-formal | 7 (10.3%) | 0 (0%) |
| **Marital status** | | |
| Married | 31 (45.6%) | 44 (64.7%) |
| Not married | 37 (54.4%) | 24 (35.3%) |
| **Occupation** | | |
| Employed | 39 (57.4%) | 49 (72.1%) |
| Unemployed | 29 (42.6%) | 19 (27.9%) |
| **Family size** | | |
| <4 | 3 (4.3%) | 4 (5.9%) |
| 5-8 | 20 (29.4%) | 43 (63.2% |
| >8 | 45 (66.2%) | 21 (30.9%) |

Table 2: Clinical signs of all the study participants

| Presenting clinical signs | Frequency (%) |
|---|---|
| **Appearance** | |
| Well-groomed | 58 (85.3) |
| Unkempt | 10 (14.7) |
| **Speech coherence** | |
| Coherent | 65 (95.6) |
| Not coherent | 3 (4.4) |
| **Pallor** | |
| Yes | 26 (38.2) |
| No | 42 (61.8) |
| **Jaundice** | |
| Yes | 17 (25.0) |
| No | 51 (75.0) |
| **Pedal oedema** | |
| Present | 1 (1.5) |
| Absent | 67 (98.5) |
| **Kernig's sign** | |
| Absent | 68 (100) |
| **Romberg sign** | |
| Absent | 68 (100) |
| **Light touch** | |
| Normal | 55 (80.9) |
| Abnormal | 13 (19.1) |
| **Vibration (256Hz) sense** | |
| Normal | 45 (66.2) |
| Abnormal | 23 (33.8) |
| **Joint position sense** | |
| Normal | 44 (64.7) |
| Abnormal | 24 (35.3) |
| **Coordination** | |
| Normal | 68 (100) |
| **Drift** | |
| Normal | 68 (100) |
| **Hyperpigmentation of palms and soles** | |
| Present | 13 (19.1) |
| Absent | 55 (80.9) |
| **Gait** | |
| Normal | 67 (98.5) |
| Abnormal | 1 ( 1.5) |

Table 3: Relationship between serum cobalamin levels and clinical symptoms

| Clinical symptoms | Normal Cbl level | Low Cbl level | $x^2$ | p-value |
|---|---|---|---|---|
| **Weakness** | | | | |
| **Yes** | 3 | 33 | 0.708 | 0.850 |
| **No** | 19 | 13 | | |
| **Visual disturbances** | | | | |
| **Present** | 2 | 4 | 0.353 | 0.553 |
| **Absent** | 20 | 42 | | |
| **Involuntary movement** | | | | |
| **Present** | 3 | 6 | 0.270 | 0.603 |
| **Absent** | 19 | 40 | | |
| **Tremors** | | | | |
| **Present** | 2 | 3 | 0.874 | 0.350 |
| **Absent** | 20 | 43 | | |
| **Cognitive state** | | | | |
| **Normal** | 16 | 36 | 0.060 | 0.806 |
| **Abnormal** | 6 | 10 | | |
| **Skin sensation** | | | | |
| **Normal** | 17 | 30 | 0.016 | 0.900 |
| **Abnormal** | 5 | 16 | | |
| **Speech disturbances** | | | | |
| **Absent** | 16 | 36 | 0.060 | 0.806 |
| **Present** | 6 | 10 | | |
| **Dysphagia** | | | | |
| **Present** | 0 | 4 | 0.076 | 0.150 |
| **Absent** | 22 | 42 | | |
| **Fits** | | | | |
| **Present** | 3 | 12 | 0.580 | 0.446 |
| **Absent** | 19 | 34 | | |
| **Unhappy most time** | | | | |
| **Yes** | 7 | 12 | 0.058 | 0.809 |
| **No** | 15 | 34 | | |
| **Disliked by everyone** | | | | |
| **Yes** | 6 | 11 | 0.002 | 0.960 |
| **No** | 16 | 5 | | |
| **Life worth living** | | | | |
| **Yes** | 21 | 41 | 0.065 | 0.799 |
| **No** | 1 | 5 | | |
| **Is it worth seeing a Doctor** | | | | |
| **Yes** | 21 | 40 | 0.253 | 0.316 |
| **NO** | 1 | 6 | | |

**Normal cobalamin level in this study: ≥150pmol/L**

Table 4: Relationship between serum cobalamin levels and clinical signs

| Presenting clinical signs | Normal Cbl level | Low Cbl level | $x^2$ | p-value |
|---|---|---|---|---|
| **Appearance** | | | | |
| **Well-groomed** | 20 | 38 | 0.184 | 0.668 |
| **Unkempt** | 2 | 8 | | |
| **Speech coherence** | | | | |
| **Coherent** | 21 | 44 | 0.565 | 0.452 |
| **Not coherent** | 1 | 2 | | |
| **Pallor** | | | | |
| **Had pallor** | 10 | 6 | 0.348 | 0.555 |
| **No pallor** | 12 | 30 | | |
| **Jaundice** | | | | |
| **Icteric** | 1 | 6 | 0.187 | 0.004 |
| **Anicteric** | 21 | 30 | | |
| **Kernig's sign** | | | | |
| **Absent** | 22 | 6 | NA | NA |
| **Romberg sign** | | | | |
| **Absent** | 22 | 46 | NA | NA |
| **Light touch** | | | | |
| **Normal** | 21 | 4 | 0.245 | 0.022 |
| **Abnormal** | 1 | 12 | | |
| **Vibration (256Hz) sense** | | | | |
| **Normal** | 19 | 26 | 0.340 | 0.037 |
| **Abnormal** | 3 | 20 | | |
| **Joint position sense** | | | | |
| **Normal** | 20 | 24 | 0.668 | 0.006 |
| **Abnormal** | 2 | 22 | | |
| **Coordination** | | | | |
| **Normal** | 22 | 46 | NA | NA |
| **Drift** | | | | |
| **Absent** | 22 | 46 | NA | NA |
| Hyperpigmentation **of palms and soles** | | | | |
| **Present** | 1 | 12 | 0.245 | **0.022** |
| **Absent** | 21 | 34 | | |
| **Gait** | | | | |
| **Normal** | 22 | 45 | 0.048 | 0.316 |
| **Abnormal** | 0 | 1 | | |

**Cbl:** Cobalamin (pmol/L)

## Discussion

This study showed a high cobalamin deficiency among the patients attending neuropsychiatric units. Neurologic manifestations may be the earliest and often the only manifestation of cobalamin deficiency.[8] However, cobalamin deficiency can go undetected for several years. During this time the neuropsychiatric manifestations may become irreversible.[9]The symptoms presented by the patients with the neuropsychiatric syndrome in this study were weakness, abnormality in skin sensation (paraesthesia), feeling of unhappiness most of the time, feeling of being disliked by everyone, abnormal cognitive state and speech disturbances (Table 2). This is similar to the findings by Wadia *et al*[10]who also reported cognitive abnormality, weakness, abnormal skin sensation and fits in individuals with vitamin $B_{12}$ deficiency. In a study similar to this by Kumar, he described abnormal skin sensation (myelopathy), optic nerve involvement (visual disturbances) and personality change were among the symptoms of cobalamin deficiency.[11]Another study conducted on paediatric patients aged 0-18 years by Serin and Arslan found that involuntary movement fits (convulsion), abnormal skin sensation (tingling) and blurring of vision were among the few presenting symptoms.[12] This is similar to this study where some of our study participants presented with these symptoms.

The clinical signs of pallor found in the neuropsychiatric patients in this study is similar to the finding by Schuitemaker and Hoogland.[13] They reported pallor and fatigue as the earliest clinical features of cobalamin deficiency. Other signs like abnormality in joint position sense, abnormal vibration sense and abnormality in light touch sensation were commonly observed in this study. This observation was similarly reported by Sethi *et al*[14], and the earliest and commonest presentations of peripheral neuropathy due to cobalamin deficiency are joint position sense abnormality and impaired vibration sense. Another two independent studies conducted by Andrès et al[9] and Kumar[11] reported similar findings of clinical signs in individuals with cobalamin deficiency. Additionally, a case report of a 66-year-old vegetarian by Ralapanawa *et al*[15] revealed similar findings except positive Romberg's sign, which is absent in this study.

This study showed no significant relationship between the clinical symptoms and cobalamin deficiency (Table 3).However, a significant relationship exists with some clinical signs elicited (Table 4). Therefore, cobalamin deficiency is better clinically identified from a thorough clinical examination during which signs like jaundice, abnormal joint position sense, abnormal light touch sensation, abnormal vibration sense and hyper pigmentation may be elicited.

## Conclusion

This study showed a high cobalamin deficiency among the patients attending neuropsychiatric units. It also showed a statistically significant relationship between serum cobalamin and clinical signs, signifying proficiency in eliciting clinical signs is paramount in detecting people with suspected cobalamin deficiency. Therefore, vitamin $B_{12}$ deficiency is a frequently ignored cause of neuropathy and psychiatric disorders.

## Recommendations

1. Baseline Vitamin $B_{12}$ assays should be instituted among neurology and psychiatry patients and possible interventions given.
2. Health education on adequate intake of animal proteins as source cobalamin should be incorporated into the existing public awareness programs by the government, the dietetic unit of ABUTH, Zaria especially during the clinic days and other non-governmental organizations.
3. Introduction of cost-effective, low-technology agricultural interventions to boost food production to sustain vitamin $B_{12}$ levels in the community, e.g. encourage the women to rear animals in their backyards or start a community garden.
4. The government should develop a policy formulation framework to increase access to health care in view of their contribution to the nutrition and economy of this country.

## Limitations

1. The study being cross-sectional and Hospital-based only gave a 'snap-shot' of the problems in the community, hence may not be a true representative of the population.
2. Being a cross-sectional study, it may not adequately establish a cause-effect relationship between Vitamin $B_{12}$ deficiency and neuropsychiatric syndromes.
3. Bone marrow examination would have added value to the study if not because of the invasive nature of the procedure and the cost.

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**Conflict of interest:** The authors declared no conflict of interest.

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