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Original Research Article

Neurological Manifestations of Vitamin B12 Deficiency

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Abstract

Introduction: Vitamin B12 deficiency can affect all age groups. This can present with varying neurological Manifestataions apart form heamatological and skin changes. This case series study is presented with an aim to identify the diverse clinical manifestations.

Materials and methods: Patients admitted in neurology department government general hospital with neurological manifestations attributable to Vitamin B12 deficiency and reduced Vitamin B12 levels were taken and analysed.

Results: The dietary differences was not the sole or significant influencing factor. Myeloneuropathy was seen in 80% with posterior column and pyramidal signs. Cognitive signs, psychiatric features, cerebellar, extrapyramidal features, urinary urgency, optic atrophy were seen in few patients.

Discussion: The most common presentation had been myeloneuropathy with posterior column and pyramidal signs. 26.66% had pyramidal signs in lower limb alone, remaining had in upper and lower limbs with earlier involvement in thoracic portion of the spinal cord. The atypical features like cerebellar, extrapyramidal features have been observed in previous studies.

Conclusion: Vitamin B12 deficiency to be suspected when confronted with any of the neurological manifestations even in an atypical presentation with any atypical features with pyramidal signs even without significant posterior column signs or neuropathy.

Keywords: Vitamin B12 Deficiency; Subacute Combined Degeneration; Myeloneuropathy.

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Introduction

Vitamin B12 deficiency can affect all age groups. This can present with varying neurological Manifestataions apart form heamatological and skin changes. It can occur in pernicious anemia, malabsorption syndromes, gastric and ileal surgeries, overgrowth of Bacterias in blind loops anasatamosis, diverticulae, nitrous oxide poisoning. Less commonly could be due to a genetic defect methyl malonyl Co A mutase. This case series study is presented with an aim to identify the diverse clinical manifestations.

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Materials and Methods

Patients admitted in Neurology Department, Government General Hospital with neurological manifestations attributable to Vitamin B12 deficiency and reduced Vitamin B12 levels were taken and analysed.

Results

Among 15 patients 13 were males and 2 were females. The age of the patients ranged between 14 and 50 years and more were between 30 to 50 years. The onset was subacute to chronic in all the patients (Fig.1).

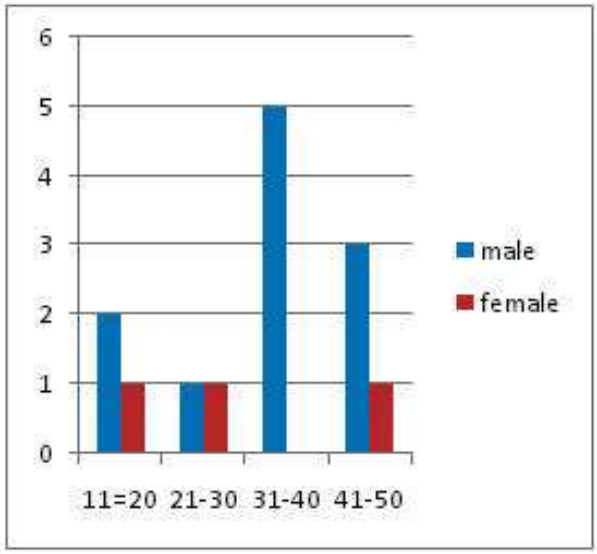

Fig. 1: Agewise distribution of male and female

Risk factors

Among The risk factors identified 2 patients were vegetarians, 2 patients had gastrointestinal surgery done, 4 patients were chronic alcoholics. There were no attributable risk factor in the remaining 7 patients (Fig. 2).

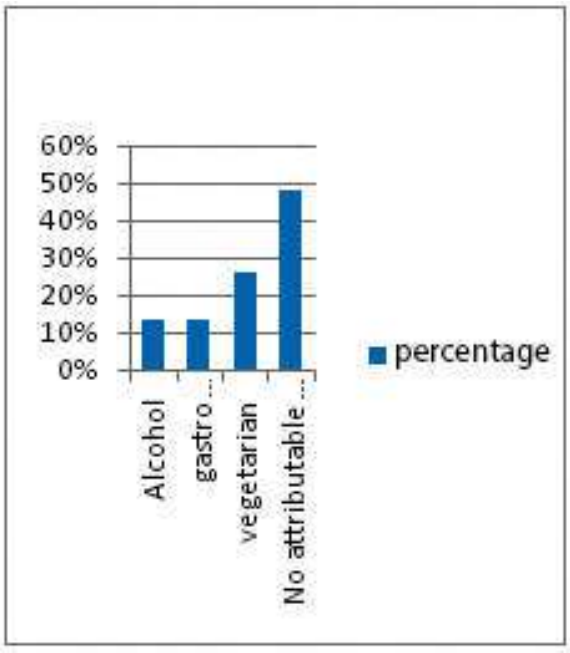

Fig. 2: Diet pattern observed with Vitamin B12 deficiency

Table 1: Clinical features seen with Vitamin B12 deficiency

Clinical features	percentage
Cognitive	26%
Psychiatric features	33%
Pyramidal signs	73.33%
Posterior column signs	86.66%
Autonomic signs	46.66%
Neuropathy	86.66%
cerebellar	0.06%
Optic atrophy	0.06%
Extrapyramidal	0.06%

Table 2: Clinical presentation of Vitamin B12 deficeiency

Clinical presentation	cases	percentage
Myeloneuropathy	12	80%
Myeloneuropathy with cognitive with psychiatric features with extrapyramidal features	1	6.66%
Myeloneuropathy with cognitive features	1	6.66%
Myeloneuropathy with cerebellar	1	6.66%

The clinical features observed with vitamin B12 deficiency have been summarized in the Table 1 and Table 2 and Figure 3. Regarding cognitive features, 3 patients had sub cortical memory disturbances and 1 patient had apathy and extrapyramidal features. 5 patients had psychiatric disturbance of mood disturbance in the form of depression.

Among 15 patients, 11 (73.33%) had pyramidal signs in the form of spasticity and weakness in upper and lower limbs and 4 (26.66%) had pyramidal signs in lower limbs alone.

Posterior column signs were seen in 13 (86.66%) patients out of 15 patients which ranged from mild proprioceptive loss in lower limb in 3 patients to significant sensory ataxia in 10 patients. 2 patients did not have posterior column signs.

Regarding neuropathy 13 (86.66%) had clinical evidence of small and large fibre neuropathy which was supported by axonal changes in electrophysiological evaluation.

Regarding autonomic manifestations, urgency of bladder was seen in 6 (40%)out of 15 patients and erectile dysfunction along with urgency in 1 patient.

Among other features one patient had cerebellar signs and one patient had optic atrophy.

Serum vitamin B12 levels were low in all patients with values less than 100pg/ml in 6 patients and values between 100 and 200 pg/ml in the remaining 9 patients.

In 5 patients, bone marrow showed megaloblastic pictue even though the peripheral smear was not contributory . In the remaining 10 patients bone marrow was not done, among them one had megaloblastic picture and one had dimorphic picture.

Neuroimaging showed posterior column hyperintensities in cervical and dorsal portion of spinal cord in 2 patients and T2 subcortical hyperintensities in one patient with memory disturbance as cognitive feature.

Nerve conduction studies showed axonal changes in sensory nerves in one patient, axonal changes in sensory and motor nerves in 12 patients and a normal study in 2 patients. Tibial SSEP were abnormal in 14 patients. It was not recordable in 11 patients and prolonged in 3 patients. It was asymmetrically prolonged in 2 patients. Visual evoked potential (VEP) was abnormal in 6 patients, P100 latency prolonged in 5 patients without any visual symptoms, 3 being bilateral and asymmetrical in 2 patients. Also the P100 amplitude was reduced bilaterally in 1 patient with optic atrophy.

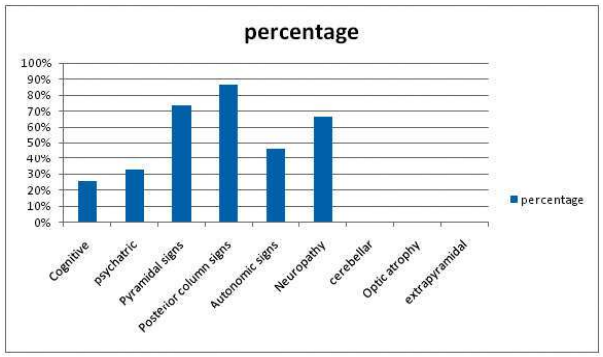

Fig. 3: Percentage representation of clinical manifestation seen with vitamin B12 deficiency

Discussion

Vitamin B12 deficiency is a systemic disease affecting heamatological, skin and mucous membranes and various parts of nervous system .The neurological symptoms can occur even in the absence of evident hematological abnormalities.

Healton [1] in his series has reported isolated neuropathy in 25% of patients, Myelopathy occurred in 12% of cases, a combination of neuropathy and myelopathy was noted in 41%. Neuropsychiatric manifestations, such as recent memory loss with reduced attention span and otherwise normal cognition, depression, hypomania, paranoid psychosis with auditory or visual hallucinations (megaloblastic madness), violent behavior, personality changes, blunted affect, and emotional liability, were reported in 8% of patients. Ocular findings included a cecocentral scotoma and occurred in 0.5% of cases. Others have described optic atrophy, nystagmus, small reactive pupils, and chiasmatic lesion causing bitemporal hemianopia.

The most frequent neurologic manifestations are the SCD of the spinal cord and polyneuropathy [2]. SCD affects the posterior columns and the corticospinal tracts and is characterized by swelling of the myelin sheaths and a patchy myelopathic spongy vacuolation of the affected regions of the cord [3-4].

The corresponding neuropathological findings are a diffuse, multifocal pattern of axonal loss and demyelination most severe in the cervical and thoracic spinal cord. The disease predominantly affects the posterior columns followed by the anterolateral and anterior tracts [5]

Regarding patho physiology, Methyl-vitamin B12 (Met B12) and 5-deoxy-5-adenosylcobalamin (Ado B12) are two physiologically active forms of vitamin B12 in the human body [6]. Met B12 is needed as a cofactor by the methyltetrahydrofolate-homocysteine methyltransferase (MTR) enzyme to generate methionine from homocysteine and tetrahydrofolate from methyltetrahydrofolate. Ado B12 is required as a cofactor by the methylmalonyl-CoA mutase (MMCoAM) for the conversion of methylmalonyl-coenzyme A to succinyl coenzyme A. The dysfunction of the AdoB12- MMCoAM pathway leads to an intracellular accumulation of both propionyl-CoA and methylmalonyl-CoA leading to the formation of abnormal fatty acids. Methionine is the precursor of S-adenosylmethionine, a universal methyl donor which is important in the methylation of myelin basic protein and myelin lipids. Decreased methionine and S-adenosylmethionine lead to instability of the myelin sheath. Recent evidences suggests that B12 deficiency decreases spinal cord synthesis and CSF levels of a myelinotrophic cytokine, interleukin 6 (IL-6), and a myelinotrophic growth factor, epidermal growth factor (EGF) [7]. Cobalamin deficiency can cause neuropsychiatric symptoms via multiple pathways, including derangements in monoamine neurotransmitter production as cobalamin and folate stimulate tetrahydrobiopterin (BH4) synthesis, which is required for monoamine synthesis, and vasculotoxic effects and myelin lesions associated with secondary increases in homocysteine and MMA concentrations .

Aaron et al. [8] have reported that

myeloneuropathy was the commonest clinical finding in 54% of patients. A combination of myeloneuropathy with cognitive impairment was seen in 34% of patients. 9% had peripheral neuropathy alone. Cognitive dysfunction as the only manifestation of B12 def was noted in 3% of patients. Neuropsychiatric manifestations were noted in 38% of patients and included dementia in 19%, depressive features in 11% and psychosis in 4%.

B12 deficiency causes a wide spectrum of neurological manifestations ranging from neural tube defects [9] to changes in cognition and behavior [10]. Many unusual manifestations have been reported in infants [11] and adults including movement disorders [12]. Extrapyramidal involvement due to vitamin B12 deficiency in adults is rare and previously reported features include rigidity, myoclonus-like involuntary movements and chorea and focal dystonia [13]. seizures have also been reported as well [14].

Usually sub acute to chronic course, but acute presentations of SCD also have been seldom reported in literature. Shukla et al. [15] described a series of five patients with SCD all of whom had presented acutely, with duration of symptoms ranging from 6-15 days, all of them the presentation was as acute posterior or posterolateral myelopathy with none as neuropathy.

Divate et al. [16] had observed that dietary differences and socio economic factors did not influence the clinical presentation and hence possibility of pernicious anemia has to be considered and evaluated.

In our study, all had an insidious onset illness. A male preponderence was observed though consistent with previous studies, could be a sampling bias also. Regarding risk factors 41% of patients did not have any identifiable attributable risk factors. This is consistent with divate et al study that dietary differences not the sole influencing factor. Regarding autonomic features 40% had urgency of urine with one patient. The most common presentation had been myeloneuropathy 80% with posterior column and pyramidal signs. Most (86.66%) had posterior column signs. 26.66% had pyramidal signs in lower limb alone, remaining had pyramidal signs in upper limbs and lower limbs which are consistent with previous studies with earlier involvement in thoracic portion of the spinal cord and patients having ED also suggestive of probable interruption of bladder fibers in the cord. One patient had cerebellar, another with extrrapyramidal and another with optic atrophy suggesting a probable demyelinating and axonal involvement of central neural network anywhere along the cerebellar connections, connections of basal ganglia and visual pathway respectively. These atypical features in the cases like cerebellar and extrapyramidal features have also been observed in the previous cases studies.

Also one patient had presented with pyramidal signs, but without neuropathy and another two patients without posterior column signs, but sensory evoked potential had been abnormal in one patient, another one without neuropathy or posterior column signs. Hence, posterior column signs can be mild to severe and neuropathy may be absent.

MRI imaging would be a typical pattern with T2 hyperintense signal alterations usually confined to the posterior columns, which may involve the lateral columns and rarely brainstem [17]. An inverted V sign may be seen in cross-sectional images. A nodular pattern of T2-hyperintensity may be seen in the thoracic cord. Symmetrical hyperintense signals in lateral columns and posterior columns in diffusion weighted imaging (DWI) have been reported [18-19]. T2 hyperintense lesions in seen periventricular region of the brain [20]. In our study, Neuro imaging showed T2 hyperintensity in cervical and dorsal cord in 8 patients along with T2 hyperintensity in periventricular subcortical region in 1 patient. The remaining 6 patients did not show any imaging abnormalities inspite of clinical evidence of cord and brain involvement.

Mishra et al. [21-22] had reported that myelopathy was the commonest manisfestation as evidenced by abnormal sensory evoked potentials SEP (80%) and motor evoked potentials MEP (67%) and vulnerability of the proprioceptive fibres of lower limb was seen in all patients with additional proprioceptive abnormalities in upper limbs in about 25%. About 76% had only spastic paraparesis and in only 11% had pyramidal signs in upper limbs also suggesting the brunt of disease affecting thoracic portion cord initially which may extend to involve cervical portion. The posterior columns are affected initially with lateral colums later as evidenced by better recovery in patients with normal MEP. The p 100 latency of VEP had been prolonged in patients even without any of visual symptoms suggesting sub clinical demyelinative changes in visual pathway. They have reported asymmetricity in potentials obtained in spite of being a systemic metabolic disease. 47% had isolated sensory or sensory motor neuropathy which had been associated with demyelinative and

axonopathy changes.

Regarding neuropathy, Saperstein examining patients with cobalamin deficient neuropathies noted none of the patients to have evidence of demyelination in nerve conductions studies [23]. On the other hand Steiner and recently Puri have clearly highlighted the conduction parameters consistent with demyelination in patients with low Vitamin B12 levels [24-25]. The pathology depends on at what stage of the disease the patient is seen, with demyelination being the predominant feature early in the course and secondary axonal changes setting in later [26]. Also a polyneuropathy presentation can occur with predominant LMN involvement due to neuropathy which may mask the clinical feature of pyramidal/posterolateral cord involvement from becoming evident clinically [27].

In our study, tibial SEP were abnormal in 13 (86%) of the patients and VEP was abnormal in 6 patients implying clinically manifested or subclinical involvement which were consistent with previous studies. Regarding neuropathy, 86.66% had neuropathy which had axonal changes in electrophysiology. This axonal pattern is differing with previous studies who had both demyelinating and axonal picture. This could be due to the fact that the patient is seen in a later and advanced stage as suggested by menon et al.

Bone marrow had showed megaloblastic picture in all the 5 patients who had bone marrow evaluation even in the absence of evidence peripheral blood This again consistent with the previous studies and emphasises the significance of bone marrow evaluation.

Hence, in addition to identifiable heamatological abnormalities in peripheral blood or atleast in bone marrow certainly, skin manifestations like hyperpigmentation over the extremities, especially over the dorsum of the hands and feet with accentuation over the terminal phalanges and inter-phalangeal joints, associated with pigmentation of the oral mucosa is characteristic of B12 deficiency [27] should provide clue to the neurological presentation in atypical cases.

A high index of suspicion of B12 deficiency is needed in patients presenting with myelopathy, cognitive decline, or neuropathy, especially among the pure vegetarians and the elderly. The duration of symptoms is highly variable. The study of metabolites may be used when the Vit B12 values are in the lower limits of normal (200 to 300 pg/ml). A normal hemoglobin and MCV, and even a boderline or normal serum B12 level does not rule out B12 deficiency. Hence, other tests like bone marrow smear might be useful in diagnosing this condition, as it is treatable and reversible in a majority.

Conclusion

B12 deficiency to be suspected when confronted with any of the neurological manifestations even in an atypical presentation with any atypical features with pyramidal signs even without significant posterior column signs or neuropathy.

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