J-MWAN 5 (2017) 1- 6

THE FULL NEUROPSYCHIATRIC SPECTRUM OF VITAMIN B12 DEFICIENCY IN A NIGERIAN WOMAN-A CASE REPORT.

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ABSTRACT

The brain, optic nerves, cerebellum, spinal cord and peripheral nerves may be affected by Vitamin B12 deficiency(VBD). The spinal cord is often affected first and exclusively giving rise to one of the classic neurological syndromes .the chief obstacle to early diagnosis is the lack of parallelism that may exist between the hematological and neurologic signs.[1]

Prognosis depends on a number of factors but most importantly on the duration of symptoms before onset of treatment and is better when the gait disturbance has been present for less than three months.[1,2]

INTRODUCTION

Vitamin B12 deficiency (VBD) causes a wide range of hematological, gastrointestinal, psychiatric and neurological disorders[3]. Megaloblastic anemia is a common and early symptom of VBD often leading to the diagnosis, although neurological symptoms may occur in the absence of hematological abnormalities, simultaneously or in sequence .It is unclear why VBD leads to neurological disease in some and hematological disease in others[4]. Some genes have been found to protect against anemia, while others have been found to cause the dissociation between the hematological and neurological disease seen in some patients[4]

The neurological syndromes associated with VBD include myelopathy, neuropathy, neuropsychiatric abnormalities and less often, an optic nerve atrophy. The spinal cord is often affected first and exclusively, giving rise to one of the classic neurological syndromes namely subacute combined degeneration of the cord (SACDC)[1].SACDC is clinically characterized by symmetric dysaesthesia, posterior column dysfunction and spastic para or tetra paresis[3]. Although most patients respond to cobalamin therapy, residual neurological deficits persist in some patients[5]. Review of studies have shown certain prognostic factors for neurological recovery.[2].

We present a patient with concomitant extensive neurological and hematological abnormalities.

CASE REPORT:

A 48 year-old woman presented with progressive difficulty in walking and generalized body weakness and tremulousness of 6- month duration; behavioral changes and memory loss of recent onset. The difficulty in walking started as a staggering gait and progressed to the extent that she could no longer ambulate without support while tremors were present both at rest and with intention and involved all parts of her body. Memory impairment was with recent events, and she had associated emotional lability as well as visual and auditory hallucinations such that she had to be restrained.

She was pale, had a beefy-red tongue, atrophic skin changes and bilateral pedal edema. She was conscious but confused, disoriented in time and place with slow mentation and reduced speech output and an MMSE score of 8/30. She was dysarthric, had horizontal nystagmus, dysmetria, and dysdiadochokinesia .She had bilateral optic atrophy but no other cranial neuropathies. There was bilateral foot drop with spastic quadriparesis more pronounced in the lower limbs. Her average MRC muscle power was 3 in the lower limbs and 4 in the upper limbs. Her ankle jerk was absent and the plantar response was flexor. Kinaesthetic sense was impaired, and Romberg's sign was equivocal as she swayed even with her eyes open.
Her laboratory results were indicative of a megaloblastic anemia with macrocytes constituting over 80% of the total red blood cell. She had macro-ovalocytes and hypersegmented neutrophils (Figure 1). As result of ongoing sepsis she had neutrophilic leucocytosis with toxic granulations. Her Packed cell volume was 23% (at entry).Bone marrow cytology showed a hypercellular marrow fragment with severe erythroid hyperplasia and megaloblastosis (Figure 2).

Her upper and lower gastrointestinal tract endoscopy were normal as were her thyroid function tests and serum electrolytes. She had hypoproteinemia (total protein-5.6mg%), and hypoalbuminemia (serum albumin-2.5mg%), while her serum immunoglobulin quantification showed reduced IgG fraction (467, reference range1272-2713mg%). Her protein electrophoresis showed normal band separation and were normal. Diagnosis of VBD was based on the peripheral film appearance and marrow cytology.
She was treated with parenteral cyanocobalamin-1000µg on alternate days, physiotherapy, nutritional supplements and antibiotics.

After a few weeks, she made clinical improvements both hematologically and neurologically as her PCV increased to 34%, she was able to feed self, speech improved and she was beginning to sit out of bed and even communicate with us.
However, she continued to have a fever in spite of being treated with antibiotics(ceftriaxone and metronidazole).A full sepsis work up revealed a urinary tract infection(associated with continuous urethral catheterization). In our teaching hospital, E. coli is responsible for 20.3-22.2% of hospital acquired infections and by site, E.coli is responsible for 35.7-44.4% of UTI acquired in this hospital, and significant growth of Candida albicans in the blood culture. She was neither diabetic nor HIV-positive. However she had other predisposing factors viz-hypogammaglobulinemia and high dose steroid given at the referral centre while attempting to treat her unexplained anemia and gait disorder. . She was commenced on oral fluconazole at 200mg daily and ciprofloxacin but later succumbed to the sepsis syndrome.

In trying to find the cause of the megaloblastic anemia, we reassessed her, she was not on any drug that could cause macrocytosis, she was not a vegetarian, and she had no previous gastrointestinal surgeries except for an exploratory laparotomy she had at the referral centre

during the course of the illness in an attempt to rule out a gastrointestinal malignancy as the cause of the anemia. Although she was malnourished, she had no bowel symtoms suggestive of malabsorption syndrome nor abdominal tuberculosis.

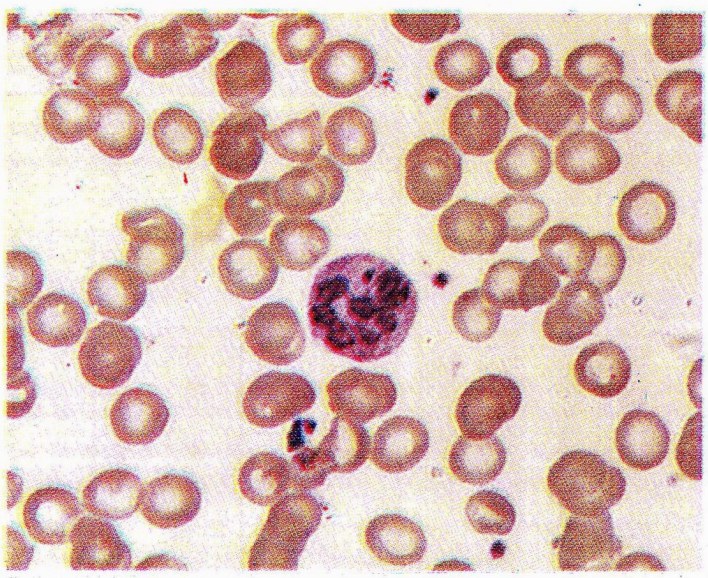

FIG. 1

Peripheral blood film showing hypersegmented neutrophil, macrocytes, macro-ovalocytes.

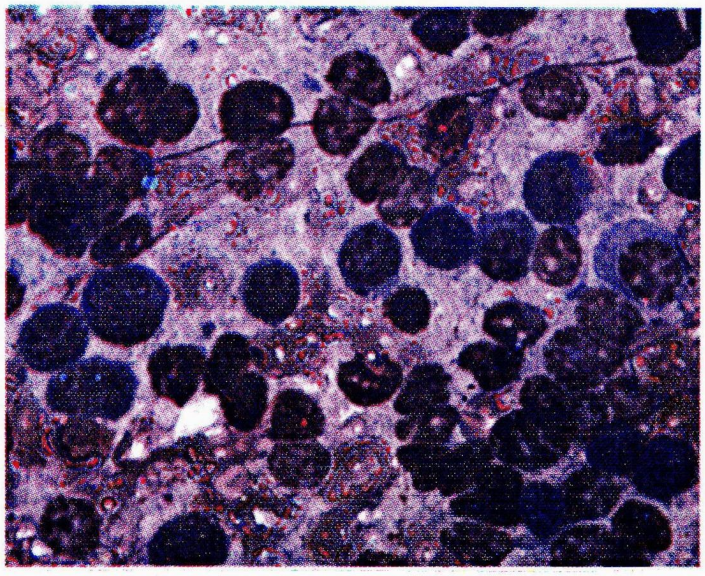

FIG.2

Bone marrow cytology showing hypercellular marrow with erythroid hyperplasia and megaloblastosis.

DISCUSSION

VBD may take decades to develop and affected patients may be asymptomatic or present with a wide spectrum of hematologic and neuropsychiatric manifestations. These can occur simultaneously, in sequence, or independently .It is unclear why VBD leads to neurological disease in some and hematological in others. Methyltetrahydrofolate reductase(MTHFR) polymorphism has been postulated to protect against anemia and homozygosity for MTHFR C677T gene could cause the dissociation between hematological and neurological disease seen in some patients.[4]

The neurologic abnormalities include paraesthesia, ataxia, and neuropsychiatric changes[5] .Our patient had progressive difficulty with ambulation, ataxia, dysarthria, and other cerebellar problems. She also had features of peripheral neuropathy, cognitive impairment and affective disorder. These can be attributed to VBD. In a study of fifty patients with VBD and megaloblastic anemia, the commonest finding was peripheral neuropathy, while SACDC was uncommon [6].However, our patient had features of this (posterior column and pyramidal tract affectation). About a quarter of the patients studied had either cognitive impairment or an affective disorder, but a third had no detectable neurological involvement[6]. Tendon reflex abnormalities have also been reported and ranged from generalized hypereflexia with clonus to absent reflexes. As demonstrated in our patient, dissociation between upper (hyperactive) and lower (decreased or absent) extremity reflexes was reported frequently and in the lower limbs, a coexistence of hyperactive knee responses and hypoactive or absent ankle jerks was also commonly observed[2]. This is due to a combination of corticospinal tract lesion and distal symmetric polyneuropathy.

Seizures have also been reported[7]. The exact mechanism of epileptogenesis is however not clear. It is likely that cerebral neurons with destroyed myelin sheaths are more susceptible to the excitatory effects of glutamate[8]. Cobalamin deficiency may share similarities with MS in this regard. Serum B12 level should be assayed in patients presenting with seizures and other known neuropsychiatric features of VBD.

Cerebellar affectation in VBD is rather uncommon and has been reported in a few instances. It was first reported by Katsaros et al in 1998[10], and later by Ahn in 2004[11]. Other unusual neurological presentations include reversible extrapyramidal syndrome[12] and cranial neuropathy other than the typical optic neuropathy in which a patient presented with hoarseness of voice due to affectation of the vagus nerve[11]..

The mechanism for neurological effects in cobalamin deficiency is not fully elucidated. Impaired methionine synthesis may lead to depletion of s-adenosylmethionine which is required for the synthesis of myelin phospholipids.[4] The second hypothesis is that a deficit of succinyl-coA leads to the generation of odd-chained fatty acids which may get incorporated into the myelin and cause the neurological syndrome of VBD[4].
Fever is an unusual finding in VBD unless it is accompanied by another disease[13]. Her fever was due to bacterial UTI and candidaemia.

In the work up for megaloblastic anemia, we suspected pernicious anemia (autoimmunity), but her thyroid function tests were normal though this is not an invariable association as it has been found to follow pernicious anaemia by several years[14].No biopsy was taken at gastroscopy and the gross appearance at exploratory laparotomy were not remarkable before being referred to us. Some cases of neurological manifestations of VBD were triggered by

exposure to nitric oxide at surgery but in this case, these preceded the surgery she had. The possibility of an infectious cause was also considered as VBD has been reported following ileal tuberculosis[15]She succumbed before other investigations could be done (Schilling's test, antibodies to parietal cells, serum gastrin level and MRI of the brain and spinal cord). Nevertheless, studies have shown that in some patients, no identifiable risk factor was found[2]. The chief obstacle to early diagnosis is the lack of parallelism that may exist between the hematologic and neurologic sign[1] and as seen in our patient, she presented with the neurological features several months before the hematological manifestations. Prognosis depends on the duration of symptoms before the onset of treatment and is better when the gait disturbance has been on for less than three months[1].Absence of a sensory level, Romberg's sign, Babinski sign and spinal cord atrophy on MRI are indicators of good recovery as they depict less severe cord injury. So also is the MRI finding of involvement of less than seven segments at diagnosis, cord oedema and/ or contrast enhancement. Other predictors of good outcome include male gender, absence of anemia, and presence of Lhermitte's sign(.Lhermitte's sign was not present in our patient, she had bilateral optic atrophy).An age less than fifty years is said to be a good prognostic feature[16]. In our patient, the gait disturbance had gone on for almost a year before she presented, age was in her favour but her gender,, the presence of anemia and absence of Lhermitte's sign were not. Nevertheless, she responded to B12 therapy only to succumb to the other co-morbidities.

The full spectrum of VBD was seen in our patient who presented first to the hematologist on account of an unexplained anemia. VBD should be considered in patients presenting in this manner or those with psychiatric manifestations that are refractory to conventional medications.

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