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Case Report

A case of carbamazepine-induced vitamin B_{12} deficiency and neuropathy

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ABSTRACT

Drug induced Neuropathy is seen commonly in patients undergoing treatment with drugs like phenytoin, dapsone, isoniazid etc. Carbamazepine is a drug used in the treatment in the treatment of focal seizure, generalized tonic - clonic seizure and trigeminal neuralgia. It is presented a case of carbamazepine induced vitamin B_{12} deficiency and neuropathy. A 21 year old male presented to our hospital with complaints of history of slipping of footwear while walking, numbness, impairment of balance and unsteadiness of gait in both lower limbs. Detailed history revealed the patient was on treatment with carbamazepine for tonic - clonic seizure for three months. He is non- smoker, non -alcoholic, not on treatment with other drugs and there is no family history of diabetes mellitus/ sensory neuropathy. On examination power was normal on both lower limbs, vibration sensation was decreased in both lower limbs, sensation was reduced, joint position was affected in bilateral toe and ankle reflex was absent. Vitamin B_{12} level was found to be 83pg/ml. The patient was discontinued from carbamazepine and started on vitamin B_{12} therapy and the symptoms subsides slowly. Causality assessment done by WHO- UMC probability method and Naranjo Adverse Drug Reactions Probability Scale showed "Probable" association.

Keywords: Adverse drug reaction, Drug safety, Epilepsy, Neurology

INTRODUCTION

Drug induced peripheral neuropathy (DIPN) is defined as damage to nerves of the peripheral nervous system caused by a chemical substance used in the treatment, cure, prevention or diagnosis of a disease.[1] The incidence of drug induced neuropathy is very less as it holds for less than 4% of all cases referred with neuropathy.[2] It is commonly seen in patients taking drugs like phenytoin, metronidazole, quinolones, isoniazid, statins, amiodarone and chemotherapeutic agents like oxaliplatin, vincristine.[3] The knowledge of drug induced neuropathy is more important because most of the time it is reversible on cessation of treatment with the particular drug. Carbamazepine is a tricyclic compound used in the treatment of tonic - clonic and partial seizure. It is also used in the treatment of trigeminal neuralgia and bipolar disorder. It acts by inhibiting voltage gated sodium channel thereby preventing repetitive and sustained firing of action potential. The adverse effects associated with treatment of carbamazepine are nausea, vomiting, diplopia, ataxia, blood dyscrasias like aplastic anaemia and agranulocytosis, transient elevation of transaminases, hypersensitivity reactions like Steven Johnson syndrome and hyponatremia and water intoxication in elderly.[4,5] In this article we have discussed a case of carbamazepine induced vitamin B_{12} deficiency and peripheral neuropathy.

CASE REPORT

A 21 year old male student presented with history of slipping of footwear while walking, numbness, impairment of balance and unsteadiness of gait in both lower limbs. On enquiry, authors came to know that he was started on treatment with tablet carbamazepine 200mg once daily following a single episode of generalized tonic clonic seizures two and half months earlier. He was taking carbamazepine regularly as prescribed when he started to develop the mentioned symptoms. He was a healthy-looking adult with BMI of 23 and on normal diet which included non-vegetarian food. On examination power was normal on both lower limbs, vibration sensation was decreased in both lower limbs, sensation was reduced, joint position was affected in bilateral toe and ankle reflex was absent. The patient gave no history of alcohol intake, cigarette smoking, no family history of diabetes mellitus / sensory neuropathy or any other drug intake during that period.

On investigation, tests for Human Immunodeficiency Virus and Hepatitis C turned out to be negative. Peripheral blood smear showed macrocytic normochromic red cells, White blood cells showed normal count with hyper-segmented neutrophils. Random blood glucose level was 115mg/dl. Renal and liver function tests turned out to be normal. EEG and CT scan was found to be normal. Vitamin B_{12} level was found to be 83pg/ml (Normal: 200-900pg/ml).[6]

Table 1: Naranjo scoring for causality analysis.

Naranjo Adverse Drug Reaction Probability Scale					
S.no.	**Questions**	**Yes**	**No**	**Don't know**	**Score**
1.	Are there previous conclusive reports on this reaction?	+1	0	0	+1
2.	Did the adverse event appear after the suspected drug was administered?	+2	-1	0	+2
3	Did the adverse reaction improve when the drug was discontinued, or a specific antagonist was administered?	+1	0	0	+1
4	Did the adverse event reappear when the drug was re-administered?	+2	-1	0	0
5	Are there alternative causes (other than the drug) that could on their own have caused the reaction?	-1	+2	0	+2
6	Did the reaction reappear when a placebo was given?	-1	+1	0	0
7	Was the drug detected in blood (or other fluids) in concentrations known to be toxic?	+1	0	0	0
8	Was the reaction more severe when the dose was increased or less severe when the dose was decreased?	+1	0	0	0
9	Did the patient have a similar reaction to the same or similar drugs in any previous exposure??	+1	0	0	0
10	Was the adverse event confirmed by any objective evidence	+1	0	0	+1
	Total score				7

≥9 = Definite 5-8 = probable 1-4 = possible 0 = Doubtful

The patient was discontinued from carbamazepine and started on Injection Vitamin B_{12} 1000microgram once a week along with tablet folate 5mg once a day. After one month of treatment, there was reduction in the neurological symptoms experienced by the patient. Causality analysis for the adverse drug reaction using Naranjo revealed the score as 'probable'.

DISCUSSION

Carbamazepine is an antiepileptic drug used in treatment of epilepsy. The common adverse effects of carbamazepine include sedation, dizziness, diplopia, ataxia and hypersensitivity reaction. The mechanism of carbamazepine induced Vitamin B_{12} deficiency and neuropathy is poorly understood and still remains unclear. There were a few studies which have reported a decrease in level of B_{12} with carbamazepine but none of these have mentioned about neurological symptoms.[7-9] However two studies did not find a reduction in B_{12} levels.[10,11] Many of these studies were done to check the effect of long term antiepileptic therapy on cardiovascular risk due to elevated homocysteine levels as a result of vitamin B_6, B_{12}, folic acid deficiencies.

So, there is still conflict of results between the carbamazepine therapy and reduction in vitamin B_{12} levels. Authors couldn't find out any previous case report on carbamazepine induced Vitamin B_{12} deficiency to our best knowledge. However a case of carbamazepine induced optic neuropathy has been reported.[12] Considering there is no other evidence of concomitant disease/ any

other drug intake or family history and assessment of the WHO probability method and Naranjo Adverse Drug Reactions Probability Scale showed "Probable" association respectively.[13,14]

Table 2: Study related to carbamazepine therapy and vitamin B_{12} deficiency.

S. no.	Title of the study	Sample size	Drugs and intervention studied	carbamazepine and B_{12} related findings	Reference
1	Effects of valproate and carbamazepine on serum levels of homocysteine, vitamin B_{12}, and folic acid	95	valproate (n=30), carbamazepine (n=36) and control (n=29) and serum levels of homocysteine, vitamin B_{12}, and folic acid	In carbamazepine group, vitamin B_{12} levels were significantly lower than the control group	7
2	The effect of antiepileptic drugs on Vitamin B_{12} metabolism	68	Carbamazepine (n=26), oxcarbazepine (n=15), valporate (n=4) and vitamin B_{12} level	75% of the patients who took carbamazepine had low serum vitamin B_{12} level	8
3	Serum level of Homocysteine, folate and Vitamin-B_{12} in epileptic patients under carbamazepine and sodium valproate treatment: a systematic review and meta-analysis	10	Carbamazepine and Sodium Valproate and Serum Level of Homocysteine, Folate and Vitamin B_{12}	Carbamazepine therapy was significantly correlated with decreased levels of vitamin B_{12} and folic acid levels	9
4	Effect of carbamazepine therapy on homocysteine, vitamin B_{12} and folic acid levels in children with epilepsy	51	Carbamazepine therapy andhomocysteine, vitamin B_{12} and folic acid level	No significant change in vitamin B_{12} levels after 6 months of carbamazepine therapy	10
5	Effects of common anti-epileptic drug monotherapy on serum levels of homocysteine, vitamin B_{12}, folic acid and vitamin B_6	75	Phenytoin (n=16), carbamazepine (n=19), or valproic acid (n=22) and no anti-epileptic drug (n=18) and homocysteine, vitamin B_{12}, folic acid and vitamin B_6 levels	No difference was found in vitamin B_{12} level in anti-epileptic drug subgroup compared to the controls on uni and multivariate analyses	11

CONCLUSION

There is no certain evidence that carbamazepine will cause Vitamin B_{12} deficiency as adverse effect which is supported by inconclusive results in previous studies. So future studies should be directed to find out association of carbamazepine therapy and vitamin B_{12} level.

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