Valproate induced Parkinsonism

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Abstracts: Drug induced Parkinsonism is common with neuroleptics drugs, antiemetic drugs but it is uncommon with antiepileptic drug such as Valproate (VAL). Neurological adverse effects of VAL are ataxia, tremor, sedation, lethargy, confusion, and more rarely encephalopathy and coma, have rarely been reported. Very rare cases of VAL induced Parkinsonism features associated with cerebral atrophy have been reported. The mechanism of these is currently unknown, but several hypotheses have been proposed. Possible mechanism can be, in vitro VAL can stimulate the activity of the GABA and Glutamate which can lead to Parkinsonism feature. Hence we reported a case of Parkinsonism developed after 6months of VAL treatment and also recovered after withdrawal of VAL. [Patel S Natl J Integr Res Med, 2018; 9(6):72-74]

Key Words: Secondary Parkinsonism, Valproate, Adverse drug reaction, Causality Assessment, Preventable.

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Introduction: Secondary Parkinsonism can occur because of stroke, tumor, infection, or exposure to toxins such as carbon monoxide or manganese and drugs. Symptomatology in this condition may differ from classical symptoms of Parkinson's disease (PD) .most of the times, it is purely clinical diagnosis and confirmation is done by reversal of symptoms after discontinuation of suspected drug. In drug induced Parkinsonism most common drugs are Dopamine-blocking agents such as the neuroleptics, Prochloperazine, Metoclopramide, Calcium channel blockers.[1] But Valproate (VAL) induce Parkinsonism is rare and unique and it is underreported also. The prevalence of the same is around 6%.[2] Hence we reported a case of Parkinsonism developed after VAL treatment and also recovered after withdrawal of VAL.

Clinical Case History: A 58 years old patient came to emergency department with c/o slowness of all daily activities, imbalance while walking and occasionally fall since 2 months. It was associated with inability to urinate and constipation. But patient had no resting tremors and rigidity. There were no History of visual hallucination, irrelevant talking and behavioral abnormalities.

Past History: Patient was k/c/o Hypertension and Diabetes Mellitus-2 since 11 years. 7 years ago he had head injury with hemorrhagic contusion in Right fronto-perital region with seizures. And for that he was on Tab. VAL (250mg) BD and Tab.Clobazam (10mg) BD.

Examination, Diagnosis & Treatment: On CNS Examination MMSE(Mini Mental State Examination)- 28/30, Power-5/5 in all 4 limbs, Plantar reflex – absent, Deep Tendon Reflex- +1/+1, - Joint Position Sense- Impaired and MRI suggesting cerebral atrophic changes. All other relevant examinations such as Motor function, Cranial Nerve, Tone, Sensory examinations, cerebellum are normal. Neurophysician suspected that it was drug (VAL) induced Parkinson's disease (PD).Other secondary causes of PD were also ruled out.[See Table:1] So they discontinued Tab. VAL (250mg) BD and patient was treated with Tab. Ropinirole (0.5mg) BD, Tab. Telmisartan (40mg) BD, Tab.Voglibose (0.3mg) BD, Tab.Clobazam (10mg) BD for 9 days. Eventually patient recovered and was discharged

Parkinsonism features were suggestive of VAL. Since patient showed steady state recovery after drug withdrawal. The case was reported via vigiflow to the National coordinating center for ADR monitoring with reference ID No. is 2017-59684. According to WHO-UMC causality assessment criteria for adverse drug reaction (ADR) causality is Probable/Likely whereas preventability according to Schumock and Thronton's ADR Preventability scale is preventable.

Discussion: Neurological side effects of valproate are well documented and many times they mimic PD, but these are very rarely seen and reported. Neurological adverse effects of VAL are ataxia, tremor, sedation, lethargy, confusion, and more rarely encephalopathy and coma, have rarely been reported. It is very difficult to differentiate them with clinical PD. Our patient has developed

these side effects after almost 7 years of use, that has progressed our period of 2 months to presentation symptoms. Although these are often associated with either starting dose is too high increasing doses too rapidly, or use with other antiepileptics. But in our case the dose was neither high nor it was suddenly increased. (500mg/day).[3] these type of cases are reported in past.[4] Very rare cases of extrapyramidal symptoms or Parkinsonism features associated with cerebral atrophy have been reported that was noticed in our patient also.

Adverse effects of VAL mimics the features like Parkinsonism like Hyperammonaemia. In such cases one should put the differential diagnosis of VAL induced Hyperammonaemia and VAL induced Parkinson's disease by S. Ammonia level. Hyperammonaemia usually occurs as an idiosyncratic response to VAL, in cases with normal liver function (normal liver enzymes and bilirubin) and normal doses and serum levels of VAL. Increase in serum ammonia is due to several mechanisms, the most important one being the inhibition of carbamoylphosphate synthetase-1, the enzyme that begins the urea cycle. Underlying urea cycle enzyme deficiency may predispose to VAL-induced Hyperammonaemia, which leads to an increase in the glutamine level in the brain, thereby producing astrocyte swelling, cerebral edema and neurotoxicity.[4] In our case patient's S.Amonnia level was normal suggesting that the case was of Parkinsonism and the other causes for secondary parkinsonism are also ruled out by investigations. And clinically symptoms of Parkinsonism were improving after withdrawal of VAL, so we can conclude that the clinical symptoms of Parkinsonism were because of VAL.
One possible mechanism can be, in vitro VAL can stimulate the activity of the GABA synthetic enzyme, glutamic acid decarboxylase, and inhibit GABA degradative enzymes.[5] Which leads to increased activity of indirect pathway in basal ganglia and neurons of substantia nigra pars raticulata and globuspellidusinterna become more active. This leads to increased inhibition of the thalamus and reduced excitatory input to the cortex.[6]

The lack of apparent susceptibility related to age and to VPA dosage, the rapid recovery from the extrapyramidal reaction, and the prevalence of negative signs such as bradykinesia and bradyphrenia can be considered the main clinical findings of this disease process. Pathophysiologic mechanisms of this rare "toxic" reaction remain unknown, although a transient imbalance between functionally reciprocal subgroups of GABA pathways leading to remediable dopamine inhibition might be hypothesized.[7]

Table: 1 Investigations

Tests	Results
Hb	11.2 mg/dl
TLC	7510 /cells/mm^3
Platelets	3.55/cc
CRP	Negative
RBS	148mg/dl
Creatinine	0.67mg/dl
Blood Urea	10mg/dl
Blood Bilirubin	0.2mg/dl
SGPT	13U/L
S.ALT	63U/L
$S.Na^+$	138mmol/L
$S.K^+$	4.3mmol/L
HbA_1C	8.2%
S.Vit B_{12}	1834pg/mL
TSH	2.25U/ml
HIV,HBSAg,HCV	Negative
Anti TPO,TG	Negative
S. Ammonia	45mcg/dL
CXR(PA), USG Abdo.& Pelvis	Normal
Cranioembryonic Antigen (CEA), Alpha Feto Protein (AFP), Prostate Specific Antigen (PSA),	Normal
ECG	Normal
2D ECHO	EF-61%, LVsize& Systolic LV function-Normal
ENT Examination	Normal
Ophthalmic Examination	Grade-1 Hypertensive Retinopathy
NCV	Decreased SNAP in both Upper limb, Lower limb
MRI Brain	Cerebral atrophy
Carotid Doppler	40% narrowing of Left. CCA, 30-40% narrowing of Rt.CCA

Several cases of Parkinsonism syndromes have been reported in the literature, but usually in children or young adults and these symptoms had an insidious and progressive onset. Clinical features can mimic Parkinson's disease and may

be confusing, especially when they occur in older patients but in our case the patient was adult so the confusion was avoided. The mechanism of these disorders is currently unknown, but several hypotheses have been proposed. Despite the good safety of VPA therapy for several years, a drug-induced mechanism of Parkinsonism or cognitive impairment must be considered in all patients treated with VPA, as discontinuation of the drug can induce significant improvement of the patient's neurological and mental status.[8] In our case also patient had clinical improvement to almost normal neurological level after discontinuation of VAL.

Conclusion: As per this case report Valproate is also another culprit for the Parkinson's disease. Although proper mechanism of this occurrence is yet to be elucidated patients on long term Valproate therapy can experience Parkinsonism features however this occurrence was reversible on discontinuation of the drug. Watchful prescribing will prevent morbidity associated with it

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