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Original Article

Internal Medicine Section

Clinical Profile of Patients on Antiepileptic Drugs Experiencing Ataxia as an Adverse Drug Reaction: A Longitudinal Observational Study

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ABSTRACT

Introduction: Ataxia is one the common adverse drug effect caused by Antiepileptic Drugs (AEDs). It can result from either single therapeutic dose of a particular drug, prolonged use of same drug or acute poisoning.

Aim: To determine the disease burden and clinical profile of patients who are on AEDs and develop ataxia.

Materials and Methods: This was a longitudinal observational study, carried out at Mahatma Gandhi Medical College and Research Institute, Puducherry, from January 2016 to March 2022. The clinical characteristics of patients who presented with ataxia on AEDs and with no previous history of ataxia were documented. Based on the time of onset of ataxia patients were divided into three groups: Group A- Ataxia developed within 24 hours of onset of drug intake; Group B- Ataxia developed within 24 to 72 hours from prescription of drug; Group C- Ataxia developed after 72 hours from the time of drug administration. Patients were further classified into those having sensory ataxia and cerebellar ataxia. Based on the time of clinical resolution patients were classified into three subgroups: Group 1- Clinical resolution within 72 hours; Group 2- Clinical resolution in 72 to 144 hours; and Group 3- Clinical resolution after 144 hours. Data was collected systematically and results were statistically analysed using Microsoft Excel spreadsheet software program.

Results: Out of the total number of epileptic patients (1600) on AEDs, 34 patients developed ataxia. Of these 34 patients, 15 (44.11%) were on Phenytoin, 12 (35.29%) were on Carbamazepine, 3 (8.82%) were on Gabapentin, 2 (5.88%) were on Zonisamide, and 2 (5.88%) were on Lamotrigine. Dose of these drugs were modified within one day, after one and three weeks and after one month in 9 (26.47%), 7 (20.58%), 12 (35.29%), and 4 (11.76%) patients, respectively. Two patients had presented with acute poisoning. Half, 50% (n=17) patients had symptoms of sensory ataxia and remaining half had symptoms of cerebellar ataxia.

Conclusion: Ataxia secondary to AEDs is seen with both the older and newer drugs. Awareness of the possibility of AEDs induced ataxia can help in early diagnosis and its management.

Keywords: Adverse effect, Carbamazepine, Phenytoin

INTRODUCTION

Epilepsy is one of the major neurological disorders with a prevalence ranging from 2.2 and 10.4 per 1,000 population across different parts of India [1]. Ataxia is a common symptom in a variety of conditions associated with epilepsy. There is a complex relationship between epilepsy and cerebellar dysfunction resulting in ataxia. In some conditions both ataxia and epileptic seizures coexist. In most of such cases there is presumably a common aetiology such as metabolic, genetic, or other central nervous system dysfunction [2]. Several AEDs are used to control the seizures which have ataxia as common adverse drug effect [2]. It can be due to either single therapeutic dose of particular drug, prolonged use of same drug or acute poisoning.

Cerebellar ataxia can be induced by a large number of therapeutic drugs. The cerebellum is prone to adverse effects of drugs such as antiepileptics, benzodiazepines, antineoplastics, lithium salts, and calcineurin inhibitors affecting in particular the cerebellar cortex and Purkinje neurons [3]. Dutch registry reported drug-induced ataxia with 93 individual drugs. The number needed to harm was below 10 for benzodiazepines and antineoplastics. Generally, ataxia is reversible, but persistent symptoms can remain for drug like lithium and certain antineoplastics [4]. In patients on epileptic drugs the truncal ataxia was associated with longer duration of use of drug, receiving more number of drugs, and had higher serum levels drug levels. Ataxic patients also have relatively lower serum folate levels which could be responsible for ataxia [5]. The use of phenytoin and benzodiazepines is associated with higher frequency of ataxia [4]. Higher levels of phenytoin are harmful to the cerebellar cortex and Purkinje cells which can result in irreversible damage and/or cerebellar atrophy. Long duration use of phenytoin is a risk factor for ataxia and lead to clinical impairment, if untreated [6]. Interestingly, gabapentin is used to treat ataxia due its Gamma-aminobutyric Acid (GABA) GABAergic properties but gabapentin itself can cause ataxia [7]. Both their effects could be attributed to the interference with cerebellar GABAergic neurons, particularly Purkinje cells, the output neurons of the cerebellar cortex. During treatment with valproate treatment tremor are more common as adverse event and ataxia could be secondary to hyperammonemic encephalopathy [8].

The exact incidence of ataxia related to antiepileptic is unknown in Indian patients. Apart from ataxia, patient may experience extra pyramidal symptoms, behaviour changes, respiratory depression etc. Hence, this study was carried to study the prevalence of AEDs-induced ataxia, identify the drugs that cause ataxia, and determine the patient clinical profile.

MATERIALS AND METHODS

The longitudinal observational study, was carried out at Mahatma Gandhi Medical College and Research Institute, Puducherry, India, from January 2016 to March 2021. The study protocol was approved by the Institutional Ethics Committee (MGM/IHEC/85/2016). Written informed consent was taken from all the patients willing to participate in the study.

Inclusion criteria: Patients with seizure disorder on newly initiated AEDs attending the outpatient department within the study duration with complaints of ataxia, with no history of ataxia, and who developed ataxia during the course of other diseases were enrolled in the study.

Exclusion criteria: Patients with history and family history of ataxia, history of alcohol intake were excluded from the study. Patient with history of fever along with ataxia, history of psychological disorders, migraine, childhood ataxia, ataxia due to substance abuse, idiopathic ataxia were excluded from the study.

Study Procedure

All patients were subjected to Computed Tomography (CT)/ Magnetic Resonance Imaging (MRI) Brain and those with normal cerebellar findings were included in the study. Based on the time of onset of ataxia patients were divided into three groups: Group A- ataxia developed within 24 hours of onset of drug intake; Group B- ataxia developed within 24 to 72 hours from prescription of drug; Group C- ataxia developed after 72 hours from the time of drug administration. Patients were further classified into those having sensory ataxia and cerebellar ataxia, based on their symptoms (cerebellar ataxia- dyssynergia, dysmetria, dysdiadachokinesia, hypotonia, ataxic gait, swaying to one side; sensory ataxia- proprioception, Rhomberg's positive, ataxic gait, loss of tendon reflexes, peripheral neuropathy). Patients with ataxic gait, being a common symptom of both cerebellar and sensory ataxia, were classified as mixed ataxia. Patients with gait abnormality as an isolated symptom or ataxic gait with cerebellar findings were allocated to cerebellar ataxia group and those with ataxic gait with additional sensory ataxia were allocated to sensory ataxia group.

The time of clinical resolution of ataxia was noted and patients were classified into three sub-groups: Group 1- Clinical resolution within 72 hours; Group 2- Clinical resolution in 72 to 144 hours; and Group 3- Clinical resolution after 144 hours.

The detailed histories of drug intake, last drug modifications were noted. The types of ataxia based upon clinical symptoms were studied. The times of onset of ataxia, time to resolve ataxia were also noted in this study. The AEDs plasma levels were also documented for these patients who had undergone the antiepileptic blood level estimations. The dose titration for patients were also documented.

STATISTICAL ANALYSIS

All data was collected systematically and results were statistically analysed. Statistical analysis was carried out using Microsoft Excel spreadsheet software program. Continuous variables were expressed as means and standard deviation while categorical variables were expressed as percentages. Charts were used in presenting percentages and proportions.

RESULTS

Out 1600 patients with seizures and on AEDs, 34 developed ataxia. Among these 34 patients 15 were males and 19 females. Of 34, 15 (44.11%) were on Phenytoin, 12 (35.29%) on Carbamazepine, 3 (8.82%) on Gabapentin, 2 (5.88%) on Zonisamide and 2 (5.88%) on Lamotrigine. Dose of these drugs were modified within one day, after one and three weeks and after one month in 9 (26.47%), 7 (20.58%), 12 (35.29%), and 4 (11.76%) patients, respectively. Two patients had presented with acute poisoning. Fifty percent patients had symptoms of sensory and remaining half had symptoms of cerebellar ataxia [Table/Fig-1,2].

The drug dose was increased in 11 (32.35%) patients. The drugs levels were high and within normal range in 13 (38.23%) and 6 (17.64%), respectively, whereas it was not measured in 15 (44.11%) patients. The duration of onset of ataxia with different AEDs after post drug administration has been depicted in [Table/Fig-3]. Ataxia developing after 72 hours from the time of drug administration was seen more commonly and the least within 24 hours. Moreover, ataxia was observed more frequently in female patients. The time of clinical resolution of ataxia has been summarised in [Table/Fig-4]. Most patients had clinical resolution of ataxia after 144 hour and least number of patients recovered within 72 hours of onset.

Signs/ Symptoms	Phenytoin (n=15)	Carbam-azepine (n=12)	Gabapentin (n=3)	Zonisamide (n=2)	Lamotrigine (n=2)
Proprioception	3	2	2	0	0
Rhomberg's +ve	3	2	1	2	1
Ataxic gait	8	10	2	0	0
Loss of tendon reflexes	2	0	0	0	0
Peripheral neuropathy	0	0	0	0	0

[Table/Fig-1]: Number of patients on different Antiepileptic Drugs (AEDs) with different symptoms of sensory ataxia.
Note: Some patients developed more than one signs/symptoms

Signs/Symptoms	Phenytoin (n=15)	Carbam-azepine (n=12)	Gabapentin (n=3)	Zonisamide (n=2)	Lamotrigine (n=2)
Dyssynergia/ Dysmetria/ Dysdiadachokinesia	6	11	0	0	1
Hypotonia	0	0	0	0	0
Nystagmus	1	0	0	0	0
Ataxic gait	8	10	2	0	0
Swaying to one side	1	0	0	0	0

[Table/Fig-2]: Number of patients on different Antiepileptic Drugs (AEDs) with different symptoms of cerebellar ataxia.
Note: Some patients developed more than one signs/symptoms

Antiepileptic Drugs (AEDs)	Group A (ataxia developing within 24 hours of onset of drug intake)		Group B (ataxia developing within 24 to 72 hours from prescription of drug)		Group C (ataxia developing after 72 hours from the time of drug administration)	
	Male	Female	Male	Female	Male	Female
Phenytoin	-	-	1	1	6	7
Carbamazepine	2	1	2	1	1	5
Zonisamide	-	-	1	-	-	1
Gabapentin	-	-	-	-	1	2
Lamotrigine	-	-	-	-	1	1

[Table/Fig-3]: Duration of onset of ataxia with different Antiepileptic Drugs (AEDs) post drug administration.

Antiepileptic Drugs (AEDs)	Group 1 (Clinical resolution within 72 hours)		Group 2 (Clinical resolution in 72 to 144 hours)		Group 3 (Clinical resolution after 144 hours)	
	Male	Female	Male	Female	Male	Female
Phenytoin	-	-	4	2	2	5
Carbamazepine	-	-	-	2	5	6
Zonisamide	1	1	-	-	-	1
Gabapentin	1	2	-	-	-	-
Lamotrigine	-	-	-	-	1	1

[Table/Fig-4]: Time to clinical resolution of ataxia in different antiepileptic groups.

DISCUSSION

Epilepsy is a common neurological disorder associated with co-morbid adverse conditions secondary due to disease itself or adverse effects of AEDs. Evidence from experimental, cross-sectional and prospective studies suggest adverse effect of some AEDs on the auditory and vestibular systems which maybe reversible or irreversible [9-12]. Identification and monitoring of patients at high risk for developing audio-vestibular can help in taking preventive and therapeutic step in AEDs induced ataxia [13].

Earlier, ataxia was described as manifestation of various uncoordinated characteristics of different diseases, such as gait, movement, heartbeat, etc. But at present, it is more specifically used to describe the symptoms of motor mismatching synchronisation

and balance disorder secondary to the brain, cerebellum, deep sensation (proprioception), vestibular and other systems damage [14]. In this study, half the patients had symptoms of sensory ataxia while had symptoms of cerebellar ataxia. Sensory ataxia is usually manifested due to impairment of somatosensory nerve, which causes the interruption of sensory feedback signals resulting in the body incoordination [15]. Study showed that patients on different AEDs experience different symptoms of sensory ataxia. Proprioception and ataxic gait was observed in patients on phenytoin carbamazepine and gabapentine. Rhomberg's +ve sign was seen with all five AEDs in this study. Loss of tendon reflexes was seen with only phenytoin. In none of the groups peripheral neuropathy was observed. There reports of risk of peripheral neuropathy due to AEDs like phenytoin, barbiturate and carbamazepine [16]. A clinical study evaluated peripheral nervous system damage using the thermal threshold test at ankle and wrist in epileptic patients and controls. The epileptics had higher threshold consistent with a toxic effect of both drugs on fine peripheral nerve fibers [17]. The exact mechanism is not clear but the relationship between folate deficiency has been hypothesised [16].

The risk that AEDs may cause damage to the peripheral nervous system led us to investigate 12 patients on carbamazepine and 12 patients on phenobarbital with the thermal threshold test. The heat and cold thresholds were measured at the end, compared with those in 30 healthy subjects, they proved to be significantly higher. When the two groups of epileptics were compared separately with the controls, their thresholds were always higher. These findings are consistent with a toxic effect of both drugs on fine peripheral nerve fibers. Cerebellar ataxia is a frequent presentation in neurological clinical practice. It may present as chronic and slowly-progressive cerebellar degenerations to the acute cerebellar lesions because of infarction, oedema and haemorrhage. It is characterised by loss of body muscle coordination caused by cerebellar disease. Trunk ataxia often suggests of cerebellar vermis lesions while limb ataxia suggests cerebellar hemisphere lesions [18]. In the present study, all patients with cerebellar ataxia on different AEDs showed dyssynergia/dysmetriad/dysdiadachokinesia, except gabapentine and zonisamide. Ataxic gait was observed with phenytoin, carbamazepine and gabapentine. Shanmugarajah PD et al., found that nystagmus and swaying to one side was only seen with phenytoin. Gait, stance and heel-shin slide were the predominant features of cerebellar dysfunction with phenytoin [19].

In this study, the duration of onset of ataxia was 72 hours from the time of drug administration in the most of the AEDs. Ataxia developing within 24 to 72 hours from time drug administration was seen with phenytoin, whereas, ataxia developing within 24 hours of onset of drug intake was seen with only with carbamazepine. The time to clinical resolution of ataxia in the entire population was more than 144 hours post onset of ataxia. However, with carbamazepine the clinical resolution of ataxia ranged from less than 72 hours to more than 144 hours.

Phenytoin is one of the most effective, economical and frequently prescribed AEDs. Its use is decreasing because of availability of new AEDs with better safety profile in terms of long-term adverse effects such as abnormal bone mineral metabolism and potentially irreversible cerebellar ataxia. In the present study, almost 44.1% patients experienced ataxia as an adverse effect, similar to those reported by Shanmugarajah PD et al., [19]. Patients with high levels of phenytoin may experience drowsiness, nystagmus, dysarthria, tremor, ataxia and cognitive difficulties. Long-term use of phenytoin is associated with cerebellar degeneration [20]. Experimental data is not conclusive and suggest that cerebellar degeneration is because of convulsion mediated cell loss rather than toxicity of phenytoin. However, there is evidence suggesting toxic effects of phenytoin on Purkinje cells in-vitro [9,10]. A study, characterising the relationship between phenytoin-induced ataxia and its concentration in rats, showed that phenytoin in Cerebrospinal Fluid (CSF) and brain, unlike serum phenytoin, equilibrates rapidly with site(s) of phenytoin neurotoxicity [21]. There exists a relationship between phenytoin concentration and toxic symptoms. In most patients, plasma concentration higher than 30 µg/mL induces ataxia. Ataxia secondary due to phenytoin involves station (standing position) and gait rather than fine motor movements. This study also observed cerebellar ataxia with phenytoin therapy as reported in earlier publications [22,23].

Carbamazepine is another commonly used drug to control seizures. Its common adverse effects are ataxia, sleep disorders, anorexia, nausea, vomiting, polydipsia, irritability and diplopia. It induces dose-dependent ataxic effects and disorientation at levels of 11-15 mg/L [24]. Generally, patients present with dizziness and experience a gaze-evoked nystagmus, action tremor, and ataxia of stance/gait. Impaired conscious state may mask the cerebellar deficits. Half of the patients with overdose develop cerebellar signs [12]. These signs may be related to involvement of afferents or efferents to the cerebellum. Elderly patients appear more susceptible to carbamazepine than young patients. Caution should be exercised in patients with pre-existing cerebellar atrophy as they at risk for developing cerebellar signs at lower serum levels. Structural lesions should be looked for in patient on carbamazepine treatment when they develop cerebellar signs. Its common adverse effects are ataxia, sleep disorders, anorexia, nausea, vomiting, polydipsia, irritability and diplopia [12,25]. It was observed that 12 (35.29%) patients in this study on carbamazepine developed ataxia.

Valproate is also one AED which is commonly used. Although rare, it can cause cerebellar ataxia secondary to hyperammonemic encephalopathy. Early diagnosis and quick drug withdrawal of valproate can mitigate this serious reversible complications [26]. The neurological adverse effects of Gabapentine are ataxia, fatigue, dizziness, sedation, and somnolence [27]. Gabapentin stimulates expression of δGABAA receptors and increases a tonic inhibitory conductance in neurons, which likely contributes to GABAergic effects as gabapentin caused ataxia in wild-type mice but not δ subunit null-mutant mice [28]. In the present study, 3 (8.8%) patients on gabapentin had ataxia which was in concurrence with the data quoted in the literature [2].

Out of the total number of epileptic patients (1600) on AEDs, 34 patients developed ataxia. Of these 34 patients, 15 (44.11%) were on Phenytoin, 12 (35.29%) were on Carbamazepine, 3 (8.82%) were on Gabapentin, 2 (5.88%) were on Zonisamide, and 2 (5.88%) were on Lamotrigine. Dose of these drugs were modified within one day, after one and three weeks and after one month in 9 (26.47%), 7 (20.58%), 12 (35.29%), and 4 (11.76%) patients, respectively. Two patients had presented with acute poisoning. Half, 50% (n=17) patients had symptoms of sensory ataxia and remaining half had symptoms of cerebellar ataxia. In this study, both zonisamide and lamotrigene caused ataxia in 2 (5.88%) patients which was lower than the prevalence quote in literature [2]. With paucity of data on the prevalence and incidence of cerebellar lesions due to high AEDs levels related to intoxication are still unknown in many cases. Therefore, the physician should be aware of all the AEDs that may be responsible for cerebellar deficits, as drug-induced cerebellar ataxias are common in clinical practice. Moreover, appropriate and immediate treatment measures should be taken in case of high drug levels [3].

Limitation(s)

This study had limitation because of the relatively small sample size. Several aspects of patient's characteristics were not readily accessible. Sufficient information about drug levels was unavailable as the drug concentration in the plasma was not estimated for all the patients Ataxia and dizziness are often dose-dependent adverse effects, especially with carbamazepine and phenytoin. Therefore, it was not possible to determine whether the ataxia was concentration dependent or not.

CONCLUSION(S)

Secondary ataxia due to AEDs is observed with both the older and newer drugs, more with phenytoin and carbamazepine. Generally, it is dose dependent and can occur even with normal therapeutic dose. Awareness of the possibility of AEDs induced ataxia and to differentiate it from symptoms of epileptic or other neurological disorder is critical as prompt intervention can mitigate the risk of ataxia. The onset and resolution of ataxia due to different AEDs is variable dyssynergia, dysmetria and dysdiadachokinesia are commonly observed and should be considered in the management of the adverse event.

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