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Case Series

Psychiatry/Mental Health Section

Clomipramine Induced Extrapyramidal Symptoms: A Case Series

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ABSTRACT

Extra Pyramidal Symptoms (EPS) are a group of symptoms that include dystonia, bradykinesia, tremor, akathisia, and tardive dyskinesia. They are caused by the blockage of D2 receptors in the nigro-striatal pathway and the imbalanced acetyl choline activity that results in the basal ganglia. It most likely happens when first-generation antipsychotics taken in large doses and some second-generation antipsychotics. A few tricyclic antidepressants, including amitriptyline and clomipramine, Monoamine Oxidase (MAO) inhibitors, such as phenelzine, and SSRI (fluoxetine), such as fluoxetine, may also cause EPS. Antiemetics (domperidone), antiepileptic medications like phenytoin and carbamazepine, and anti-migraine medications like sumatriptan are a few additional causes of EPS. Schizophrenia patients who have never been prescribed medication may also exhibit similar movement problems. The Tricyclic Antidepressant (TCA) clomipramine is a tertiary amine that has potent D2 blocking and serotonin and norepinephrine reuptake inhibitor characteristics. Constipation, dry mouth, nausea, dizziness, drowsiness, tachycardia, sweating, arrhythmia, and seizures at high doses are common side effects associated with clomipramine. In this case series, three patients from different age groups are presented, the first one being a 38-year-old female with a diagnosis of paranoid schizophrenia, the second one was a 26-year-old male with the Obsessive Compulsive Disorder (OCD)- washer type, and the third one was a 62-year-old female with dementia, all of whom developed signs of EPS like dystonia, bradykinesia and tremors following the introduction of clomipramine. In all the patients, the drug was stopped and the patients were cured. This case series stresses that a clinician should be cautious about the possibility of extrapyramidal side effects while using the TCA Clomipramine which is commonly known for its anticholinergic side effects.

Keywords: Acetyl choline, Dementia, Dopamine, Dystonia, Obsessive compulsive disorder, Rigidity, Tremors

INTRODUCTION

Extra Pyramidal Symptoms (EPS) are group of symptoms characterised by dystonia, bradykinesia, tremor, akathisia and tardive dyskinesia. The main mechanism of action behind EPS is blocking of D2 receptors in nigro-striatal pathway and resulting unbalanced activity of acetyl choline in basal ganglia [1]. It occurs most likely with high doses of high potency first generation antipsychotics, and with some second-generation antipsychotics [1]. EPS is rare but might also occur with some tricyclic antidepressants (amitriptyline, clomipramine), MAO inhibitors (phenelzine), SSRI [2]. Some other causes of EPS can be antiemetics (domperidone), antiepileptic drugs like phenytoin, carbamazepine and anti-migraine drugs like sumatriptan [3]. Similar movement disorders can also be present in never medicated patients of schizophrenia [4].

Clomipramine is a tertiary amine TCA with strong D2 blocking [3,5] and serotonin and norepinephrine reuptake inhibitor properties. Common adverse effects reported with clomipramine are constipation, dry mouth, nausea, vertigo, sedation, tachycardia, headache, increased perspiration, arrhythmia and seizures at high dose. Side effects due to dopamine blocking is not commonly known in case of clomipramine, rather on the contrary anticholinergic side effects are more [6].

In the following case series, three patients from different age groups are presented with a diagnosis of paranoid schizophrenia, OCD, and dementia developing dystonia, bradykinesia and tremors following introduction of clomipramine. This case series is unique in the sense that as per knowledge no other case has been reported from the eastern part of the country on this topic. Some vulnerability factors have also been explored as a part of the case series. Consent was taken from all three patients for publication of their clinical details without exposing personally identifiable information.

CASE SERIES

Case 1

A 38-year-old, divorced female, belonging to middle class family. was diagnosed with paranoid schizophrenia four months back following ICD-10 criteria. After a failed trial of olanzapine, tab Amisulpride was added and was increased up to 600 mg over six weeks with gradual tapering off olanzapine with normal prolactin level. Her delusion of persecution and delusion of reference decreased after six weeks, PANSS score was P21N18G26 to P10N6G6 within six weeks. But she kept complaining about a choking sensation in her throat with significant distress. She was referred to the ENT department, but a local oro-pharyngeal examination and laryngoscopy revealed no significant abnormality.

On a detailed mental status examination, she explained the choking sensation was ego-dystonic in nature. She tried to distract herself away from that feeling by different means without much improvement. The choking sensation was diagnosed as an obsessive symptom and clomipramine was started at a dose of 25 mg and was rapidly titrated up to 75 mg.

The patient presented in the Psychiatry emergency on the 10th day of being on Clomipramine with extra-pyramidal signs of tremors and cogwheel rigidity in both hands, drooling of saliva from the mouth.

On examination, she was oriented to time, place, person and responsive to verbal commands. Her pulse was 90/min, blood pressure 130/70 mm hg and the temperature was 98 degrees F. Neurological consultation was taken and she was advised to put on Tab Trihexyphenidyl 2 mg BD. Other general physical examinations were within normal limits.

Modified Simpson-Angus scale (SAS) score was 21/40 which was significant [7]. The patient was admitted in the in-patient department and blood investigations (total and differential counts, thyroid profile,

liver function tests, lipid profile, Na^+, K^+, urea, creatinine, creatine phosphokinase) and a CT scan of the brain were done. All of them were within normal range. Clomipramine was stopped and the patient was started on 2 mg of Trihexyphenidyl twice daily which was increased up to thrice daily after two days, along with 2 mg of Lorazepam twice daily.

Within the next three days, the EPS improved and she scored 3/20 on Modified SAS scale on day five of admission. But her choking sensation kept on increasing day by day, and this time she felt some external agent was choking her which wishes her to die. This choking sensation was diagnosed to be a somatic delusion. Tab Clozapine was started at a dose of 25 mg and was increased up to 100 mg and Amisulpride was also tapered off within next one week.The patient was discharged with 100 mg of Clozapine. In the next follow-up after two weeks, the choking sensation persisted but at a low intensity. The dose of Clozapine was increased up to 200 mg following which her choking sensation resolved within four to six weeks.

Case 2

A 26–year-old male visited with a history of repeatedly checking for the things already done, like checking if the door was locked, if the tap was closed properly, etc. Since last three years, this repeatedly checking behaviour was causing severe distress to him and persist, despite trying to resist himself from checking again and again. He was diagnosed to have obsessive-compulsive disorder (OCD) as per ICD-10 criteria. His YBOCS score was 28 which indicated moderately severe OCD. All of his blood parameters like complete blood count, liver and thyroid function test, blood sugar, CT brain, EEG were normal.

He as prescribed 80 mg Fluoxetine and 0.5 mg Clonazepam at night on SOS basis with weekly exposure and response prevention therapy (ERP).

His YBOCS score changed from 28 to 15 after three months of after his first visit. Tab clomipramine was added to augment the effect at a dose of 25 mg which was increased to 50 mg within five days. The patient presented in OPD after seven days of being on clomipramine 50 mg with coarse tremors of both hands with cogwheel rigidity, drooling of saliva and turning of his neck to right-side. He was speaking with a bit of difficulty, but had no problem in swallowing food or liquids. He scored 12/40 on SAS. Clomipramine was stopped, tab Trihexyphenidyl was added 2 mg twice daily.

On his next visit after one week, he scored 1/20 on SAS, Trihexyphenidyl was tapered over next two weeks, and Tab Fluoxetine has increased up to 100 mg as the patient had responded well to Fluoxetine earlier. The patient's YBOCS score was six in the next two months and remission was achieved.

Case 3

A 62-year-old female presented with a history of forgetfulness, difficulty in performing day to day household work, with decreased sleep since last one year. She was diabetic with good glycaemic control (HbA1c was 5.6) and was on metformin 500 mg twice daily since last three years.

She scored 22 on MMSE which revealed cognitive impairment. Her CT brain revealed mild cortical atrophy, and all other blood tests, and ECG revealed no abnormalities. A diagnosis of Alzheimer's dementia was made and she was started on 5 mg donepezil once daily and melatonin 3 mg once at bedtime.

On her follow-up, after two months, she complained of obsessive symptoms. She felt that everything around her was dirty, and she repeatedly washed her hands and feet, and even bathed several times a day. She complained that the symptoms started two years years back, but were very mild so she forgot to mention about those during her first visit. But her symptoms of repeatedly washing were currently aggravating and she has been spending more than three to four hours daily washing and cleaning.

The YBOCS score was 18. Being diagnosed with an obsessive disorder and she was started on 25 mg clomipramine once daily (she had a history of severe gastric irritation with Fluoxetine in the past) which was prescribed by a local physician as she complained of low mood sometimes. After four days, she presented with tremors in both hands with a sense of inner restlessness. It was considered as EPS (tremors with akathisia), and she was started on Propranolol 20 mg BD and clomipramine was stopped.

On her next visit after one week, the tremors and restlessness were resolved, propranolol was stopped and she was maintained on 5 mg donepezil. After two weeks a dose of fluoxetine 20 mg was started. YBOCS score was 7 from 15 within four weeks and remission was achieved after eight weeks.

DISCUSSION

Acute dystonia, tremor and other symptoms of EPS can be triggered by many offending agents, but most commonly with drugs like neuroleptics (FGA>SGA). With FGA there is a 2.3% to 60% chance of developing acute dystonia while second generation antipsychotics have a risk of 2% to 3% [8]. Though rare, antidepressants can also cause symptoms of EPS namely dystonia, and tremor, but the severity is much less than with antipsychotics. The first case of EPS due to antidepressants was reported around 1950s [3]. Baykara et al., had reported a case of anxiety disorder along with conversion disorder. They reported a risk of EPS with sertraline, a SSRI class drug [9]. Paroxetine and fluvoxamine can also increase the risk of acute dystonia in patients [10]. There is a substantial number of cases in the literature that developed extra pyramidal symptoms with the introduction of TCAs like amitriptyline, clomipramine, and amoxapine. In an article by Gill et al., on extrapyramidal symptoms associated with cyclic antidepressant treatment, akathisia was present in 26% of TCA users, 17% of cases had dystonia, and reversible dyskinesia and Neuroleptic malignant syndrome was found in 52% and 4% cases respectively [11]. Few other articles and case reports have also reported EPS caused by tricyclic drugs like amitriptyline, doxepin, imipramine [12]. SSRI increases serotonin release in the brain that in turn can reduce dopamine activity and theoretically increase the potential of EPS. Also, while combining a TCA with a potent enzyme inhibitor like Fluoxetine, Paroxetine, the chances of drug interactions between two needs special attention. The half-life of Clomipramine is approximately 17-28 hours, but if combined with a CYP2D6 inhibitor like fluoxetine or a CYP2A1 inhibitor like fluvoxamine, the concentration of Clomipramine and it's active metabolitedesmethyl-clomipramine may rise in blood and give rise to adverse effects [6,10,13].

Clomipramine has high selectivity towards serotonin receptor, hence acts as a serotonin reuptake inhibitor (SRI), But at the same time, it has significant anticholinergic effect, that can be a protective factor against EPS. It also acts as 5HT 2A antagonist. This activityhave a dopamine release property that can reduce EPS hence EPS reports with clomipramine is rarity [14]. Chithramohan et al reported a young lady with depression, who developed acute dystonia on clomipramine (75 mg) after five days of starting the drug [15]. A recent publication reported acute dystonia in a 19-year-old boy with a diagnosis of anxiety disorder, which appeared on fifth day of starting clomipramine treatment [3].

On one hand, serotonin can increase dopamine release by stimulating post synaptic 5HT2A receptor by stimulating glutamate release, while on the other hand, it can reduce dopamine release by acting on somato-dendritic receptors in prefrontal cortex stimulating GABA mediating inter-neuron. Hence, the final effect of serotonin on dopamine depends on the duration of treatment and presence of receptor profile in that area of brain [16]. Hence,

5HT2A antagonist action may affect dopamine release in both ways. Increase of midbrain dopamine release by antidepressant medications decrease dopamine release in nigrostriatal pathways. Disbalanced dopaminergic cholinergic system on one hand, and GABAergic system on other hand in nigrostriatal pathways results in development of EPS [17,18] These extrapyramidal effects are more common in elderly females and CYP2D6 inhibiting drugs and presence of D2 receptor polymorphism [13,18].

In all three of the cases, the spasms, and tremors began after a short span of time (approximately 4-5 days) after starting clomipramine and as soon as the treatment was started and clomipramine was removed, the response was quick. In case of treating EPS with oral anticholinergics, it needs to be continued for a period of a minimum of seven days to prevent further relapse of EPS [19].

In the first case, it could be considered as superadded pharmacodynamic effect on already dopamine blocked system. Though existing literature only support the potential for increase of QTc prolongation risks, and there is probably no report of increase of extrapyramidal syndrome risk with Amisulpride and clomipramine combination, in the first index case, the EPS could be considered as superadded pharmacodynamic effect ofclomipramine on already dopamine blocked system by amisulpride [20].

The third case can also be considered to be the action of clomipramine on an ageing brain, which may be already subjected to degeneration, making it more vulnerable to EPS. Donepezil, by its increased activity of acetylcholine, can increase the chance of extrapyramidal symptoms [21]. Also, donepezil may reduce the clomipramine metabolism which can increase the blood levels of clomipramine [20]. But the second index case (26-year-old) of EPS that developed after adding clomipramine, refutes the possibility of any age-related vulnerability, though co-prescription with SSRI can be a risk factor. As serotonin in general is known to reduce dopamine activity, adding two serotonergic agents together can increase the vulnerability. Though the only known drug interaction of SSRI and clomipramine are increase in chances of QTc, but Fluoxetine co-prescription can also increase clomipramine blood levels in the body. Hence, drug interaction might add to the vulnerability [20].

In the three cases, rechallenge tests were not needed. But the temporal relationship with challenge and de-challenge along with biological plausibility assessment, and existence of few previous reports pin point the side effect as a recognisable one [22].

CONCLUSION(S)

To conclude, clomipramine is a drug used to treat OCD. It is also used for depression, somatoform disorders etc. Though, it is known for anticholinergic side effects but while introducing the drugs, a clinician needs to be cautious about it's rare but potential side effect of extra pyramidal symptoms. Also, if the symptom arises, doctors need to be aware of the possibility to intervene appropriately. Special attention needs to be given while combining a TCA (clomipramine) along with SSRI with strong enzyme inhibitor property (Fluoxetine) due to high-risk of causing EPS. Patients are vulnerable across the dose and age range. Along with possible natural genetic predisposition, drug interaction can be a potential factor for precipitation of such symptoms.

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