Parkinsonism and Related Disorders 66 (2019) 267–268

Contents lists available at ScienceDirect

Parkinsonism and Related Disorders

journal homepage: www.elsevier.com/locate/parkreldis

Correspondence

Drug induced parkinsonism: Symptomatic beyond 22 months

ARTICLE INFO

Keywords:
Drug induced parkinsonism
DAT scan
Timeline

ABSTRACT

We report 2 cases of drug induced Parkinsonism followed longitudinally that remained symptomatic 22 and 27 months after stopping causative agents with normal dopamine ioflupane iodine-123 (DaT) single-photon emission computed tomography (SPECT) scans at 8 and 16 months.

Parkinsonian symptoms develop secondary to loss of dopamine transmission in the niagrostriatal pathway. Drug induced parkinsonism (DIP) is suspected in patients with parkinsonian symptoms that begin after a causative agent is started. In contrast, Parkinson's disease (PD) is a progressive neurodegenerative disorder due to loss of niagrostriatal dopaminergic neurons. Although difficult to distinguish DIP from PD apart from reversibility after stopping the offending drug, it is important for differences in prognosis and management [1]. A 6 months latency between stopping the offending drug and resolution of DIP is widely accepted, although 2 elderly patients with persistent symptoms at 9 months were previously reported [2]. A dopamine ioflupane iodine-123 single-photon emission computed tomography scan (DaT Scan) seems to be the only reasonably available technique to aid in diagnosis [3]. DaT scans help visualize the amount of transporter present which normally reuptakes dopamine on the presynaptic neurons from the synaptic cleft. In PD, there is more than 50% reduction of presynaptic dopaminergic neurons, resulting in an abnormal study [4]. On the other hand, drugs causing parkinsonism act most often via postsynaptic dopamine receptor resulting in normal DaT scans. A normal DaT scan can also help rule out concomitant PD in a patient on dopamine transmission blocking agent (DTBA) [5].

We report 2 cases of DIP followed longitudinally with normal semi-quantitative DaT scans despite remaining symptomatic at 22 and 27 months after stopping the causative agents.

The first patient, a 42 year old left-handed man with history of depression, presented with abrupt onset rest and action tremor, rigidity and bradykinesia (defined as progressive decremental amplitude on repetitive movements) after starting aripiprazole 10 mg daily. He was first seen in our clinic 4 months later and switched to quetiapine 200 mg nightly. Quetiapine, although a dopamine antagonist, is deemed to have a low risk of DIP and can be used to treat psychotic symptoms in some patients with PD [5]. Subsequent visits over the following year revealed improving but persistent tremor, rigidity and bradykinesia. Because of persistent parkinsonism, a semi-quantitative DaT scan was ordered and was normal 16 months after discontinuing aripiprazole (see Fig. 1). A CT head was also normal. At his last visit, 27 months after aripiprazole discontinuation, the patient continued to have persistent but improved which argued against a progressive degenerative disorder such as PD.

The second patient, a 70 year old woman with history of bipolar disorder, presented with bradykinesia, rigidity, yes-yes head tremor, shuffling and freezing of gait 3 months after starting valproic acid (VPA) 500 mg twice daily and risperidone 1 mg twice daily. VPA is thought to cause parkinsonism secondary to oxidative stress and mitochondrial dysfunction [5]. Risperidone, a second-generation antipsychotic, binds to dopamine receptors in a dose-dependent manner, thus inducing parkinsonism to a similar extent as high doses of typical antipsychotics [5]. The patient was seen in our clinic for the first time at least 21 months after symptom onset. Unable to discontinue DTBAs due to concern from her psychiatrist, the patient was started on carbidopa/levodopa 25–100 mg 1 tablet three times a day with improvement of rigidity, bradykinesia, tremor, freezing of gait on initiation and shuffling gait. Thirty months after symptom onset, under the guidance of another psychiatrist, risperidone was switched to quetiapine but VPA was continued. Examination at that time revealed further improvement but persistent rigidity, bradykinesia, tremor, freezing of gait on initiation and shuffling gait. Patient was lost to follow-up and seen again in clinic 57 months after symptom onset but off all medications. It is unclear as to when she had stopped medications in the interim. A semi-quantitative DaT scan performed 65 months after symptom onset, 35 months after discontinuation of risperidone and at least 8 months after discontinuation of VPA, was normal despite continued parkinsonism. MRI revealed incidental cerebellar atrophy that was deemed not to contribute to her parkinsonism. Our last visit, 22 months after discontinuation of all DTBA, revealed that the patient's gait was essentially normal but bradykinesia and rigidity persisted.

Our observation is that DIP can persist beyond the accepted 6 months since stopping causative agents and in our cases beyond 22 and 27 months. Parkinsonism persisted at our last visit but improved during longitudinal follow-up, arguing against a progressive degenerative disorder such as PD. DaT scans showing normal dopamine transporters at 8 and 16 months since discontinuation of DTBA persuade us that the patients did not evolve or concurrently suffer from neurodegenerative causes of parkinsonism [3]. While latent parkinsonism can be unmasked by neuroleptics, and is then known as drug unmasked parkinsonism, DaT scans are usually abnormal in these cases, distinguishing them from drug induced parkinsonism [6].

It is unclear why our two patients had persistent symptoms 2 years after discontinuing their medications. One hypothesis would be a persistent dopamine receptor blockade, from synaptic effect or pathway alteration, needing a longer time to reverse. This could be the case of our older patient, but persistent parkinsonism in 2 elderly patients was

https://doi.org/10.1016/j.parkreldis.2019.08.009
Received 19 May 2019; Received in revised form 6 August 2019; Accepted 11 August 2019

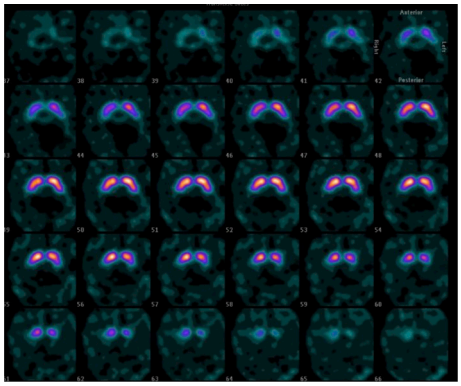

Fig. 1. Normal DaT scan 18 months after discontinuation of DTBA in our first patient but withpersistent parkinsonism.

reported as far as only 9 months from medication discontinuation [2] compared to 22 months in our case. With normal DaT scan and neuroimaging, and no other explanation as to why parkinsonism lasted so long after discontinuing the offending drug in our 2 patients, an updated consensus regarding the timeline for when to pursue other etiologies of parkinsonism in patients diagnosed with DIP after discontinuation of causative agents is needed, as it seems DIP may last longer than 6 months after DTBA withdrawal to resolve [3].

Funding sources

None.

Conflicts of interest

None.

Disclosures

Dr. Randhawa has nothing to disclose.

Dr. Mehanna serves as a consultant for Global Kinetic Corporation and is on the speaker bureau for TEVA, Adamas Pharmaceuticals and Acorda Therapeutics. He has received research grants form Lundbeck, Acorda and Solstice Neurosciences.

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