



# Freezing of saccades in dopa-responsive parkinsonian syndrome

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## ABSTRACT

**Purpose:** Ocular motor abnormalities such as abnormal saccades are common in idiopathic Parkinson's disease (PD) and atypical parkinsonian syndrome, such as progressive supranuclear palsy (PSP) and corticobasal degeneration (CBD). In this study, we describe a case of patient with PD and show a video illustrating severe delay of reflexive saccades.

**Observations:** A 68-year-old Caucasian woman with diagnosis of PD presented for evaluation of diplopia. Neuro-ophthalmic examination revealed good visual acuity in both eyes and normal optic nerves but prominent ocular motor abnormalities, including hypometric saccades, impaired smooth pursuit, and convergence insufficiency causing diplopia at near. Despite treatment with carbidopa-levodopa three times per day, she exhibited episodic, severe delay of reflexive saccades. During these episodes, the patient appeared frozen and unable to initiate reflexive saccades for 20 s or longer. This freezing of reflexive saccades was variable and occurred suddenly during exam but could be interrupted by smooth pursuit. There was no gait freezing, eyelid apraxia, or prominent exacerbation of other motor symptoms. Freezing of saccades dramatically resolved after increasing dosage of carbidopa-levodopa.

**Conclusions and Importance:** We describe a patient with dopa-responsive parkinsonian syndrome with intermittent difficulty initiating reflexive saccades mimicking ocular motor apraxia. Resolution of saccadic freezing with higher carbidopa-levodopa is consistent with ocular motor impairment as a result of degeneration and dysfunction of the dopaminergic pathways in supranuclear ocular motor control.

## 1. Introduction

Visual impairment is common in patients with neurodegenerative diseases such as idiopathic Parkinson's disease (PD), the most common neurodegenerative disease affecting motor control.<sup>1,2</sup> The hallmark of PD is progressive motor symptoms, such as bradykinesia, tremors, rigidity, and gait instability, which are related to loss of dopaminergic neurons in the substantia nigra as well as other neurons and their connections to the basal ganglia and the rest of brain.<sup>3,4</sup> PD is also associated with non-motor symptoms, and there is substantial overlap between idiopathic PD and atypical parkinsonian syndromes.<sup>5</sup> Important supportive criteria for the diagnosis of PD also includes marked response to dopamine replacement therapy.<sup>6</sup> Visual issues in PD are often overlooked because the symptoms may be vague and intermittent, such as blurry vision, asthenopia, and difficulty reading.<sup>7,8</sup> In contrast,

ocular motor abnormality in PD is well recognized and include hypometric saccades, fixation instability, saccadic pursuit, and impaired vergence leading to diplopia during near activities.<sup>9-11</sup> Altered blink frequency is also common in PD.<sup>12</sup> Although eye movement abnormality is not part of the supportive criteria for the diagnosis of PD, certain patterns of eye movement abnormality are part of the absolute exclusion criteria in PD.<sup>6</sup> Supranuclear vertical gaze abnormality, such as supranuclear vertical gaze palsy in PSP and ocular motor apraxia in CBD, may be used to distinguish idiopathic PD from atypical parkinsonian syndromes.<sup>9,13,14</sup>

Studies of ocular motor difficulties have shown that prolongation of saccade latency is one of the most quantitative ocular motor measurements in idiopathic PD and in atypical parkinsonian syndrome.<sup>15-17</sup> Saccades are fast eye movements used to explore the visual world.<sup>18</sup> Saccades can be divided into reflexive saccade, in response to a target, or

**Abbreviations:** PD, Parkinson's disease; PSP, Progressive supranuclear palsy; CBD, Corticobasal degeneration.

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volitional saccade, which is self-generated. Prolonged reflexive saccade latencies correlate with older age, longer disease duration, and greater severity of disease.<sup>15–17</sup> Although the effect of dopamine replacement on reflexive saccade latencies has been mixed,<sup>19–21</sup> treatment has been shown to improve the latency of volitional saccades.<sup>19–23</sup> Subthalamic deep brain stimulation has also been shown to improve saccade latencies.<sup>24–26</sup>

In this paper, we report a patient with probable idiopathic PD who presented for evaluation of diplopia and was found to exhibit episodic difficulty of saccadic initiation, we called this freezing of saccades, which to our knowledge has not previously been reported. We show video of the ocular motor abnormalities and discuss how eye movement findings contributed to this patient's care.

Supplementary video related to this article can be found at <https://doi.org/10.1016/j.ajoc.2021.101124>

## 2. Case report

A 68-year-old Caucasian woman with 8-year history of typical motor symptoms of PD presented with binocular diplopia. She had right hand resting tremor, bradykinesia, and gait instability. She also had vascular risk factors, including hypertension, insulin-dependent diabetes mellitus, hyperlipidemia, and depression. To treat PD symptoms, she was on carbidopa-levodopa 25–100 mg 3 times per day. She was also on multiple medications to address other medical issues, including treatment to lower vascular risk factors and clonazepam. Brain magnetic resonance imaging three years prior revealed mild, nonspecific periventricular white matter changes presumed consistent with small vessel ischemic changes without evidence of stroke in the brainstem or basal ganglia. There was no history of dementia or visual hallucinations.

On examination, she had visual acuity with pinhole of 20/25 in the right eye and 20/40 in the left eye, normal intraocular pressure, normal pupils, and unremarkable optic nerves. She had epiretinal membrane and macular cystic degeneration temporal to the fovea of left eye. She had mild atherosclerotic retinal vascular changes but no evidence of hypertensive or diabetic retinopathy. Her optical coherence tomography retinal nerve fiber layer was within normal limits bilaterally. Her neurological examination was significant for decreased facial expression, decreased blink rate, no apraxia of eyelid opening, and no obvious cognitive issues.

Her eye movement examination revealed full version and duction in both eyes, good fixation without square wave jerks, and no gaze-evoked nystagmus. Her smooth pursuit was slightly saccadic in horizontal and vertical directions (Video; 11 s to 1 min 12 s). She had orthophoric ocular alignment at distance and convergence insufficiency at near (Video; 1 min 13 s to 1 min 18 s). Her horizontal reflexive saccades were mildly hypometric with latency less than 1 s (Video; 1 min 20 s–1 min 30 s). Optokinetic responses were present and symmetric in horizontal and vertical directions.

During examination, patient exhibited intermittent severe difficulty with saccades initiation. Despite initially able to initiate reflexive saccades, she was suddenly unable to do so and appeared frozen for about 20 s before being able to initiate horizontal and vertical saccades (Video; 1 min 31 s to 3 min 43 s). During this time, she verbally expressed distress that she knew she was supposed to perform the saccade task but was unable to initiate eye movement. Her speech was also slower and more dysarthric than earlier, and her blink rate was decreased – both common symptoms in parkinsonian syndrome. Notably, she did not blink or use head thrust to help initiate eye movement, which is sometimes seen in ocular motor apraxia (Video; 1 min 45 s and 2 min 33 s). Interestingly, she was able to break the freezing episode by performing smooth pursuit (Video; 3 min 50 s to 4 min 12 s), although her pursuit eye movement was initially more jerky than earlier and improved with repetition (Video; 4 min 13 s–4 min 58 s). After successfully performing smooth pursuit, she was immediately able to initiate reflexive saccades again, although these saccades were more hypometric and slower than

those at the beginning of exam and had prolonged latencies of about 7 s (Video, 4 min 58 s–5 min 29 s).

This freezing of saccades, a prominent eye movement abnormality, raised the possibility that she may have atypical parkinsonian syndrome such as PSP or CBD rather than idiopathic PD. This freezing of saccades was observed in 2 separate visits, both in the morning, 2 and 5 hours after taking carbidopa-levodopa 25–100 mg. She did not exhibit similarly severe freezing of her speech, gait, or other motor movements, although she generally moved and walked slowly and took several steps to turn. The differential diagnosis of this eye movement abnormality includes incorrect diagnosis of PD (e.g. PSP instead of PD), suboptimal treatment of PD with dopamine medication, episodic ocular motor apraxia (not described in PD but well-reported in CBD and PSP), or side effect of medications, (carbidopa-levodopa, clonazepam).

Since the definitive diagnosis of parkinsonian syndrome is only possible in post-mortem examination of the brain, we asked whether adjustment of dopaminergic medication may improve her eye movement abnormality. At follow-up visit, after increasing carbidopa-levodopa from 1 pill three times per day to 2.5 pills four times a day, patient had complete resolution of freezing of saccade and improved eye movement. Her speech and facial expression also improved. Eight months after the initial evaluation, she was doing well but still complained of episodic double vision, primarily at near, but she did not elect to try prism reading glasses to correct for convergence insufficiency.

## 3. Discussion

We present a patient with dopa-responsive parkinsonian syndrome with striking episodic freezing of saccades with latencies of about 20 s. This severe prolongation of saccade initiation was much longer than any that we found in the literature and not accompanied by similarly severe decompensation of other symptoms. Freezing of saccades could not be broken by blinking but could be terminated with smooth pursuit. Based on this striking eye movement abnormality, we wondered whether her diagnosis of idiopathic PD was correct, given severe eye movement abnormality is an exclusion criterion for PD and more likely of atypical parkinsonian syndromes such as PSP and CBD. We also wondered whether this freezing of reflexive saccades was consistent with ocular motor apraxia. Fortunately, further optimization of her therapy led to dramatic improvement of her eye movement. While severe saccade abnormality can be due to a variety of different causes, resolution of these freezing episodes on higher dose of levodopa combined with typical motor symptoms in our patient is most consistent with degeneration of the dopamine pathways and a diagnosis of probable idiopathic PD. Patients with atypical parkinsonian syndrome like PSP and CBD tend to be less responsive to dopaminergic medication but may still demonstrate transient mild to moderate improvement on treatment.<sup>27,28</sup> Notably, while levodopa responsiveness is required for the diagnosis of idiopathic PD, a lack of response is not required for atypical parkinsonian syndrome like PSP and CBD.

Eye movement examination is often helpful in PD and parkinsonian disorders. Eye movement in PD is characterized by hypometric saccades, saccadic pursuit, impaired vergence, and increased errors in antisaccade testing.<sup>9–11,23</sup> Previous reports demonstrated that some of these eye movement manifestations improve with dopamine replacement therapy.<sup>29–32</sup> Saccade latency in healthy subjects is generally around 200 ms.<sup>33</sup> Previous studies show that reflexive saccade latency in PD may have no difference from control subject,<sup>22,23,34</sup> or may be prolonged, particularly when associated with other conditions such as dementia or freezing of gait,<sup>35,36</sup> and that prolongation in PD is typically less than 1 s.<sup>37</sup> The study of Bronstein and Kennard shows that freezing could occur during a rhythmic saccade task, but the period of freezing typically lasts just 1.8 s.<sup>38</sup> Although our patient did not exhibit freezing of gait, there is an association between delayed saccade latency and freezing of gait in PD,<sup>36</sup> which is associated with degeneration of the supranuclear motor pathway.<sup>39–41</sup>

Freezing of saccades in our patient led to the possibility that these episodes may be due to acquired ocular motor apraxia – inability to coordinate eye movements not due to muscle weakness. Ocular motor apraxia is a rare condition characterized by the inability to initiate saccades and can be congenital or acquired.<sup>40</sup> Congenital ocular motor apraxia often affect voluntary saccades.<sup>42,43</sup> Patients with congenital ocular motor apraxia, such as ataxias with oculomotor apraxia (AOA), are typically diagnosed in early months of life and associated with cerebellar ataxia, and patients may compensate for difficulty with saccade initiation using blink or head thrust (to activate the vestibulo-ocular response) to initiate saccades.<sup>44,45</sup> Our patient is different from congenital ocular motor apraxia since she is diagnosed much later in life, after onset of parkinsonian symptoms, and did not try to initiate saccades using blink or head thrusts as compensatory mechanisms. Acquired ocular motor apraxia has been reported in CBD but not PD,<sup>13,14</sup> and these patients may also exhibit apraxia of limb movement and ideomotor function.<sup>13</sup> Acquired ocular motor apraxia has been reported following stroke or as complication of cardiac and aortic surgeries.<sup>46–48</sup> It is also associated with ataxia-telangiectasia, ataxia with oculomotor apraxia, or Balint syndrome.<sup>49–51</sup> Unlike our patient, patients with acquired ocular motor apraxia have difficulty initiating voluntary saccades while reflexive saccades are preserved.<sup>52</sup> Our patient is also different from acquired ocular motor apraxia since these saccade freezing episodes resolved with increasing dosage of carbidopa-levodopa treatment, a feature common in idiopathic PD.

Medications can impact saccade latencies. Although carbidopa-levodopa has been shown to improve saccade latency,<sup>19,24</sup> recent on vs. off studies indicate that in some patients, carbidopa-levodopa can lead to worsening of reflexive saccade latencies.<sup>20,21,29,53</sup> In our patient, these freezing episodes were observed as early as 2 hours after taking carbidopa-levodopa, so we cannot rule out the potential contribution of this medication. In addition, clonazepam, a benzodiazepine, has been associated with increased saccadic latency.<sup>54–56</sup> However, her dramatic improvement with increased dopamine therapy provides the strongest evidence that freezing of saccades in this case is related to degeneration of the dopaminergic pathway and not due to medication side effect.

#### 4. Conclusions

We report a case of dopa-responsive parkinsonian syndrome with freezing of saccades characterized by delay of reflexive saccades of 20 s despite. This freezing of saccades could be broken by smooth pursuit, consistent with selective impairment of the saccade system. Although these symptoms occurred while patient was already on treatment with carbidopa-levodopa, they completely resolved with increased dosage of dopamine medication. This case illustrates the selective impact of dopaminergic neurodegeneration on eye movement and highlights the episodic impairments of saccades, which may be particularly debilitating.

#### Patient consent for publication

The patient provided written informed consent to the publication of her personal information, clinical details, and video recordings of her eye movement. Copy of the consent will be available from the corresponding author on request from the editor.

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#### Authorship

All authors attest that they meet the current ICMJE criteria for authorship.

#### Declaration of competing interest

All authors have no financial disclosures.

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