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Letter to the Editor

## Eye movements in genetic parkinsonisms affecting the α-synuclein, PARK9, and manganese network

Specific saccadic abnormalities follow basal ganglia dysfunction. Eye movements are indeed often analyzed to differentiate parkinsonian syndromes and to provide new insights into the modulatory role of the basal ganglia. Nevertheless, the oculomotor description of most inherited parkinsonisms is still lacking. Here, we analyzed the eye movement characteristics of three inherited parkinsonian syndromes (genetic Parkinson's disease, PDG): Parkinson's disease 9 (or Kufor-Rakeb syndrome, *PARK9*, #606693), due to recessive mutations in *ATP13A2* encoding the lysosomal P-type ATPase PARK9 (Ramirez et al., 2006; Gitler et al., 2009); hypermanganesemia with dystonia, polycythemia, and cirrhosis (HMNDYT1, #613280) due to recessive mutations in *SLC30A10* leading to manganese accumulation in the liver, bone marrow, and nervous system (Quadri et al., 2012), and Parkinson's disease 1 (*PARK1*, #168601) associated with dominant mutations in *SNCA* encoding α-synuclein (Golbe et al., 1990). Recently, PARK9, α-synuclein, and manganese have been interconnected in a functional network (Gitler et al., 2009; Peres et al., 2016). Loss of PARK9 increases α-synuclein accumulation and manganese toxicity. Manganese regulates α-synuclein homeostasis and accumulation (Peres et al., 2016). Alpha-synuclein normally protects against manganese toxicity, but its overexpression causes neurodegeneration (Peres et al., 2016). It is thus interesting to compare the phenotypes resulting from mutations in the three genes at the extremes of this metabolic network.

Six patients with PDG were recruited. Two brothers (44 and 35yo) (PARK9) harbored homozygous *ATP13A2* and heterozygous *FBXO7* (*PARK15*) mutations. Both patients showed pyramidal, extrapyramidal, and cerebellar signs, hyposthenia, facial minimyoclonus, and cognitive decline (Santoro et al., 2011). Unified Parkinson's Disease Rating Scale (UPDRS) score was 67 in the older brother and 16 in the younger. Mini Mental Status Examination in the younger brother was 19/30, Montreal Cognitive Assessment 13/30. Brain MRI revealed reduced gray and white matter in motor, prefrontal, and somatosensory cortex, cingulate, caudate, thalamus, and cerebellum. [123I] FP-CIT–SPECT showed decreased dopamine transport in the striatum.

Two brothers presented with parkinsonism due to HMNDYT1 (60yo, UPDRS 27 and 59yo, UPDRS not applicable for marked genu recurvatum) (Quadri et al., 2012). Brain MRI T1-w images showed, in both, hyperintensities of the caudate and lentiform nuclei, thalamus, corticospinal tracts, substantia nigra, posterior pons, and bulbar olives, cerebellum and cerebello-rubro-thalamic pathways. Cognitive status was normal.

A 49yo woman and her 29yo son harbored a *SNCA* mutation (PARK1*)* (UPDRS 57 and 28, respectively) with bradykinesia, hypomimia, and resting tremor resembling typical sporadic Parkinson's disease (PD), except for early onset and, in the mother only, mild cognitive decline. The son's neuro-psychological studies were normal. Neuroimaging was negative in both.

Nineteen healthy volunteers (11 males, range 20–65 yrs) acted as controls (CT).

Main saccadic parameters and statistical comparisons are reported in Table 1 and Fig. 1a. Latencies of reflexive single-step saccades were longer than normal in all PDG, latencies of multistep saccades (three or more steps) were longer only in PARK9. All PDG showed increased latency of voluntary saccades (both antisaccades and corrective saccades). Longer latencies might reflect impaired saccade planning because of direct or indirect involvement of frontal and parietal areas, or might result from increased basal ganglia inhibitory output onto the superior colliculus. Only PARK9 showed average hypometric saccades. Increased saccadic latency and hypometria are common in sporadic PD (Terao et al., 2011).

Saccadic precision was worse than normal in PARK9 and HMNDYT1. In controls, but not PDG, precision of single-step saccades was better than that of multistep saccades. PDG made more frequent and fragmented multistep saccades than normal (PARK9 42%, HMNDYT1 10%, PARK1 24%, CT 4%). Intersaccadic intervals of most multistep saccades were <100 ms in CT, 50–200 ms in PARK9, <100 ms in HMNDYT1, and 50–150 ms in PARK1; intersaccadic intervals of most double-step saccades were 100–200 ms in CT, 50–200 ms in PARK9, 100–150 ms in HMNDYT1, and 100–200 ms in PARK1. Thus, only PARK9 showed hypometric saccades separated by intervals long enough to allow visual feedback. This finding, together with the decreased velocity (see below), and inability of the cerebellum to compensate for the main sequence discrepancy, suggests a broader impairment of the saccadic system in PARK9. Conversely, shorter latency multistep saccades in HMNDYT1 and PARK1 might indicate facilitation of smaller saccades, as already suggested for sporadic PD (Terao et al., 2011), rather than abnormally interrupted or hypometric movements.

In all PDG, latencies of correct antisaccades were longer and they made more directional errors than normal. HMNDYT1 and PARK1 corrected errors as frequently as controls, but with longer latencies. PARK9 never corrected their errors. Increased antisaccade errors in PDG supports an interaction of the basal ganglia

*Abbreviations*: PARK9, parkinson disease 9
PARK1, parkinson disease 1
HMNDYT1, hypermanganesemia with dystonia, polycythemia, and cirrhosis
PDG, genetic Parkinson disease
CT, controls
UPDRS, Unified Parkinson's Disease Rating Scale

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**Table 1**
**Horizontal and vertical main saccadic parameters**. CT: control subjects, PARK9: Patients with Parkinson disease type 9, HMNDYT1: patients with hypermanganesemia with dystonia, polycythemia, and cirrhosis patients, PARK1: patients with Parkinson disease type 1, ctrl: controls. Values are means with relative 95% confidence interval.

| Type of saccade | Group | Horizontal saccadic parameters | | |
|---|---|---|---|---|
| Single-step+ Multistep | | Latency (ms) | Gain | Precision |
| | PARK9 | 304 [−28, 38] | 0.64 [−0.04, 0.04] | 0.26 [−0.03, 0.03] |
| | HMNDYT1 | 318 [−37, 50] | 0.90 [−0.06, 0.06] | 0.30 [−0.04, 0.05] |
| | PARK1 | 259 [−26, 43] | 0.93 [−0.04, 0.05] | 0.21 [−0.05, 0.08] |
| | CT | 232 [−11, 12] | 0.93 [−0.01, 0.01] | 0.16 [−0.02, 0.02] |
| Single-step saccades | PARK9 | 321 [−36, 49] | 0.69 [−0.05, 0.05] | 0.25 [−0.03, 0.04] |
| | HMNDYT1 | 333 [−41, 53] | 0.92 [−0.06, 0.05] | 0.31 [−0.04, 0.05] |
| | PARK1 | 268 [−33, 53] | 0.96 [−0.05, 0.06] | 0.22 [−0.07, 0.08] |
| | CT | 232 [−11, 13] | 0.93 [−0.01, 0.01] | 0.14 [−0.02, 0.02] |
| Multistep saccades (first step) | PARK9 | 264 [−38, 51] | 0.54 [−0.07, 0.07] | 0.24 [−0.03, 0.05] |
| | HMNDYT1 | 188 [−26, 45] | 0.77 [−0.15, 0.10] | 0.22 [−0.05, 0.09] |
| | PARK1 | 229 [−37, 42] | 0.83 [−0.08, 0.04] | 0.28 [−0.06, 0.08] |
| | CT | 232 [−46, 101] | 0.74 [−0.12, 0.09] | 0.15 [−0.02, 0.04] |
| Single-step+ Multistep | | Vertical saccadic parameters | | |
| | PARK9 | 349 [−40, 62] | 0.56 [−0.06, 0.07] | 0.28 [−0.05, 0.08] |
| | HMNDYT1 | 509 [−54, 66] | 1.03 [−0.08, 0.08] | 0.39 [−0.04, 0.05] |
| | PARK1 | 275 [−46, 91] | 0.78 [−0.07, 0.10] | 0.28 [−0.06, 0.16] |
| | CT | 317 [−19, 21] | 0.96 [−0.02, 0.02] | 0.22 [−0.02, 0.02] |
| Single-step saccades | PARK9 | 378 [−51, 71] | 0.60 [−0.06, 0.08] | 0.28 [−0.05, 0.08] |
| | HMNDYT1 | 525 [−61, 63] | 1.06 [−0.08, 0.08] | 0.38 [−0.04, 0.05] |
| | PARK1 | 275 [−52, 108] | 0.80 [−0.08, 0.11] | 0.29 [−0.06, 0.14] |
| | CT | 320 [−20, 20] | 0.97 [−0.02, 0.02] | 0.22 [−0.02, 0.02] |
| Multistep saccades (first step) | PARK9 | 229 [−45, 71] | 0.38 [−0.06, 0.08] | 0.28 [−0.05, 0.08 |
| | HMNDYT1 | 252 [−62, 62] | 0.57 [−0.26, 0.26] | 0.57 [−0.26, 0.26] |
| | PARK1 | 268 [−73, 73] | 0.65 [−0.21, 0.21] | 0.65 [−0.21, 0.21] |
| | CT | 251 [−31, 58] | 0.83 [−0.07, 0.07] | 0.18 [−0.03, 0.07] |

| Group | Horizontal antisaccadic parameters | | | |
|---|---|---|---|---|
| | Latency (ms) | | | Gain |
| | Erroneous prosaccade | Correct antisaccade | Secondary antisaccade | Correct antisaccade |
| PARK9 | 291 [−69, 133] | 676 [−326, 326] | NA | 0.71 [−0.40, 0.40] |
| HMNDYT1 | 190 [−19, 70] | 466 [−59, 83] | 408 [−35, 25] | 0.85 [−0.09, 0.09] |
| PARK1 | 232 [−34, 55] | 328 [−39, 77] | 510 [−94, 192] | 0.92 [−0.12, 0.14] |
| CT | 223 [−23, 30] | 304 [−13, 13] | 344 [−96, 96] | 0.92 [−0.03, 0.03] |

with frontal areas, e.g., dorsolateral prefrontal cortex, to prevent reflexive movements in favor of voluntary behaviors. Despite efforts in ensuring the correct instructions understanding, we cannot distinguish whether inability of PARK9 to perform antisaccades might be due to severe cognitive deficit or impairment in areas involved in inverting the saccadic vector, e.g., posterior-parietal cortex.

Main sequences showed slower peak velocities for horizontal and vertical saccades in PARK9, HMNDYT1 had slightly shorter vertical saccade duration and faster peak velocities horizontally, and PARK1 had higher peak velocities only horizontally, but normal durations (Fig. 1b).

Oculomotor abnormalities such as supranuclear gaze palsy and slow saccades have already been described in PARK 9 (Williams et al., 2005), but only one patient was previously recorded: his saccades were slow, hypometric, and fragmented, as in our patients, but latency was normal (Machner et al., 2010). Eye movements in HMNDYT1 have not been previously analyzed, but oculomotor impairment is a known complication of manganese intoxication in exposed workers and drug abusers (Bonnet et al., 2014). Subjects with ephedrone-induced parkinsonism showed hypometric and slow horizontal saccades with normal latency, and increased latency of vertical saccades; antisaccades showed normal latency, but increased error rate with normal correction frequency (Bonnet et al., 2014). Differences with our findings (increased latency, but normal velocity and amplitude) might be ascribed to the dissimilar nature of neurodegeneration in the two conditions: acute/sub-acute damage in manganese-intoxication and slow manganese accumulation, perhaps allowing for some adaptation, in HMNDYT1. Eye movements in PARK1 have not been reported.

It is difficult to recruit patients with rare pathologies. Although limited by having only two patients with each disease, this study suggests that when dysfunction of the PARK9, α-synuclein, and manganese network starts from different genes the severity of manifestations is also different, PARK9 being the most severe. The three phenotypes also shared abnormalities, reflecting common basal ganglia dysfunction.