Clinical/Scientific Notes

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RAPID-ONSET DYSTONIA-PARKINSONISM IN A CHILD WITH A NOVEL ATP1A3 GENE MUTATION

Rapid-onset dystonia-parkinsonism (RDP) has been linked to mutations in the *ATP1A3* gene.[1] We present a case with onset of symptoms at age 4 years, with previously undescribed clinical features including episodes of flaccidity and lack of motion for hours, later evolving into episodes of stiffness. Sequencing of *ATP1A3* revealed a novel heterozygous nucleotide substitution c.2767G>A, resulting in an aspartic acid (D) to asparagine (N) substitution at amino acid position 923. This mutation is predicted to impair the activity of the neuron-specific α_3 subunit of Na,K-ATPase.

Diagnostic criteria for RDP include abrupt onset of dystonia with features of parkinsonism over a few minutes to 30 days, rostrocaudal progression, and prominent bulbar findings.[2] Antecedent symptoms such as mild dystonia involving hands and arms may precede acute onset. Primary onset of symptoms is frequently associated with physical or emotional stress. Patients do not respond to L-dopa or dopamine agonists.[3] The parkinsonian symptoms are limited to bradykinesia and truncal instability. The most common age at onset of symptoms is young adulthood.[2] Onset at age 4 years was reported by Pittock et al.[4] The described 38-year-old man had intermittent episodes of dysarthria and hemidystonia associated with stress and anxiety from an early age, lasting from hours to weeks. At baseline, he had only mild dysarthria and slight increase in tone in the left upper limb.

Case report. We report a child with RDP who had very early onset of symptoms. Birth history was unremarkable. He had mild gross motor delay but excellent cognitive and language development. Hypotonia and left foot intoeing were noted at age 3 years. Ancestry is Caucasian (father) and Chinese (mother) with no family history of dystonia or Parkinson disease.

The patient had a typical initial presentation. On the day of onset, he sustained mild trauma to his forehead. Within 30 minutes he became mute, developed episodes of eye convergence, and was unable to walk. Over several hours he developed prominent hypotonia that later evolved into severe dystonia. He also developed mutism that subsequently evolved into severe dysarthria and drooling. All evaluations, including multiple metabolic tests, skin and muscle biopsies, and brain MRIs, were unrevealing. About 1 month after onset, F-18 fluorodeoxyglucose (FDG)-PET scanning demonstrated moderate hypermetabolism in the striatum involving caudate nuclei and putamen bilaterally. A recent FDG-PET study showed mildly decreased metabolic activity in both thalami and the left putamen. CSF neurotransmitter metabolites, including homovanillic acid, were normal in the acute period and several years later.

The patient's condition became stable over several months with mild improvement over the subsequent 8 years. Dystonia became less prominent, particularly in the lower extremities. He started to walk with difficulty, but without support (video on the *Neurology*® Web site at www.neurology.org, seconds 36–58). About a year after onset, however, he developed exceptional symptoms: episodes of flaccidity lasting for hours, later replaced by episodes of stiffness that were shorter and less frequent than the "flaccid" episodes and lasted for 20 to 40 minutes. He did not respond to trials of L-dopa in either the acute period or later, or to dopamine agonists (pergolide, pramipexole) or anticholinergic medications (trihexyphenidyl, benztropine). Over the years, there has been no improvement in his bulbar symptoms, a very striking oromotor dystonia, and apraxia (video, seconds 5–34). He is unable to produce words and has significant swallowing difficulty.

DNA sequencing of the *ATP1A3* gene revealed a heterozygous nucleotide substitution (c.2767G>A) in exon 20 (figure), resulting in an amino acid substitution from aspartic acid (D) to asparagine (N) at codon position 923 (p.D923N), which neither parent carried. False paternity was excluded using 5 DNA markers on 5 chromosomes (certainty >99.9%). This mutation was absent from 338 Caucasian control chromosomes screened by DHPLC.[1] The finding of a de novo mutation in the α_3 subunit gene of Na,K-ATPase in RDP is not uncommon, with 4 out of 10 previously reported cases being de novo.[2]

Discussion. Based on a crystal structure of Na,K-ATPase α_1 subunit,[5] the mutated residue is buried in

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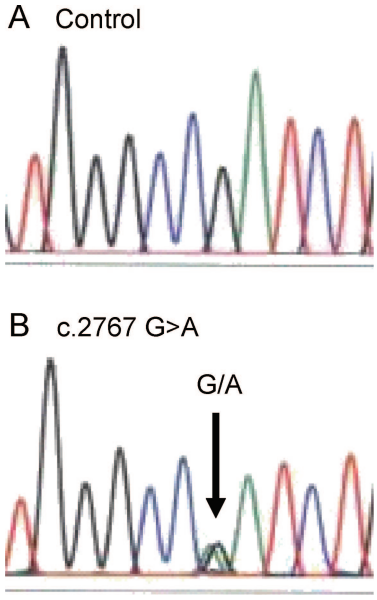
Figure **Chromatograms illustrating a novel *ATP1A3* gene mutation in a child with rapid-onset dystonia-parkinsonism**



Sequence from the patient and a control. Chromatograms show the mutation found in the patient in the *ATP1A3* gene. (A) Wild type sequence. The arrow in (B) shows the heterozygous mutant sequence at position c.2767 G>A that results in a D923N amino acid substitution in the protein.

the membrane and lies close to the ion-binding residue Q920. Prior mutations of Na,K-ATPase provide insight into the D923N mutation. In α_2, mutations of the equivalent residue, D925L or D925N, had residual Na,K-ATPase activity; however, affinities for both Na^+ and K^+ were significantly reduced.[6] In α_1 subunit, mutation of the glutamine equivalent to Q920 in the human α_3 subunit gene abolished activity, consistent with its role in ion binding.[7] Thus D923 is close enough to the ion-binding cavity to affect enzyme activity when mutated. Based on the behavior of the same substitution in the α_2 subunit, we expect Na,K-ATPase in patients with this mutation to have impaired activity and ion-binding affinities.

The novel mutation detected in our patient seems to be a causative one. This patient's presentation has distinctive features and demonstrates that early childhood onset of RDP may occur.

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PARKINSONISM IN HIV-INFECTED PATIENTS ON HIGHLY ACTIVE ANTIRETROVIRAL THERAPY

Highly active antiretroviral therapy (HAART) has significantly prolonged the lives of HIV-infected patients but low level chronic immune activation remains in some. Neurodegenerative diseases are often associated with immune activation which likely plays a role in their pathogenesis.[1] Recently, increased alpha-synuclein deposition in the substantia nigra in aging HIV-infected patients has been identified,[2] although there was no clear clinical correlate. These observations suggest that HIV and HAART may facilitate the development of neurodegeneration and accelerate the appearance of diseases such as Parkinson disease (PD) via mechanisms including inflammation, mitochondrial dysfunction, and interference with the ubiquitin proteasome pathway.[1] Here we describe 3 patients with relatively young onset of parkinsonism in the context of HIV and HAART.

Table Patient clinical data

	Patient 1	Patient 2	Patient 3
Gender	Male	Male	Male
Age, y	55	44	53
Duration of HIV, y	10	4	13
Duration of HAART, y	3	4	10
Previous HAART	Efavirenz, emtricitabine, tenofovir	Ritonavir, indinavir, lamivudine, abacavir, atazanavir, efavirenz	Zidovudine, lamivudine, nelfinavir, nevirapine, ritonavir, saquinavir, atazanavir, didanosine
Current HAART	Nevirapine, emtricitabine, tenofovir	Raltegravir, abacavir, lamivudine	Efavirenz, emtricitabine, tenofovir
Current HIV viral load	<50 copies/mL	<50 copies/mL	<50 copies/mL
Nadir and current CD4 count	180/380	510/728	88/450
Duration of parkinsonism, y	2	3	3
Initial symptoms	Rest tremor of the left hand	Rest tremor of the right hand	Rest tremor of the right hand
Clinical features	Hypomimia, monotonous speech, left-sided rest tremor, rigidity and bradykinesia, loss of left arm swing	Rest tremor of the right hand, mild symmetric limb rigidity, bradykinesia, bilaterally reduced arm swing, foot dystonia	Hypomimia, right-sided rest tremor, rigidity, bradykinesia, bilaterally reduced arm swing, REM sleep behavior disorder
Hoehn and Yahr score (1–5)	1	2	2
Cognitive impairment	No	No	No
L-dopa response (max dose)	Nil (400 mg/d)	Nil (600 mg/d)	Good (300 mg/d)
Brain MRI	Spectroscopy reduced NAA/creatine in caudate, otherwise normal	Spectroscopy reduced NAA/creatine in caudate, otherwise normal	Normal
CSF	Not sampled	No cells, protein 906 mg/L, neopterin 40 (0–13 nmol/L), β2 microglobulin 2.3 (<2.2 mg/L), HIV viral load 100 copies/mL	Normal protein, glucose, cell count, β2 microglobulin, neopterin HIV viral load 230 copies/mL

HAART = highly active antiretroviral therapy.

Case series. The patients were HIV-infected men aged between 44 and 55 years on HAART who were examined prior to the development of parkinsonism. None had been exposed to neuroleptic medications or recent amphetamine use. All developed initial unilateral upper extremity rest tremor, followed by rigidity, bradykinesia, and mild gait involvement with preserved postural stability. Importantly, cognitive, oculomotor, pyramidal, cerebellar, and autonomic features were absent. Only patient 3 responded well to levodopa; however, the dose in patients 1 and 2 could not be raised due to side effects. In all patients, parkinsonism developed and progressed in the context of effective HAART (plasma HIV viral load <50 copies/mL). Brain MRI was normal apart from reduced *N*-acetylaspartate spectroscopy peaks (relative to creatine) in the caudate in 2 patients. In 2 patients, CSF showed low levels of HIV RNA and 1 had evidence of inflammation with raised neopterin and β2 microglobulin. The patient details are described in the table.

Discussion. HAART has transformed HIV to a chronic disease with near-normal life expectancy. There is accumulating evidence that HIV and HAART accelerate the aging process, thereby possibly promoting the development of neurodegenerative diseases such as Alzheimer disease and PD.[1]

We observed 3 new cases of parkinsonism among our cohort of 2,500 HIV-infected patients over a 2-year period, which is 4–8 times higher than the reported incidence of PD among people age 40–59 years.[3] This estimate suggests HIV and HAART may preferentially predispose to the development of parkinsonism. Early HIV disease can rarely be associated with parkinsonism, probably reflecting viral involvement of the basal ganglia soon after seroconversion.[4] Later in the course of HIV, in patients with HIV-associated dementia, features of parkinsonism may also occur, with postmortem studies confirming presence of HIV preferentially in inflammatory infiltrates and glial cells of the basal ganglia including the substantia nigra.[5] The pattern of parkinsonism in the present series differs from these existing reports: 1) patients had chronic HIV infection with viral suppression in the plasma and minor replication in the CSF when symptoms developed, and 2) none had features of dementia. In fact, it remains possible that our patients have PD. We hypothesize that chronic HIV infection with very low level replication and HAART, particularly protease inhibitors, may predispose to neurodegeneration through persistent low level inflammation, mitochondrial dysfunction, and interference with the

ubiquitin proteasome pathway.[1] Proteasome dysfunction has been described at least with some of the protease inhibitors used in HAART. It may be advisable to avoid their use where possible in patients with parkinsonism.[1] In our patients, it was not possible to stop or reduce antiretroviral medications because of risk of HIV progression or the development of drug resistance. There is accumulating evidence that neurodegeneration occurs in patients with chronic HIV, even in the context of maximal viral suppression, at least in the plasma. Several groups have reported a 10%–40% incidence of cognitive impairment among virally suppressed chronically HIV-infected patients, particularly those with longer disease duration.[6] Further evidence for neurodegeneration in patients with chronic HIV infection and HAART comes from a recent study which found that incidence of mild extrapyramidal signs is increased in patients with chronic HIV infection and HAART, particularly older patients and those with cognitive impairment.[7] This can be interpreted as loss of nigrostriatal neuronal reserve in aging patients with HIV-HAART, which could predispose to the later development of parkinsonism. This view is supported by the significant finding of overexpression of neuritic alpha-synuclein in the substantia nigra of long surviving patients with HIV-HAART in the absence of HIV-associated neuropathology.[2] The present study extends these observations by confirming that chronic HIV infection with HAART may be associated with parkinsonism of relatively young onset, with rest tremor, that may be indistinguishable from idiopathic PD.

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