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Prominent Neuroleptic Sensitivity in a Case of Early-onset Alzheimer Disease due to Presenilin-1 G206A Mutation

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Abstract

Objective—We describe atypical motor and cognitive features in a case of familial Alzheimer disease (FAD) due to presenilin-1 (PS-1) mutation.

Background—Extrapyramidal signs (EPS) typically are a late-presenting feature of sporadic Alzheimer disease (AD), but relatively little data are available regarding EPS in FAD.

Method—A 59-year-old, right-handed man of Caribbean-Hispanic descent underwent brain imaging studies, laboratory tests for AD, and serial neurologic and neuropsychologic evaluations.

Results—The patient presented with recent-onset delusional ideation associated with cognitive decline. Prominent EPS developed soon after initiation of an atypical neuroleptic agent. Neuropsychologic evaluation revealed global cognitive deficits; he was found to be a carrier of a PS-1 point mutation at position G206A. EPS resolved completely after discontinuing the neuroleptic agent and coincided with improved motor speed, set initiation, and verbal fluency.

Conclusions—Severe neuroleptic sensitivity and associated deficits of cognitive speed occurred in response to a dopaminergic antagonist agent; both responded readily to withdrawal of the offending agent. Patients with PS-1 AD may be at substantially increased risk of neuroleptic-induced EPS. That feature underscores the heterogeneity of the FAD clinical phenotype.

Keywords

Alzheimer disease; presenilin-1; extrapyramidal signs; neuroleptic sensitivity

Mutations affecting the gene for presenilin-1 (PS-1) are the most common cause of familial Alzheimer disease (FAD), accounting for roughly half of all cases, and are associated with the earliest onset and most aggressive expression of Alzheimer disease (AD). Yet, the phenotype of PS-1 FAD is remarkably heterogeneous. In some cases, cognitive disturbance deviates substantially¹ from the characteristic selective episodic memory impairment of “classic” early-stage AD. Additional salient aspects of heterogeneity include extrapyramidal signs (EPS) and psychosis, which occur frequently in other neurodegenerative disorders. Moreover, age at onset among disorders overlaps substantially. FAD clinical heterogeneity thus confronts the clinician with a substantial diagnostic dilemma.

We describe a patient with PS-1 FAD who developed prominent EPS soon after beginning treatment with an atypical neuroleptic for delusional ideation. After withdrawal of the offending agent, EPS resolved. Serial neuropsychologic evaluations revealed progressive cognitive decline with concurrent interval improvements on measures of processing and motor speed that were probably attributable to discontinuing the neuroleptic.

CASE REPORT

Presenting Illness

The patient (P.R.) developed persecutory delusions about 1 year before his first-lifetime psychiatric admission at the age of 59 years. At that time, he scored 25/30 on the Mini-Mental State Examination (MMSE); recall was 2 of 3 items. Risperidone 2 mg/d was started, and the following day he experienced orthostasis and syncope. There was no known prior history of syncope or autonomic dysregulation. Risperidone was discontinued and restarted after 3 days, titrated slowly to 1.5 mg b.i.d., and was well-tolerated through discharge 3 weeks later. He continued to endorse delusions, but acknowledged medication noncompliance for 2 months after discharge. Within 1 month of restarting risperidone, his family reported progressive slowing of mentation, paucity of speech, reduced eye blinking, and prolonged staring episodes.

Medical and Psychiatric History

P.R. incurred blunt head trauma with brief loss of consciousness twice during adulthood; he denied sequelae associated with either event. He was treated effectively for syphilis at the age of 52 years; human immunodeficiency virus status was negative. He underwent successful interferon and ribavirin therapy for hepatitis C at the age of 54 years. He takes levothyroxine for hypothyroidism and has stable, inactive pulmonary sarcoidosis. The psychiatric history is notable for combat-related post-traumatic stress disorder (PTSD) and depression treated with buspirone and sertraline intermittently since the age of 52 years. As much as 2 years before admission, symptoms of PTSD and depression were described as “minimal.”

Social History and Habits

P.R. is a Puerto Rico native; he relocated to the United States during childhood. After completing an Associate degree, he worked in management until alcohol abuse and dependence led to unemployment. With admission for detoxification at the age of 54 years,

he stopped drinking after a 30-year history. He abused cannabis, cocaine, amphetamine, and intravenous heroin for about 4 years during his 30s, and had a brief cocaine relapse at the age of 51 years. His father had a history of alcohol abuse and died in his late 50s. His mother died at the age of 43 years from complications of childbirth; neither parent showed evidence of cognitive decline. An elder brother who died at the age of 61 years and a brother who is 1 year younger were diagnosed with probable AD. Three sisters, one of whom died of an unrelated medical condition at the age of 66 years, were apparently unaffected (Fig. 1).

MATERIALS AND METHODS

Medical documentation was reviewed. Comprehensive neuropsychologic evaluations were obtained 5 months after psychiatric discharge (at the age of 59 y) and at 1-year follow-up. He underwent neurologic examination 7 months after admission. Standard laboratory studies were collected at that time and at 1-year follow-up. Assays for AD included cerebrospinal fluid (CSF) levels of amyloid β ($A\beta$) 42-peptide isoform ($A\beta_{42}$), total τ , and phosphorylated τ (p- τ) determined by enzyme linked immunosorbent assay (Athena Diagnostics, Worcester, MA). Genetic testing for PS-1 mutations was obtained and apolipoprotein E (ApoE) genotype was determined via the serial invasive signal amplification reaction using genomic DNA (both Athena Diagnostics). Computed tomography and magnetic resonance imaging (MRI), both without contrast, were obtained at 8 and 13 months after presentation, respectively.

RESULTS

Physical Examination and Standard Laboratory Studies

P.R.'s seated blood pressure was consistently below 120mm Hg systolic and 80mm Hg diastolic; the highest single measurement was 132/88. Comparison standing blood pressure, electrocardiograph R-R interval test, and iodine-123 metaiodobenzylguanidine cardiac scintigraphy were not obtained, nor were available in the medical record. Thyroid stimulating hormone, free T4, cyanocobalamin, and folate levels were normal. Repeat rapid plasma reagin was nonreactive; repeat enzyme linked immunosorbent assay human immunodeficiency virus testing was also negative. Lumbar puncture yielded normal CSF protein and glucose, with 2 lymphocytes/mm.³ Gram stain and cultures were negative. At 1-year follow-up, hepatic and renal functions were normal. Total cholesterol (248 mg/dL), low-density lipoprotein (214 mg/dL), and triglycerides (186 mg/dL) were all elevated. Erythrocyte sedimentation rate was mildly elevated (40 mm/h).

Neurologic Examination and Brain Imaging

The neurologic presentation was dominated by masked facial expression, reduced eye blinking, and bradykinesia involving the face, trunk, and all extremities. He had stooped posture, shuffling gait with reduced pace and stride length, and decreased arm swing. The pull test was negative. Mild cogwheeling was present bilaterally at the wrists, but no tremor was evident at rest or with action. Cranial nerves, strength, coordination, reflexes, and sensorium were unremarkable. Computed tomography and magnetic resonance imaging both revealed mild, diffuse volume loss particularly affecting prefrontal regions bilaterally,

and mild periventricular subcortical white matter disease. Functional brain imaging studies and electroencephalogram were not obtained. Donepezil was started and maintained at 5 mg/d due to sinus bradycardia. Memantine was titrated to 10 mg b.i.d. Risperidone was discontinued, and EPS resolved within 6 months.

AD-related Analyses

P.R. was heterozygous for the PS-1 mutation involving guanine to cytosine nucleotide transition at position 617, resulting in glycine to alanine substitution at codon 206 (G206A). Lumbar puncture revealed low CSF A β ₄₂ level (392.3 pg/mL), consistent with prior reports of PS-1 patients.² CSF total τ (380.1 pg/mL) and p- τ (75.3 pg/mL) levels were both elevated. The A β ₄₂-total τ index (ATI) was 0.57. ApoE genotype was ϵ 3/ ϵ 4.

Neuropsychologic Assessments

P.R. first complained of subjective memory decline at the age of 52 years. At the age of 53 years, he noted difficulty retaining information from a vocational training program. At initial neuropsychologic evaluation, he had only a vague recollection of events leading to psychiatric admission. Prominent EPS were present. Medications included risperidone (1.5 mg b.i.d.), sertraline, and levothyroxine. He scored 22/30 on the MMSE. Global cognitive deficits were elicited (Table 1), most prominently involving memory, semantic fluency, visuospatial processing, initiation, flexibility, processing speed, and olfactory perception. Attention, phonemic fluency, confrontation naming, abstraction, and motor speed were less affected. There was no evidence of depressed mood. MMSE scores at 1-month and 2-month follow-up screening were 23/30 and 21/30, respectively. At 1-year follow-up, multidomain deficits were again elicited and reflected substantial declines in verbal learning and recognition memory, visuospatial processing, and concept formation; equivocal declines were found in visual recognition memory and speed of visual search. His MMSE score declined to 18/30. In contrast, improvements were found in attention, motor speed, initiation, and verbal fluency. Naming, visual recall memory, and abstraction remained stable.

DISCUSSION

This case further expands the range of PS-1 AD phenotypic heterogeneity described in the literature. Many aspects of the clinical presentation were consistent with prior reports of the G206A mutation, which has been identified among individuals of Puerto Rican and Dominican ethnicity.³ P.R.'s cognitive disturbance generally comported with the classic presentation of AD and prior reports of PS-1 FAD patients.⁴ However, it is unique in demonstrating severe neuroleptic sensitivity and improvements of verbal fluency and initiation that seemed to reflect withdrawal of dopaminergic blockade. Moreover, neuroleptic discontinuation had no corresponding effect on the progression of AD. Although factors accounting for heterogeneity among PS-1 mutations are not well understood, progress has been made in identifying sources of variability.

Spontaneous EPS is common in sporadic AD, but is typically delayed until advanced illness, and is a predictor of functional decline and mortality.⁵ In PS-1 FAD, spontaneous EPS also

seems to be uncommon⁶ and tends to begin late, but cases with early manifestation have been described,⁷ and rarely may precede the onset of dementia.⁸ Notable variability in movement disorder is evident even within families bearing the same mutation.⁷ Determinants of the duration to onset of EPS in PS-1 FAD have not been characterized. Moreover, the literature is limited in that many case reports are silent with respect to EPS, raising the possibility that the prevalence of EPS in PS-1 FAD has been underestimated.

Parkinsonian EPS in the context of neurodegenerative disorder may also be induced by psychotropic medication, particularly dopamine-antagonist agents, typically for treatment of psychosis. Neuroleptic sensitivity occurs in 50% or more of dementia with Lewy bodies (DLB) patients,⁹ but is less frequent and not as pronounced in sporadic AD. Severe reactions occur in <10% of patients with late-onset AD, and generally, 20% to 40% of cases show sensitivity of any degree.¹⁰ Putative risk factors include advanced age, concurrent medical illness, dementia severity, type of neuroleptic, and baseline bradykinesia.¹¹ P.R.'s sole risk factor, concurrent medical illness, was well-controlled. In contrast to sporadic AD, neuroleptic sensitivity in PS-1 FAD has not been reported previously.

Severe neuroleptic sensitivity is a suggestive diagnostic criterion for DLB; autonomic dysregulation is a supportive diagnostic criterion. However, P.R. demonstrated no core criteria in support of DLB as a superimposed diagnosis.¹² Although P.R. developed syncope on risperdal, there was no evidence of chronic autonomic dysregulation; however, as specific tests of autonomic dysregulation were not conducted, that possibility cannot not be ruled out. Moreover, CSF p- τ was elevated and the combined ATI¹³ was <1.0 as would be expected in AD. In contrast, DLB patients have p- τ levels that are significantly lower than in AD, and in some studies are no different from controls.¹³ ATI is also typically >1.0, further suggesting the low likelihood of DLB as a contributing factor despite the absence of supporting evidence from measures such as metaiodobenzylguanidine cardiac scintigraphy.¹⁴

Pathophysiologic Mechanisms of EPS in AD Lewy Body Pathology in AD

Parkinsonian EPS in neurodegenerative disorders is linked to derangement of dopaminergic transmission and subserving cerebral structures. EPS is a predictor of the prospective diagnosis of DLB.¹² Similarly, bradykinesia-predominant parkinsonism is a predictor of Lewy body (LB) pathology in patients carrying a clinical diagnosis of sporadic AD.¹⁵ LB formation is common in AD, occurring in 20% to 60% of sporadic AD,¹⁶ PS-1,⁶⁻⁸ and amyloid precursor protein cases.¹⁷ Conversely, EPS never develops in a substantial proportion of patients with autopsy-confirmed AD and coexisting LB pathology.¹⁸

AD pathology may potentiate LB formation. ApoE ϵ 4 may confer risk for concomitant LB pathology via abnormal processing of α -synuclein,¹⁹ a major constituent of LBs. LB pathology also seems to be enhanced by A β deposition.²⁰ However, the precise mechanisms of interaction involving ApoE, A β , and α -synuclein have not yet been elaborated.²¹ Possession of 1 ϵ 4 allele suggests our patient may have been at increased risk for LB pathology, which in turn may have contributed to EPS.

No data are available regarding LB pathology in PS-1 mutations occurring at codon 206. Neurologic examination in a patient with the glycine to valine substitution at codon 206 (G206V) was described as normal, but postmortem pathology was not obtained.²² A population-based study of patients with the G206A mutation was silent with respect to LB pathology and EPS.³ Thus, the existence of LB pathology in the G206A mutation and its potential influence on manifestation of EPS await further study.

Abnormalities of Dopaminergic Neurons and the Dopamine Receptor Subtype-2

Abnormal presynaptic dopamine (DA) transporter activity within the striatum and failure to up-regulate postsynaptic striatal DA subtype-2 (D₂) receptors have been identified in neurodegenerative syndromes with parkinsonism,²³ and may be a critical factor determining neuroleptic sensitivity.²⁴ The balance of evidence suggests D₂-receptor system abnormalities are limited or absent in AD. Measures of D₂-receptor function are normal among sporadic AD patients without EPS.²³ However, selection bias and other methodologic issues have apparently contributed to variability in those data. For example, striatal D₂-receptor density seems to be lower in sporadic AD patients with coexisting LB pathology compared with AD patients without LBs.²⁵ Furthermore, no data exist regarding striatal D₂-receptor variability in FAD.

Risperidone is a potent D₂-receptor antagonist, which may partially explain the sensitivity reaction in this case. Severe neuroleptic sensitivity occurs frequently among dementia patients treated with olanzapine,⁹ which has D₂ occupancy characteristics comparable to risperidone. In contrast to olanzapine, risperidone also has high affinity for binding and inhibiting the serotonin (5HT) type 2A (5HT_{2A}) receptor.²⁶ 5HT normally inhibits presynaptic striatal DA release within the substantia nigra and striatum.²⁷ Striatal 5HT_{2A} receptor inhibition effectively increases available DA, which may account for the lower risk of EPS with risperidone, and data suggest risperidone carries a relatively low short-term risk of inducing EPS in late-onset AD.²⁸ In this case, 5HT_{2A} receptor inhibition may nonetheless have been insufficient to overcome potent striatal D₂ blockade by risperidone. Compromised D₂-receptor function may account for early or severe EPS described in some FAD patients, but characterization of D₂-receptor function in FAD remains to be determined.

Striatal A β Deposition

Recent evidence among some presymptomatic PS-1 mutations carriers shows focal striatal A β deposition that is distinct from characteristic spatiotemporal patterns of cortical A β deposition in sporadic AD.²⁹ In those kindreds, transition from cysteine to tyrosine at codon 410, or alanine to proline at codon 426, both occur within a different transmembrane domain than the causative mutation in the present case. Nonetheless, it would be interesting to speculate that the unique striatal distribution of A β deposition in PS-1 FAD may contribute to the risk of EPS in some patients.

Potential Mediating Influences on EPS Development

Independent of D₂-receptor blockade, interactions between 5HT and DA systems may have contributed to neuroleptic sensitivity in this patient through any of several potential mechanisms. At presentation, P.R. had been taking the selective serotonin reuptake inhibitor

(SSRI) sertraline over several years for treatment of PTSD. SSRIs effectively decrease striatal DA levels,³⁰ consistent with evidence of presynaptic 5HT inhibition of striatonigral DA release,²⁷ which may explain the occurrence of EPS in some patients taking SSRIs.³¹ Consequently, in our patient, 5HT-mediated inhibition of striatal DA may have increased the likelihood of neuroleptic sensitivity when coupled with the introduction of D₂-receptor inhibition by risperidone. P.R. had a history of alcohol and stimulant abuse in remission for 5 years. Among alcoholics, imaging and postmortem studies show reduced striatal D₂-receptor function that may be sustained even with extended abstinence.³² Chronic alcohol abuse is associated with increased risk of EPS,³³ possibly reflecting low striatal D₂-receptor availability. Chronic stimulant administration is also linked to reduced D₂-receptor availability³⁴ and may be a risk factor for EPS among several clinical populations.³⁵ The brief duration of stimulant abuse and extended periods of abstinence may, however, mitigate the importance of that factor in this case. It is also conceivable that EPS reflected a cumulative or interactive effect of the individual risk-conferring factors.

Genetic Variation and Psychosis in AD

In addition to phenotypic variability manifesting as neuroleptic sensitivity, early delusional ideation seems to be an atypical feature in this case. The onset of the patient's delusions occurred around the age of 58 years, about 5 to 6 years after the estimated onset of cognitive decline. Moreover, no evidence of delusional ideation was elicited during psychiatric evaluation and management of PTSD between the ages of 52 and 58 years.

Prevalence estimates of psychosis in sporadic AD are 20% to 50%.³⁶ Psychosis may also occur frequently in PS-1 AD, but precise estimates are elusive. Moreover, it is not clear whether psychosis typically develops in advanced disease, as in sporadic AD, or is more likely to occur earlier in the clinical course. Several cases of PS-1 AD have reported onset of delusions or hallucinations within 1 to 4 years of symptom onset,^{1,6} but whether those are representative of the PS-1 AD population remains to be determined.

Proposed risk factors for psychosis involve DA and 5HT receptor variation. AD patients who are homozygous for the D₁ receptor gene (DRD1), or either the B1 or B2 allele of the D₃ receptor gene (DRD3), are more likely than heterozygotes to develop psychosis.³⁷ Furthermore, DRD3 B1 allele homozygosity may specifically predispose AD patients to delusional ideation.³⁸ Polymorphisms for the 5HT_{2A} and 5HT_{2C} receptor subtypes are associated with psychosis that remains clinically silent until manifestation of neurodegenerative symptoms.³⁹ Given those data, it is possible that sertraline treatment and substance abuse may have mediated early manifestation of delusions in this case via mechanisms involving DA and 5HT systems. However, it is not known if 5HT receptor morphology influences the risk of psychosis in FAD as it does in sporadic AD.

Factors not directly related to neurotransmission may also influence the likelihood of psychosis in sporadic AD. Delusions occur more frequently, particularly in advanced illness, with possession of at least 1 ApoE ϵ 4 allele.⁴⁰ P.R.'s ApoE phenotype was ϵ 3/ ϵ 4, raising the possibility of its influence on his psychosis. However, no data exist regarding the relationships among specific PS-1 mutations, ApoE genotype, and development of psychosis in FAD.

Summary and Conclusions

In summary, patients with PS-1 AD may be at increased risk of developing severe neuroleptic sensitivity. Given evidence suggesting that risperidone is well-tolerated in AD, including among older patients with advanced dementia, we argue that neuroleptic-induced EPS most likely reflected underlying PS-1-related pathology, or an interaction of PS-1 pathology with confounding factors, in this patient who was not otherwise at substantially increased risk of developing EPS.¹¹ Two primary implications for treatment are raised. First, neuroleptic agents, including atypical antipsychotics, should be used judiciously in early-onset dementia. Second, patients developing psychosis with neuroleptic sensitivity between the fourth and seventh decades of life should be suspected for neurodegenerative disorder, particularly FAD.

Directions for future research should include examination of determinants of phenotypic heterogeneity in FAD. Mutation-specific cognitive profiles in FAD and their relationships to neuropsychiatric manifestations should be elaborated. Factors contributing to the development of EPS and psychosis in FAD are poorly understood. Characterization of D₂-receptor variation in FAD is warranted. Finally, determining the contribution of atypical cerebral A β distribution and LB pathology to the development of EPS in the G206A substitution and their broader implications for understanding PS-1 AD await further investigation.

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Note: Arrow indicates proband
 Filled shapes indicate affected kin
 Numbers represent age at proband's initial examination or age at death

FIGURE 1.
 Pedigree for patient P.R.

TABLE 1

Neuropsychologic Assessment Findings

Cognitive Domain/Test	Raw Score		Z-score	
	1	2	1	2
Estimated premorbid level				
WTAR				
Total correct/50	35	NA	+0.3	NA
Estimated FSIQ	103			
Global level				
MMSE/30	22	18	-4.7	-8.5
Attention and executive functions				
WAIS-III digit span				
Total score/30	9	10	-1.3	-1.3
Span length				
Forward (F)	4	6	-1.6	-0.2
Backward (B)	3	2	-1.0	-1.6
Difference (F – B)	1	4	-0.6	-1.5
Trail making (second)				
Part A	55	75	-2.0	-2.7
Part B	506	347	4.0	3.8
SDMT/110	13	4	-4.6	-5.7
CDT/18	15	16		
MCST/48				
Total errors	NA	27	NA	-2.1
Perseverative errors	NA	14	NA	-2.2
Nonperseverative errors	NA	13	NA	-0.9
Categories completed/6	NA	0	NA	3.1
DRS subtests				
Initiation/37	28	33	-2.5	-0.8
Conceptualization/39	34	35	-1.2	-0.8
Sensorimotor				
Grooved pegboard (second)				
Dominant (R)	91	72	-1.5	+0.1
Nondominant (L)	100	83	-1.1	-0.5
SPE (errors/12)				
Hemisensory				
Tactile right	0	0	—	—
Visual right	0	0	—	—
Tactile left	0	0	—	—
Visual left	0	0	—	—
Hemiattention				
Tactile right	0	0	—	—

Cognitive Domain/Test	Raw Score		Z-score	
	1	2	1	2
Visual right	0	0	—	—
Tactile left	0	0	—	—
Visual left	0	0	—	—
PST	1/3	3/6	—	—
Language				
COWA-FAS	23	42	-1.6	+0.3
Animal fluency	6	15	-3.5	-0.8
BNT/60	52	50	-1.1	-1.3
Visuospatial processing				
CDT copy/5	4	2		
ROCFT copy/36	21	12.5	-9.3	-8.0
Learning and memory				
HVLT-R/12 words				
Learning trials	4, 5, 6	3, 4, 4	-3.0	-3.9
Delayed recall	0	0	-5.1	-5.1
Retention (%)	0	0	-6.4	-6.4
Recognition discrimination				
Delayed	5	1	-4.6	-7.8
True positives	9	7		
False positives	4	6		
ROCFT				
Delayed recall/36	2	2	-3.3	-3.9
Recognition/24	15	13	-3.4	-4.7
Psychopathology/emotion				
BDI-short/39	0	0		

1 indicates initial evaluation; 2, follow-up evaluation.

Z scores: average=0.

SD= ±1.0.

BDI-short indicates Beck Depression Inventory-short version; BNT, Boston Naming Test; CDT, Clock Drawing Test; COWA-FAS, Controlled Oral Word Association; DRS, Mattis Dementia Rating Scale; FSIQ, full scale IQ; HVLT-R, Hopkins Verbal Learning Test-Revised; MCST, Modified Wisconsin Card Sorting Test; MMSE, Mini-Mental State Examination; NA, not assessed; PST, Pocket Smell Test; ROCFT, Rey-Osterrieth Complex Figure Test; SDMT, Symbol Digit Modalities Test; SPE, Sensory-Perceptual Examination; WAIS-III, Wechsler Adult Intelligence Scale-Third Edition; WTAR, Wechsler Test of Adult Reading.