CASE RECORDS of the MASSACHUSETTS GENERAL HOSPITAL

Case 8-2011: A 32-Year-Old Woman with Seizures and Cognitive Decline

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PRESENTATION OF CASE

A 32-year-old woman was seen in the neurogenetics clinic at this hospital because of seizures and cognitive decline.

Absence seizures (staring spells) had reportedly begun when the patient was approximately 5 years of age, and atonic seizures (sudden loss of muscle tone resulting in dropping of the head and falling to the floor) had begun during adolescence. She briefly received an unknown medication for atonic seizures in childhood. When she was in her mid-20s, she began to have frequent episodic tremors at rest that worsened with action, occasional ballistic (sudden and jerking) movement of the arms, slowed speech, progressive difficulties with memory, and diminished reading comprehension, concentration, and sequence recall. At the age of 28 years, generalized tonic–clonic seizures lasting 1 to 15 minutes developed and increased in frequency, occasionally requiring hospitalization. Anticonvulsants were administered.

When the patient was 29 years of age, after the onset of generalized seizures, 24-hour video electroencephalography (EEG) was performed at another institution. The results showed normal background and generalized high-voltage bursts of spike-wave and polyspike discharges at a rate of 3 per second. These discharges were more prominent with hyperventilation and photic stimulation, with a frequency of 1 to 2 per second. Her responses to a personality assessment inventory at that time were thought to indicate a high level of psychological distress and suggested an attempt to portray herself in a negative light; however, scores on scales that were sensitive to psychotic and paranoid thinking were more elevated than those on scales that were sensitive to depression, as is typically seen in a "cry for help" profile. When she was 31 years of age, neuropsychological testing showed weaknesses in the domains of language, attention, executive functioning, and memory. No tests of mood or personality were administered. Cranial magnetic resonance imaging (MRI) without magnetic resonance spectroscopy was performed elsewhere 8 months before this evaluation and was reportedly normal.

On the initial visit to the neurogenetics clinic, the patient was accompanied by a family member who assisted with the history. The patient had had increasing myoclonic seizures during the preceding weeks. She had normal early development

and average academic performance, and she attended college but did not graduate. She reported that she had a history of migraine headaches, occasional shortness of breath, nausea, weight fluctuations, depression for which she had been hospitalized, and a remote history of alcohol abuse. She lived with her partner of many years. She had taught art classes intermittently but was currently receiving disability payments. Psychoactive medications had included fluoxetine, risperidone, olanzapine, and donepezil. Current medications included levetiracetam, lorazepam, fluoxetine, zonisamide, phenobarbital, and olanzapine, with zolpidem at night. She reported that she had smoked cigarettes heavily for 15 years, drank alcohol rarely, and did not use illicit drugs. Her father had seizures that began at 30 years of age, was hospitalized in a vegetative state for many years, and died at 48 years of age. Four of his siblings had intractable epilepsy, dementia, and early death.

On examination, the patient was alert and oriented, with a flushed face. The blood pressure and pulse were normal. There were no dysmorphic features, and the general physical examination was normal, with no cutaneous pigmented lesions, hepatosplenomegaly, or bone abnormalities. On neurologic examination, she followed all commands; she had slow, hesitant speech with occasional paraphasic errors, decreased attention and concentration, and deficits in short-term memory. Her ability to copy intersecting pentagons was mildly impaired. She reported pain with eye movements; and horizontal movements were full, ocular pursuit movements were smooth, and refixation was normal. Vertical eye movements were not full, and no retinal abnormalities were noted. Visual acuity was normal. Motor movements were initiated slowly. Tone was normal, without dystonia. There was no focal motor weakness, major sensory deficit, dysmetria, or ataxia. There was no tremor; there were occasional myoclonic jerks but no atonic postural loss. No overt seizures were noted.

Three months later, a skin biopsy was performed; the pathological examination revealed no evidence of lysosomal storage disease. The results of selected genetic and metabolic tests were normal.

During the next 18 months, the patient was followed by a neurologist near her home, and she returned to the neurogenetics clinic at regular intervals. She had headaches of increasing frequency and progressive cognitive decline, with slower mentation and increasing difficulties with short- and long-term memory. Despite the cognitive decline and extremely slow expressive language and processing, she continued to have a sense of humor. She had increasing seizure activity, with generalized tonic–clonic and atonic seizures, myoclonus and ataxia, and episodes of tremor. Her gait became shuffling, and decreasing mobility and balance made her wheelchair-dependent. She was hospitalized on several occasions because of frequent and intractable myoclonic seizures. Anticonvulsant medications during that period included lamotrigine, pyridoxine, zonisamide, lorazepam, levetiracetam, phenobarbital, topiramate, donepezil hydrochloride, phenytoin, clobazam, and diazepam rectal gel. Smoking-cessation counseling was offered, but the patient declined.

Eighteen months after her initial evaluation, cranial MRI revealed mild cerebral and cerebellar atrophy and mild periventricular hyperintensities on fluid-attenuated inversion recovery images, with normal magnetic resonance spectroscopy and magnetic resonance perfusion. Neuroophthalmologic examination showed no abnormalities. Neurologic examination showed stuttering speech, marked cogwheel rigidity, decreased rapid alternating movements, and mild dysmetria on finger-to-nose testing; no myoclonus was noted. An EEG was abnormal, showing generalized background slowing during brief wakefulness, as well as bifrontal spikes during sleep, without associated clinical symptoms. There were no electrographic seizures.

One month later, while the patient was alone and smoking, her shirt caught fire, and she sustained second- and third-degree burns to her face, neck, chest, and shoulders, with an estimated 15% of the total body involved. She was taken to another hospital, where intravenous fluids and tetanus toxoid were administered, the trachea was intubated, and mechanical ventilation was initiated. She was transferred to this hospital, where sedatives, anticonvulsants, glucocorticoids, magnesium, potassium, calcium, albumin, folate, thiamine, dalteparin, enteral nutrition, and inhaled ipratropium were administered. Topical wound care was provided, and skin grafting was per-

formed. Pneumonia due to methicillin-resistant *Staphylococcus aureus* developed. On the 10th day, in consultation with the family and her partner, and in accordance with the previously expressed wishes of the patient, comfort measures only were instituted. Mechanical ventilation was discontinued, and the trachea was extubated. The patient died shortly thereafter.

An autopsy was performed.

DIFFERENTIAL DIAGNOSIS

Dr. Katherine B. Sims: As the patient's neurologist, I am aware of the diagnosis. The patient had a normal birth and early neurodevelopmental history. There was no history of central nervous system infection, clinically significant head trauma, childhood developmental regression, or deterioration under metabolic stress.

The patient had a history suggestive of childhood absence epilepsy. Childhood absence epilepsy (Online Mendelian Inheritance in Man [OMIM] number 600131) and juvenile absence epilepsy (OMIM number 607631) are common idiopathic generalized epilepsies (OMIM number 600669).[1,2] Distinguished by the age at onset, both childhood absence epilepsy and juvenile absence epilepsy feature absence, early-morning, generalized tonic–clonic, and myoclonic seizures. A number of genes or susceptibility loci have been identified.[3,4] Both childhood and juvenile absence epilepsies are relatively benign and usually remitting, although they can be a prelude to more progressive myoclonic epilepsy syndromes, as may be true in this case.

This patient's history of falls and childhood seizures raises the possibility of atonic or myoclonic astatic seizures or childhood epileptic encephalopathy.[5] These epilepsies, often referred to as the Lennox–Gastaut syndrome,[6] are characterized by the onset in childhood of atonic or myoclonic astatic seizures and usually have a poor prognosis. They characteristically occur during the period from infancy through 10 years of age, with neurodevelopmental failure. They can be associated with a number of prenatal central nervous system diseases that result in maldevelopment, including primary cortical malformations, tuberous sclerosis, congenital infections, and stroke. They also can be associated with perinatal causes such as hypoxia and ischemia or intracranial hemorrhage and with postnatal causes, including meningoencephalitis, postinfectious syndromes, cerebrovascular disease, and hereditary degenerative disorders. In our patient, the Lennox–Gastaut Syndrome is exceedingly unlikely in view of the benign childhood course, normal neurodevelopmental history, and absence of infectious, postinfectious, and vascular disease. Degenerative neurogenetic disorders, however, remain in the differential diagnosis.

With the onset of myoclonus in this patient's teenage years and the background of relatively normal development and cognition, possible absence seizures, and normal EEG findings, one might consider the juvenile myoclonic epilepsies (OMIM number 254770), which account for 5 to 25% of idiopathic epilepsies, with an onset between 8 and 20 years of age[7] (Table 1). The patient's history of a psychiatric or mood disorder would not be incompatible with juvenile myoclonic epilepsies, which may occur with or without psychiatric features. However, the diagnosis of juvenile myoclonic epilepsies is not supported by her subsequent dementia, characterized by memory loss, aphasia, and generalized cognitive slowing. Myoclonus or myoclonic seizures could have been provoked by a variety of infections (e.g., subacute sclerosing panencephalitis, Lyme disease, infection with the human immunodeficiency virus [HIV], Creutzfeldt–Jakob disease, and neurosyphilis), but in this patient there was no known history or exposure suggestive of infection, and the results of cerebrospinal fluid examination were reportedly normal.

Although it was not clear what contributing role medications and psychosocial history had in the patient's clinical history and examination, the onset of generalized tonic–clonic seizures at 28 years of age, as well as concern about worsening cognitive function, caused us to consider the genetic progressive myoclonic epilepsies,[8-10] especially those with an onset in youth or early adulthood. The long list of these disorders (Table 1) includes the late-onset form of Tay–Sachs disease (GM_2 gangliosidosis), an autosomal recessive disorder characterized by psychiatric issues and mild cognitive difficulties and a later onset of proximal weakness, ataxia, and seizures; juvenile Gaucher's disease type IIIA, which is characteristically manifested as oculomotor ataxia, generalized tonic–clonic and myoclonic seizures,

Table 1. Myoclonic Epilepsies.*

Disorder	Subtype and Susceptibility Gene	Locus and Chromosome	MIM No.
Juvenile myoclonic epilepsies	EJM1 — *EFHC1;* EJM5 — *GABRA1;* EJM6 — *CACNB4;* EJM7 — *GABRD;* EJM8 — *CLCN2*	EJM2 — 15q14; EJM3 — 6p21; EJM4 — 5q12-q14	254770
Progressive myoclonic epilepsies			
Storage disorders			
Gangliosidoses			
GM_2 (juvenile or late onset)	*HEXA*		272800
Gaucher's disease, type III (juvenile)	*GBA*		231000
Neuronal ceroid lipofuscinosis			
Juvenile (Batten's disease)	*CLN3*		607042
Adult (Kufs' disease autosomal recessive; Parry type, autosomal dominant)			Autosomal dominant: 162350; autosomal recessive: 04300
Mucolipidosis			
Type I sialidosis (ML I, cherry-red-spot myoclonus epilepsy)	*NEU*		256550
Galactosialidosis (juvenile or adult)	*PPCA*		256540
Neuroaxonal dystrophy (adolescent or adult)	*NBIA2B*		610217
Syndromes			
Autosomal recessive			
Unverricht–Lundborg disease	*EPM1*, *CTSB*		254800
Progressive myoclonic epilepsy with ataxia	*EPM1B, PRICKLE1*		612437
Lafora's disease	*EPM2A*, *EPM2B*; laforin		254780
Spastic paraplegia with myoclonus epilepsy			270805
Ataxia with myoclonic epilepsy and presenile dementia			208700
Myoclonus, ataxia, and deafness			159800
Autosomal dominant			
Dentatorubral-pallidoluysian atrophy	*ATN1*		125370
Benign adult familial myoclonic epilepsy	*BAFME1*		601068
Benign adult familial myoclonic epilepsy	*BAFME2*		607876
Myoclonic epilepsy, Hartung type			159600
Myoclonus–dystonia	*DYT11*, *SGCE*		159900
X-linked recessive (progressive myoclonic epilepsy with ataxia)			310370
Mitochondrial disorders			
Myoclonic epilepsy with ragged-red fibers			545000
Leigh's disease			256000, 161700

* MIM denotes Mendelian Inheritance in Man.

and late dementia; and Gaucher's disease type IIIB and IIIC, in which adolescents typically have mild neurologic difficulties without myoclonus. Patients with Gaucher's disease type IIIA may also have non-neurologic manifestations, including hepatosplenomegaly, anemia or thrombocytopenia, infiltrative bone disease (which in types IIIB and IIIC systemic disease is more aggressive and severe), or all of these conditions. Progressive myoclonic epilepsy of the Unverricht–Lundborg type and that associated with Lafora bodies as well as with sialidosis (cherry-red-spot myoclonus) would also be on the list of possible diagnoses. In addition, one would have to consider the early-onset neurodegenerative disorders with psychiatric features, including Niemann–Pick type C disease, late-onset metachromatic leukodystrophy, juvenile Huntington's disease, Wilson's disease or juvenile Parkinson's disease (parkin type), and the neuronal ceroid lipofuscinosis disorders — both the juvenile CLN3 form (Batten disease)[11] and the adult form (Kufs' disease).[12,13]

If we approach the differential diagnosis for genetic juvenile or early-onset dementias with epilepsy from the other end of the age spectrum, it would include Alzheimer's disease (early-onset familial),[14] Huntington's disease-like 2, and the multiple-system tauopathies (MAPT-related) with presenile dementia.[15] These conditions include familial encephalopathy with neuroserpin inclusion bodies and the frontotemporal dementias (Pick's disease; frontotemporal dementia with parkinsonism; *GRN*-related frontotemporal dementia; inclusion-body myopathy with Paget's disease, frontotemporal dementia, or both; and *CHMP2B*-related frontotemporal dementia (FTD-*CHMP2B*). Of the MAPT-related disorders, only familial encephalopathy with neuroserpin inclusion bodies[16] and frontotemporal dementia with parkinsonism[17] have been associated with epilepsy.

At this point, Dr. Cole will review the EEG data, Dr. Caruso will present the neuroimaging findings, and Dr. Sherman will summarize the results of the neuropsychological testing, to clarify how these results might be helpful in establishing a diagnosis.

EEG FINDINGS

Dr. Andrew J. Cole: Reports on two EEG studies performed at another hospital when the patient was 29 years old were available. The first study showed frequent bursts of generalized spike-and-wave discharges at 3 Hz, each lasting up to 10 seconds. Discharges were activated by hyperventilation, drowsiness, and photic stimulation. One month later, after the patient received zonisamide at a dose of 200 mg per day, bursts of high-amplitude 3-Hz delta were observed, but the spike component had largely disappeared. Photic stimulation no longer elicited discharges. An EEG study performed at this hospital 2 years later, when the patient was 31 years of age, showed slowing of the background posterior dominant rhythm, high-amplitude bursts of delta slowing every 5 to 15 seconds, and both unilateral and bilateral epileptiform spike discharges arising from the anterior regions of the head every 30 to 60 seconds. A repeat study 3 weeks later showed more frequent and regular bursts of delta slowing occurring every 4 to 7 seconds and with continued focal and bilateral independent epileptic discharges intermingled.

The paroxysmal slowing observed in this patient is most frequently associated with diseases affecting diencephalic and brain-stem structures, whereas the slowing of background rhythm and the epileptic spikes are markers of cortical dysfunction. In patients with early progressive myoclonus epilepsies, the EEG may be indistinguishable from that in patients with common idiopathic, generalized epilepsy syndromes, with normal background frequencies and bursts of well-formed 2.5- to 4-Hz spike-and-wave complexes. As the illness progresses, generalized slowing and loss of the posterior dominant rhythm are seen in all the major diseases causing progressive myoclonus epilepsy.[18] Patient's with Kufs' disease have photosensitivity, often at unusually low flash frequencies of 1 to 3 Hz, and an anterior predominance of epileptic discharge, whereas patients with Lafora's disease typically have occipital discharges. In this patient, the photosensitivity and anterior predominance of epileptic discharges was consistent with, but not diagnostic of, Kufs' disease.

NEUROIMAGING FINDINGS

Dr. Paul A. Caruso: The MRI scan showed diffuse, largely symmetric, supratentorial and cerebellar atrophy. The frontal and parietal lobes along the high convexities and the superior vermis and cerebellar hemispheres were most conspicuously involved (Fig. 1). The thalami showed normal signal and volume. There was no evidence of cortical

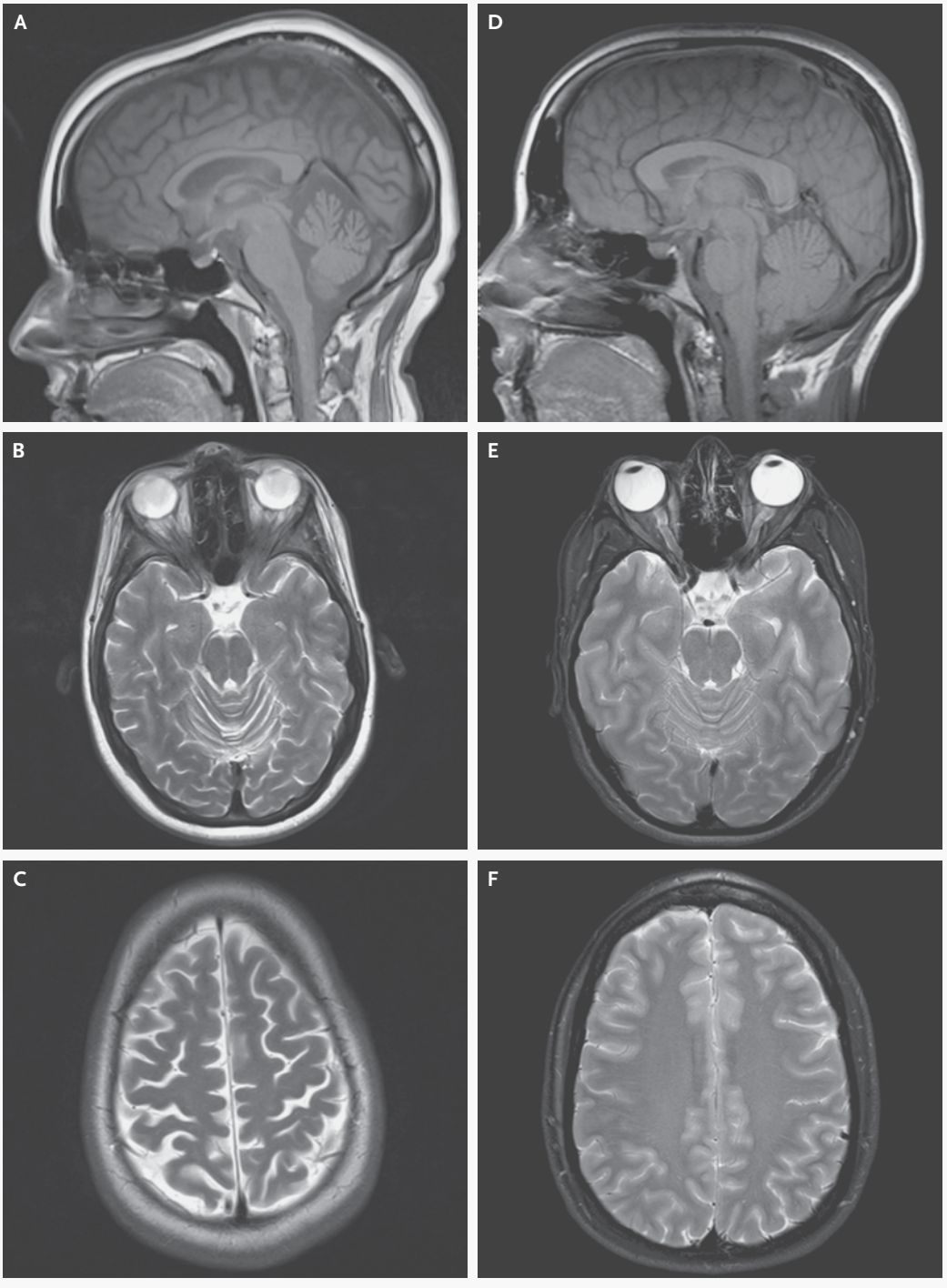

Figure 1. MRI Scans of the Brain from the Patient at 33 Years of Age and an Age-Matched Control.

A sagittal T_1-weighted image (Panel A) and axial T_2-weighted images at the level of the superior cerebellar hemispheres and vermis (Panel B) and the frontal and parietal lobes (Panel C) show largely symmetric atrophy in the brain of the patient. Atrophy involves the superior vermis and frontal and parietal lobes, as evidenced by abnormally wide sulci and cortical volume loss. Images of the brain of an age-matched control are shown in the same views (Panels D, E, and F).

malformation, phakomatosis, sequelae of prior TORCH infection (toxoplasmosis, other [syphilis, varicella, parvovirus infection, HIV infection], rubella, cytomegalovirus infection, and herpes simplex virus infection), hypoxic–ischemic injury, stroke, meningoencephalitis, or granulomatous disease. There were no findings to allow a diagnosis of an inborn error of metabolism or a disorder of myelin such as a gangliosidosis, mucolipidosis, mucopolysaccharidosis, or dentatorubral-pallidoluysian atrophy (DRPLA). Proton magnetic resonance spectroscopy over the left basal ganglia showed a slight decrease in levels of *N*-acetylaspartate. Decreased levels of *N*-acetylaspartate may be seen in Unverricht–Lundborg disease, Lafora's disease, and neuronal ceroid lipofuscinosis, but the findings were not specific for a particular neurodegenerative disorder.

RESULTS OF NEUROPSYCHOLOGICAL TESTING

Dr. Janet C. Sherman: The patient underwent a neuropsychological assessment at another hospital at the age of 31 years. She presented with memory difficulties of several years' duration. The onset and progression of her cognitive difficulties were unclear, although psychiatric symptoms were a prominent feature of her clinical presentation. The patient reported extreme levels of psychiatric distress, and an inventory that she completed at a different outside hospital 1 year before this neuropsychological evaluation showed psychotic and paranoid thinking.

The neuropsychologist assessed the patient's functioning across a broad range of cognitive domains on norm-referenced, standardized tests. She was generally cooperative during testing but occasionally declined to complete more difficult tasks. In contrast to her estimated range of premorbid abilities from low average to average, her full-scale, verbal, and performance IQ scores were borderline. Her most prominent areas of deficit were in measures of attention and executive functioning. She had difficulty on tests requiring working memory (e.g., digit sequence reversals and mentally solving arithmetic problems), cognitive flexibility (e.g., alternate sequencing of numbers and letters in a visual test and complex problem solving in which her rate of perseverative responses was elevated), and strategic aspects of memory. Specifically, her performance on memory tests was characterized by impaired encoding but preserved retention of information. The patient also had a severely impaired ability to name pictured objects.

The patient's combined psychiatric symptoms and her specific cognitive findings are consistent with a pattern of deficits associated with either frontal or subcortical systems dysfunction.

Dr. Sims: Our patient had childhood absence seizures, followed by the onset in her late 20s of myoclonus, generalized seizure disorder, and dementia. Generalized atrophy detected on MRI and abnormalities on EEG studies and neuropsychological testing suggested a subcortical dementia, and given the history of autosomal dominant transmission (Fig. 2), the autosomal recessive disorders could be excluded.

The differential diagnosis for the late-onset autosomal dominant myoclonic epilepsies with dementia excludes the majority of lysosomal disorders, with the exception of rare cases of late-onset autosomal dominant neuronal ceroid lipofuscinosis[13,19-23] (Table 2). The neuropsychiatric features in this patient, even in the absence of a history or evidence of multisystem dysfunction, would not necessarily rule out consideration of mitochondrial encephalopathy with ragged-red fibers, but one would expect maternal inheritance of that disorder. Leigh's disease, a mitochondrial encephalopathy, can result from nuclear DNA mutations but is usually an autosomal recessive disorder. It would be exceedingly rare for Leigh's disease to develop in the fourth decade of life. Huntington's disease might be considered, given the history of autosomal dominant familial, neuropsychiatric, and generalized myoclonic epilepsy; however, the patient did not have the dystonia, rigidity, or chorea that typically accompanies Huntington's disease.

Severe, progressive myoclonic epilepsy would be rare in Huntington's disease. Patients with benign adult familial myoclonic epilepsy type 1 and type 2 have tremors, and the disorder is nonprogressive, making this diagnosis unlikely in our patient. The diagnosis of myoclonic epilepsy of the Hartung type (without Lafora bodies) might be considered in this patient, but it is not rapidly progressive and thus unlikely. Although one cannot exclude X-linked disorders from consideration, these manifestations in a female patient would be exceedingly rare. Only a single family with X-linked progressive myoclonic epi-

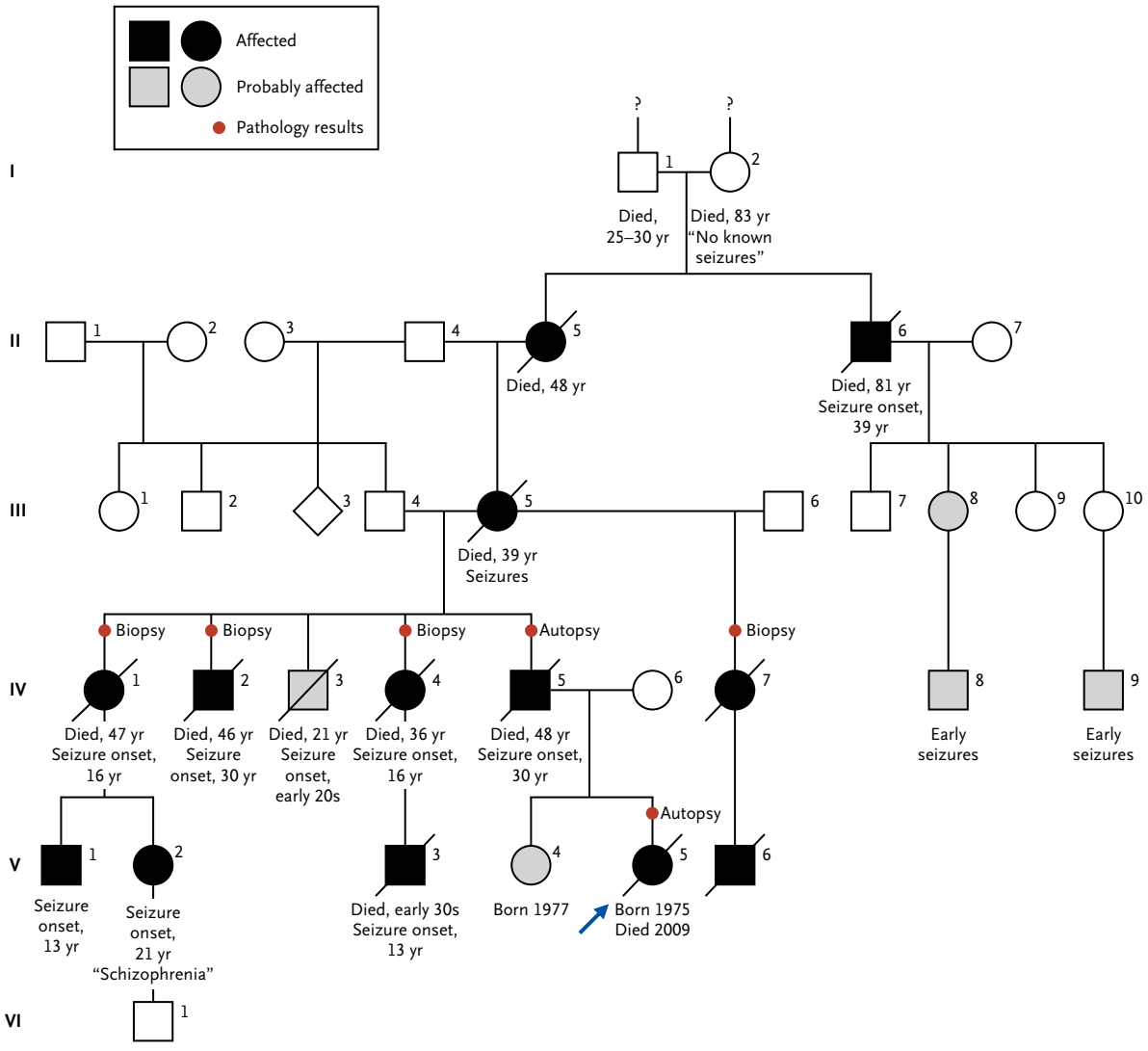

Figure 2. Family Pedigree.

The family pedigree of the patient (indicated by the arrow) suggests autosomal dominant inheritance. Red dots indicate patients with pathological features (granular osmophilic deposits and fingerprint bodies) shown on biopsy to be consistent with neuronal ceroid lipofuscinosis. Squares indicate male family members, circles female family members, diamonds sex unknown, and slashes deceased family members who were affected or probably affected.

lepsy has been described, and that family had prominent ataxia.[24] The absence of a cherry-red spot on ophthalmologic examination would usually rule out the diagnosis of sialidosis. Lafora's disease would, by definition, be associated with periodic acid–Schiff (PAS)-positive cytoplasmic inclusions in biopsy specimens of skin, muscle, or other tissues. If biopsy specimens were obtained from patients with familial encephalopathy with neuroserpin inclusion bodies, the hallmark neuroserpin inclusion bodies would be expected to be present in neurons. Patients with the Unverricht–Lundborg type of progressive myoclonic epilepsy would typically have a more protracted course of dementia.

Biopsy and autopsy specimens obtained from

Table 2. Cases of Autosomal Dominant, Late-Onset, Neuronal Ceroid Lipofuscinosis (Kufs' Disease, Parry type) Reported in the Literature.

Family No.	Age at Onset	Age at Death	Clinical Features	Neuropathological Findings	Electron-Microscopical Findings	Reference and Yr
	(mean or range, yr)					
1	32	42	Seizures, myoclonus, dementia, ataxia	Storage in the thalamus, substantia nigra, midbrain and pons, spinal cord		Boehme et al., 1971[19]
2	40	47	Weakness, incoordination, ataxia, myoclonus, dementia, aphasia	Hypothalamus, thalamus, substantia nigra, midbrain, cerebellum		Boehme et al., 1971[19]
3	38	Alive at publication	Seizures, facial dyskinesia, dementia	Storage in the hypothalamus, thalamus, substantia nigra, midbrain, and cerebellum		Ferrer et al., 1980[21]
4	32–40	41–58	Seizures, myoclonus, dementia (within 3 yr after onset), dyskinesias (choreiform), rigidity, ataxia	Frontal parietal, temporal, cerebellar atrophy; substantia nigra cell loss; storage in the cortical, basal ganglia, thalamus, brain stem, cerebellar nuclei		Josephson et al., 2001[13]
5	40–50		Myoclonus, seizures, dementia, or depression then Parkinson's disease	Generalized neuronal loss in the substantia nigra (pars compacta and reticulata), loss of D2-receptor binding in striatum	Granular osmophilic deposits, fingerprint inclusions, curvilinear inclusions	Nijssen et al., 2002[23]
6*	27–30	46–49	Myoclonus, dysarthria, ataxia, seizures, dementia, Parkinson's disease (course over 2–5 yr)		Granular osmophilic deposits	Burneo et al., 2003[20]
7			Dementia, behavioral issues, extrapyramidal movements, suprabulbar and cerebellar dysfunction		Fingerprint inclusions	Ivan et al., 2005[22]

* This family was related to the patient under discussion.

family members of this patient showed electron-microscopical inclusions (granular osmophilic deposits and fingerprint bodies) suggestive of a neuronal ceroid lipofuscinosis.[20] Families with autosomal dominant or autosomal recessive disease with the Kufs' type of neuronal ceroid lipofuscinosis have been described, although reports of families with autosomal dominant disease are exceedingly rare (Table 2). Electron microscopy of skin-biopsy specimens from this patient was performed three times, and all three samples were negative. Enzyme testing to detect palmitoyl-protein thioesterase 1 (PPT1; *CLN1*) and tripeptidyl-peptidase 1 (TPP1; *CLN2*), as well as molecular DNA testing for *CLN3*, *CLN5*, *CLN6*, *CLN7*, and *CLN8* mutations, were negative. Without the family history and electron-microscopical findings in family members, we would have performed more extended testing appropriate to this case and its differential diagnosis. These tests would have included liver-function studies, measurement of biochemical markers of oxidative-phosphorylation dysfunction in blood and muscle-biopsy specimens, and blood tests to detect ceruloplasmin and lysosomal enzymes. We would have performed molecular testing for Huntington's disease; mitochondrial encephalopathy with ragged-red fibers; DRPLA; *PARK2*; *EPM1* (Unverricht–Lundborg disease); and *EMP2A* (Lafora's disease). We would also have performed cholesterol-esterification studies and filipin staining in fibroblasts to detect Niemann–Pick disease type C. In addition, a brain biopsy might have been considered.

DR. KATHERINE B. SIMS'S DIAGNOSIS

Autosomal dominant lysosomal disorder, onset in young adulthood, most likely neuronal ceroid lipofuscinosis (Kufs' disease).

PATHOLOGICAL DISCUSSION

Dr. Matija Snuderl: The brain weighed 1360 g (normal weight, 1250 to 1400). The hemispheres were symmetric, and there was no evidence of trauma or herniation. Coronal sections of the brain revealed a preserved cortical band and a sharp junction between gray and white matter, with no macroscopical defects in the gray or white matter. The basal ganglia and hippocampus were of normal size and shape.

Microscopical examination showed a massive accumulation of lipofuscin in virtually all neurons of the central nervous system (Fig. 3), including the cortex, subcortical structures, cerebellum, brain stem, and spinal cord. The accumulated material in neurons was PAS-positive and showed strong autofluorescence with a broad excitation and emission spectrum. Electron-microscopical studies revealed an accumulation of dense osmophilic material with a vague internal architecture resembling fingerprint shapes and occasional curvilinear bodies. There was some loss of neurons in the substantia nigra pars compacta, locus ceruleus, and cerebellar granule-cell layer, accompanied by reactive gliosis.

The white matter was relatively unaffected, with well-preserved myelin. There was mild astrogliosis with some microglial activation. The normal brain weight, with no clinically significant loss of neurons or secondary white-matter degeneration, suggested that the disease had not reached its end stage.[25]

General autopsy findings included an enlarged heart with biventricular hypertrophy and biatrial dilatation but no clinically significant coronary artery disease. PAS, PAS with diastase, Luxol fast blue, and iron stains revealed modestly increased levels of lipofuscin in the myocardium, which were confirmed on electron microscopy.

In summary, the findings are diagnostic of adult-type neuronal ceroid lipofuscinosis, or Kufs' disease.

Dr. Sims: The autopsy findings confirmed the clinical suspicion of late-onset neuronal ceroid lipofuscinosis (Kufs' disease). Because the genes for the autosomal dominant and autosomal recessive forms of Kufs' disease have not been identified, molecular testing was limited to the exclusion of known genetic loci of neuronal ceroid lipofuscinosis. Further genetic studies involving families with Kufs' disease may in the future identify the cause of the disease, and fibroblasts from this patient are being used to model the disease and to provide a resource for preclinical testing of possible therapeutic agents. Until we have a better understanding of the basis of this disease, the treatment of myoclonic epilepsy with dementia will remain challenging, as it was in this patient.

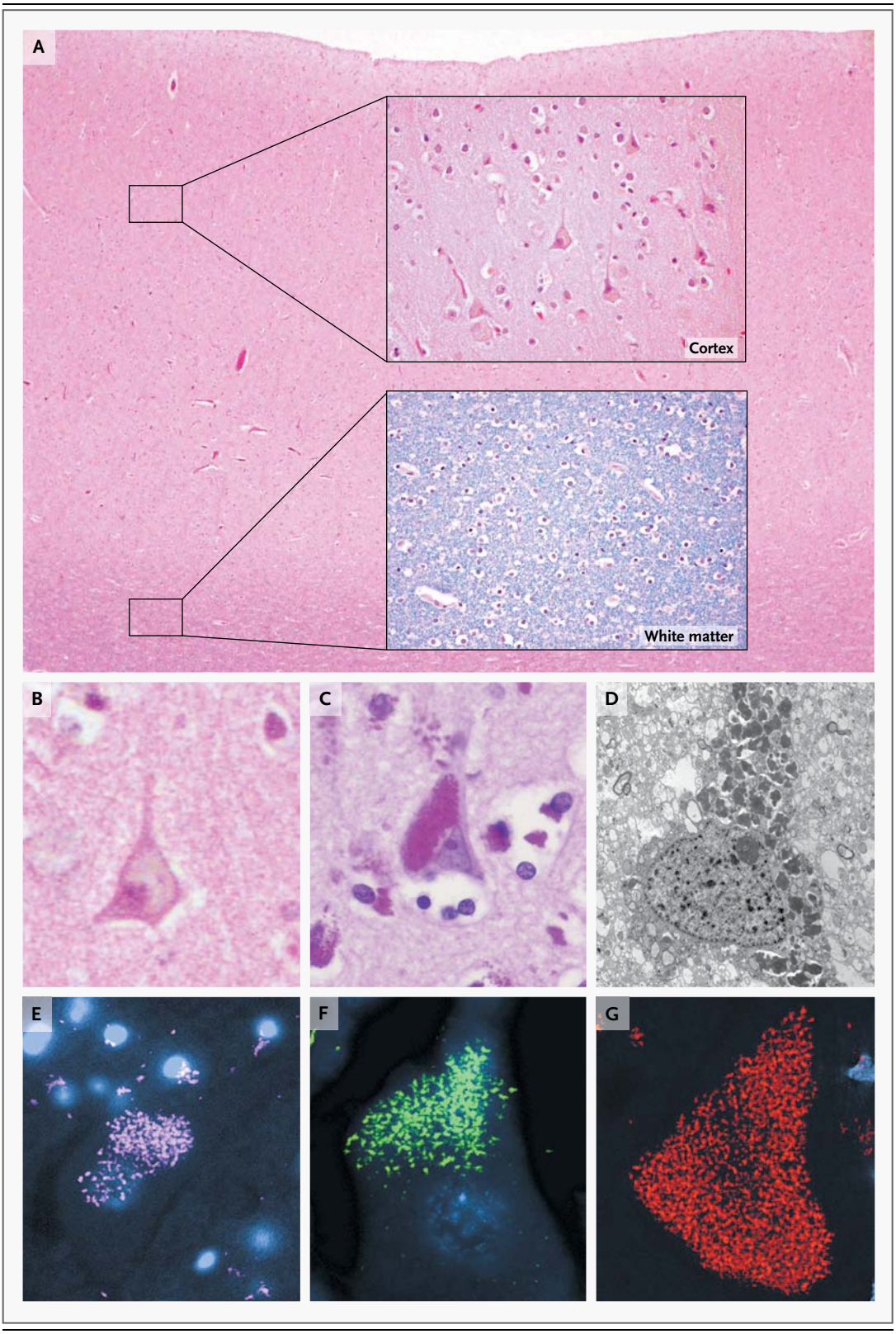

Figure 3 (facing page). Neuropathological Findings at Autopsy.

A low-magnification view of the cerebral cortex (Panel A, Luxol fast blue–hematoxylin and eosin stain) shows a preserved cortical band and underlying white matter. On higher magnification, white matter has preserved myelinated tracts, whereas cortical neurons have an accumulation of pale golden brown material (Panel A, insets). The accumulated lipofuscin in the cytoplasm of neurons (Panel B, Luxol fast blue–hematoxylin and eosin stain) is positive on periodic acid–Schiff staining (Panel C) and appears as dense osmophilic material with vague internal architecture on electron microscopy (Panel D). In tissue sections stained with nuclear 4′-6-diamidine-2-phenylidole dihydrochloride (DAPI), the accumulated material is strongly autofluorescent, with a broad excitation and emission spectrum (Panels E, F, and G).

DISCUSSION OF MANAGEMENT

Dr. Cole: The treatment of seizures in patients with progressive myoclonus epilepsies is unsatisfactory. General principles of treatment should include avoiding potentially neurotoxic agents such as phenytoin and avoiding drugs that may exacerbate generalized spike-and-wave discharges such as carbamazepine, tiagabine, gabapentin, pregabalin, and vigabatrin. Modest benefit has been reported or observed in some patients treated with valproate, lamotrigine, benzodiazepines (e.g., clonazepam), piracetam, levetiracetam, or zonisamide. No data are available regarding the role of lacosamide or rufinamide.

ANATOMICAL DIAGNOSIS

Kufs' disease (autosomal dominant, Parry type, young-adult–onset neuronal ceroid lipofuscinosis).

This case was presented at the Neurology Grand Rounds, May 13, 2010.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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