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Sporadic Fatal Insomnia in an Adolescent

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KEY WORDS

adolescent, Creutzfeldt-Jakob disease, prion disease, sporadic fatal insomnia, transmissible spongiform encephalopathy

ABBREVIATIONS

NPDPSC—US National Prion Disease Pathology Surveillance Center

PK—proteinase K

PrP^{Sc}—scrapie prion protein

sFI—sporadic fatal insomnia

vCJD—variant Creutzfeldt-Jakob disease

Ms Blase performed the case investigation (medical record review, conducted family interviews), and drafted, edited, and finalized the manuscript as submitted; Dr Cracco performed the laboratory testing, drafted the laboratory findings, created figures and drafted the legends for each figure, and critically reviewed the manuscript; Dr Schonberger provided guidance on the case investigation and critically revised the manuscript; Dr Maddox assisted in obtaining the medical records, provided guidance on the case investigation, and critically revised the manuscript; Ms Cohen and Mr Cali performed the laboratory testing, drafted the laboratory findings, assisted in creation of figures, drafted figure legends, and critically reviewed the manuscript; and Dr Belay conceptualized the case report, coordinated the collaboration between the Centers for Disease Control and Prevention and the US National Prion Disease Pathology Surveillance Center, assisted in drafting the article, and critically reviewed and revised the manuscript. All authors approved the final manuscript as submitted.

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abstract



The occurrence of sporadic prion disease among adolescents is extremely rare. A prion disease was confirmed in an adolescent with disease onset at 13 years of age. Genetic, neuropathologic, and biochemical analyses of the patient's autopsy brain tissue were consistent with sporadic fatal insomnia, a type of sporadic prion disease. There was no evidence of an environmental source of infection, and this patient represents the youngest documented case of sporadic prion disease. Although rare, a prion disease diagnosis should not be discounted in adolescents exhibiting neurologic signs. Brain tissue testing is necessary for disease confirmation and is particularly beneficial in cases with an unusual clinical presentation. *Pediatrics* 2014;133:e1–e5

Prion diseases are rare, invariably fatal, neurodegenerative diseases characterized by long incubation periods and an absence of host immune response. The hallmarks of prion diseases include neuronal accumulation of scrapie prion protein (PrP^{Sc}), the abnormal isoform of a cellular glycoprotein known as the prion protein,¹ and neuropathologic features of spongiform changes, astrogliosis, and neuronal loss.² PrP^{Sc} is believed to replicate by recruiting and misfolding neighboring cellular prion proteins through an autocatalytic process.^{3,4}

In humans, prion diseases occur in 3 forms: genetic, acquired, and sporadic. Genetic prion diseases are associated with mutations in the prion protein gene and account for 5% to 15% of all cases. Acquired prion diseases result from iatrogenic exposures and, in the case of variant Creutzfeldt-Jakob disease (vCJD), from consumption of bovine spongiform encephalopathy-contaminated beef products.²

Sporadic prion diseases are believed to be caused by the spontaneous, random conversion of the normal prion protein to PrP^{Sc} without an environmental source of infection.^{5,6} Sporadic Creutzfeldt-Jakob disease accounts for ~85% of human prion diseases whereas sporadic fatal insomnia (sFI) accounts for ~1% to 2%.⁶ Patients with sFI share phenotypic similarities with patients who have the genetic prion disease fatal familial insomnia⁷ but lack a mutation at codon 178 of the prion protein gene.⁸ Fatal insomnia patients usually suffer from insomnia, motor abnormalities, and altered autonomic functions.^{7,8} Polysomnography typically shows reduction of sleep-related EEG activities, such as K-complexes and spindles,⁹ and positron emission tomography scans may show focal thalamic hypometabolism.¹⁰ Neuropathologic studies demonstrate prominent lesions in the thalamus relative to other brain regions.^{7,11}

In April 2012, the US National Prion Disease Pathology Surveillance Center (NPDPSC) confirmed a prion disease based on the autopsy findings of a deceased boy with illness onset at 13 years of age. This article describes the results of the case investigation and alerts pediatricians that, although rare, prion disease may occur in teenagers.

CASE REPORT

Clinical Features

On February 16, 2009, a 13-year-old boy presented to an emergency department with slow, slurred speech, mood lability, and double vision. The patient had suffered 2 previous concussions: 2 weeks earlier when he was elbowed in the temple, fell, and hit the back of his head and ~4 months earlier during football practice. Computed tomography, MRI, and magnetic resonance angiogram of the head and neck were normal. Due to his neurologic signs and history of concussions, the patient was diagnosed with probable post-concussive syndrome. In late March, the patient returned to the hospital for an evaluation by a pediatric neurologist who noted a mild, coarse tremor in his upper extremities. The patient also complained of slowed cognition, memory problems, and difficulties in fine motor function, including writing and occasional balance problems. In May 2009, the patient underwent eye surgery to correct esotropia. Approximately 2 weeks later, dysmetria was noted on physical examination as well as prominent sulci with mild to moderate cerebellar atrophy indicated by an MRI.

On June 8, 2009, the patient was hospitalized for worsening coordination and ataxic gait with fever and malaise. Influenza A H1N1 was documented and he was treated with oseltamivir. During hospitalization, a physician noted hyperkinetic movements of the upper and lower extremities. The patient was transferred to a rehabilitation center

where several laboratory studies were conducted, including a paraneoplastic panel, the results of which were negative. Over the next 3 weeks, the patient developed partial bowel and bladder incontinence and progressive ataxia. Given the patient's lack of progress, he was transferred to another rehabilitation center. On admission, the patient was noted to have shuffling gait and marked memory difficulties. The admitting physician observed the absence of prion disease laboratory tests, but this diagnosis was not pursued. Possible diagnoses of limbic encephalitis or paraneoplastic processes were considered. At discharge, the patient's working diagnosis remained an ill-defined neuroimmunologic disorder or subacute encephalopathy. According to the patient's mother, until this hospitalization, the patient had full mobility, was attending school, and could perform activities of daily living. When the patient left the facility he was discharged with a wheelchair, no longer able to perform activities of daily living, and he began homeschooling.

The patient continued to gradually decline, and in July 2010 he presented to the emergency department with a broken ankle from climbing out of a second story window. While in the hospital, choreoathetosis, truncal ataxia, and ballistic movements of the arms, legs, and head were observed. Delirium was also noted, but physicians were unsure whether this was due to psychoactive medications or to progression of the underlying condition. A diagnosis of mitochondrial disorder was proposed. After this hospitalization, the patient's mother noted her son's increased difficulty with chewing and swallowing, and his food had to be mashed or blended.

In late September 2011, the patient was rehospitalized for fever and difficulty breathing. He was diagnosed with aspiration pneumonia, treated with a 7-day course of clindamycin, and placed on

a feeding tube. Generalized full-body twitches not resulting from seizure activity and possible myoclonic jerking, ankle clonus, and increased body tone were noted during this visit.

Five months later, the patient arrived at the hospital with fever and acute respiratory distress and was admitted to the PICU. He continued to deteriorate and eventually had to be intubated and placed on ventilatory support. Multiple attempts to extubate him were unsuccessful due to worsening respiratory distress. The patient died in February 2012 at the age of 16 years (35 months after illness onset). The cause of death was indicated as respiratory failure secondary to progressive neurodegenerative disorder. An autopsy was performed, and the brain tissue was sent to the NPDSC.

Diagnostic Studies

Neurohistologic examination demonstrated moderate to severe spongiform changes and astrogliosis in the cerebral neocortex. The thalamic medio-dorsal, anteroventral and pulvinar nuclei,

and the olivary nuclei showed severe neuronal loss and astrogliosis (Fig 1A). Fine prion protein deposition and occasional clusters of aggregates were observed in the cerebral cortex according to immunohistochemistry, and prion protein deposition was focal in the molecular layer of the cerebellum (Fig 1 C and D).

Standard western blot analysis, performed on tissue samples from different brain regions by using previously described methods,¹² showed that the unglycosylated form of proteinase K (PK)-resistant PrP^{Sc} migrated to 19 kDa and was consistent with PK-resistant PrP^{Sc} type 2. This pattern was observed in all areas examined except the cerebellum, where no signal was detected (Fig 2A). However, after a sodium phosphotungstic acid enrichment procedure,¹³ PK-resistant PrP^{Sc} type 2 was also visible in the cerebellar cortex (Fig 2B). The amount of PK-resistant PrP^{Sc} varied by location and was greater in the cerebral cortex compared with the subcortical regions. Densito-

metric analyses on PK-resistant PrP^{Sc} in the cerebral cortex revealed a glycoform ratio similar to other sFI cases (Fig 3).⁸ Methionine homozygosity at codon 129 with no mutations was established with prion protein gene analysis, performed as described previously.¹⁴

DISCUSSION

Neuropathologic, biochemical, and genetic analyses of the patient's autopsy brain tissue are consistent with that of other patients with sFI.⁸ The analyses showed: (1) methionine homozygosity at codon 129 and lack of mutation in the prion protein gene; (2) severe neuronal loss and astrogliosis in the thalamic nuclei; (3) the presence of PK-resistant PrP^{Sc} type 2; (4) glycoform ratios different from those of fatal familial insomnia and consistent with those associated with sFI^{8,15}; and (5) lower amounts of PK-resistant PrP^{Sc} in subcortical regions than the cerebral cortex.¹⁶ No evaluation of insomnia or dysautonomia was performed, and their presence or absence is unknown. Insomnia is often difficult to

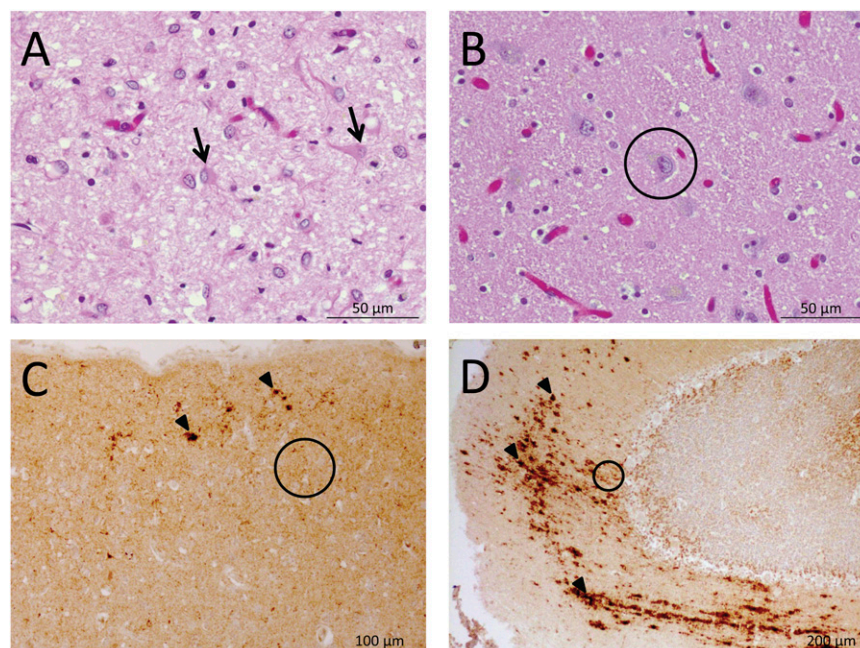


FIGURE 1

Histopathology and immunohistochemistry. A, The mediadorsal thalamic nucleus of the propositus shows intense reactive astrogliosis (arrows) and absence of neurons. B, The same brain region from a control subject showing normal tissue histology with prominent neurons (circle). C and D, Patterns of granular (circles) and plaque-like (arrow heads) prion protein immunostaining by using antibody 3F4 in the (C) occipital cortex and (D) molecular layer of the cerebellum.

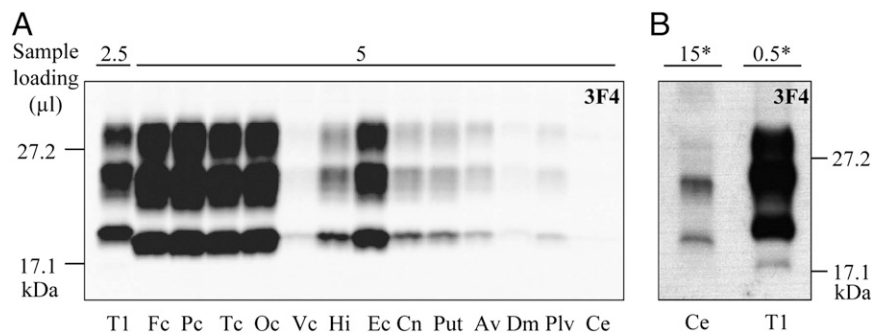


FIGURE 2

Electrophoretic profile of PK-resistant PrP^{Sc}. A, Twelve different brain areas showing PK-resistant PrP^{Sc} consistent with type 2. B, PK-resistant PrP^{Sc}-enriched preparations showing type 2 PrP^{Sc} in the cerebellum. Av, anterior ventral thalamic nucleus; Ce, cerebellum; Cn, caudate nucleus; Dm, mediodorsal thalamic nucleus; Ec, entorhinal cortex; Fc, frontal cortex; Hi, hippocampus; Oc, occipital cortex; Pc, parietal cortex; Plv, pulvinar; Put, putamen; T1, PK-resistant PrP^{Sc} type 1; Tc, temporal cortex; Vc, visual cortex. PK: 10 U/mL (1 U/mL equal to 17.2 g/mL of PK). *Samples concentrated 10 times.

detect without polysomnography, which was not performed in this case.

The patient had no recorded iatrogenic exposures, no exposure to deer and elk with possible chronic wasting disease, and did not travel outside of the United States, thus reducing the likelihood of exposure to bovine spongiform encephalopathy. More importantly, the clinical manifestations, neuropathology, and western blot profiles were inconsistent with a vCJD diagnosis. The laboratory findings along with these features support the diagnosis of sFI.

A diagnosis of prion disease was surprising in this patient due to his

exceptionally young age and unusual clinical presentation. Younger cases often indicate an environmental source of infection as shown by the unusually young age of initial cases of iatrogenic transmission in the United States and vCJD in the United Kingdom.^{17–22} Deaths from sporadic prion disease in those aged <20 years are extremely rare, with only 7 cases of sporadic Creutzfeldt-Jakob disease previously recorded.²³ In addition to his age, the patient's multiple concussions were diagnostically deceptive. Although the early clinical signs could overlap with those found in post-concussive syndrome, their progressive

worsening and development of additional neurologic signs led to considerations of alternate diagnoses later in the disease course.

Although rare, a prion disease should not be discounted in adolescents exhibiting neurologic signs. When results of testing for common causes are unrevealing, radiologic studies are nonindicative, and no alternative explanations exist for neurologic deterioration, a prion disease should be considered in the differential diagnosis. Positive cerebrospinal fluid test results for 14-3-3 and tau proteins strongly support a prion disease diagnosis. However, results of these tests

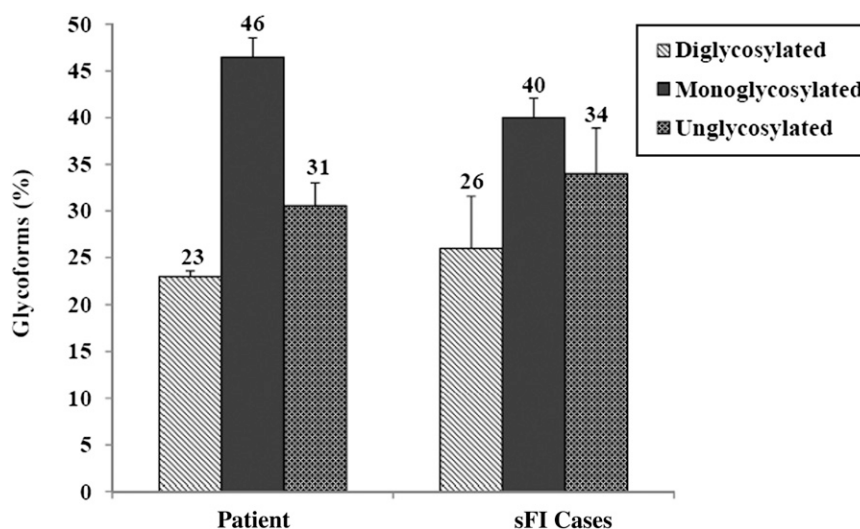


FIGURE 3

The mean relative proportions of PK-resistant PrP^{Sc} glycoforms sampled from 4 cortical regions (frontal, parietal, temporal, and occipital cortices) in the present case (23, 46, and 31). This case shows a higher representation of the monoglycosylated, followed by the unglycosylated and diglycosylated forms, similar to that of previously published sFI cases (26, 40, and 34).⁸

may not be positive in patients with sFl. Positron emission tomography scans and polysomnography have a higher diagnostic yield for sFl,⁶ but they were not performed in this case. Clinicians should also carefully evaluate patients for dysautonomia when considering sFl. Brain biopsy testing may be helpful in ruling out other potentially treatable conditions and in confirming a prion disease, but the benefits should be weighed against the risks associated with such an invasive

procedure. Furthermore, depending on the area of the brain affected and sampled, a negative brain biopsy sample may not necessarily rule out the diagnosis of prion disease. Fresh and frozen tissue samples may increase diagnostic sensitivity.²⁴ As demonstrated by this case, a brain autopsy should be performed in patients who die of a progressive neurodegenerative disorder of unknown cause. Such testing is necessary to confirm the presence and type of most prion diseases.

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