CASE REPORT

Case of fatal familial insomnia caused by a d178n mutation with phenotypic similarity to Hashimoto's encephalopathy

Jessica M Stevens, Matthew R Levine, Anne E Constantino, Gholam K Motamedi

Department of Neurology,
MedStar Georgetown University
Hospital, Washington, District of
Columbia, USA

Correspondence to
Dr Gholam K Motamedi,
motamedi@georgetown.edu

Accepted 20 June 2018

SUMMARY

Fatal familial insomnia (FFI) is a rare prion disease commonly inherited in an autosomal dominant pattern from a mutation in the PRion Protein (PRNP) gene. Hashimoto's encephalopathy (HE) is characterised by encephalopathy associated with antithyroid peroxidase (TPO) or antithyroglobulin (Tg) antibodies. These two conditions characteristically have differing clinical presentations with dramatically different clinical course and outcomes. Here, we present a case of FFI mimicking HE. A woman in her 50s presented with worsening confusion, hallucinations, tremor and leg jerks. Several maternal relatives had been diagnosed with FFI, but the patient had had negative genetic testing for PRNP. MRI of brain, cervical and thoracic spine were unremarkable except for evidence of prior cervical transverse myelitis. Cerebrospinal fluid analysis was normal. Anti-TPO and anti-Tg antibodies were elevated. She was started on steroids for possible HE and showed improvement in symptoms. Following discharge, the results of her PRNP gene test returned positive for variant p.Asp178Asn.

BACKGROUND

Fatal familial insomnia (FFI) is a rare prion disease commonly inherited in an autosomal dominant pattern from a mutation in the PRion Protein (PRNP) gene, or less commonly from a non-inherited sporadic mutation. It typically presents with sleep disturbance and inevitably progresses to death. However, previous studies have noted a great deal of phenotypic variability of the initial presentation of the disease.^{1,2} On the other hand, Hashimoto's encephalopathy (HE) is characterised by encephalopathy associated with antithyroid peroxidase (TPO) or antithyroglobulin (Tg) antibodies, in the absence of alternative causes.^{3,4} These two conditions characteristically have differing clinical presentations with dramatically different clinical course and outcomes. Here, we report a clinical case of a patient with FFI with initial clinical presentation resembling HE, with a transient initial improvement in symptoms in response to corticosteroid therapy.

CASE PRESENTATION

A woman in her 50s presented to an outside hospital with worsening confusion, hallucinations, hand tremor and irregular leg jerks. Her medical history included hypothyroidism and cervical transverse

myelitis of unknown aetiology two decades earlier with residual neuropathic pain and bilateral hand tremor.

Her family history was strongly positive for FFI including her mother and multiple maternal relatives. The patient had been tested two decades prior because of her family history while she was undergoing workup for transverse myelitis and reportedly had a negative genetic test result. She had two siblings who had declined testing, but had not had any symptoms suggestive of FFI.

Starting 3 months prior to admission, she began to have worsening of her bilateral hand tremors, bilateral leg jerking and more recently she had become very 'fidgety'. She presented with bilateral hearing loss and saw an audiologist with no clear aetiology found. In the few weeks prior to presentation, she developed difficulty in walking and progressively worsening visual and auditory hallucinations. She experienced worsening confusion, hallucinations and agitation at night, along with talking and acting out her dreams during sleep. Her progressive fatigue and excessive daytime sleepiness were attributed to lack of sleep at night due to hallucinations and possibly rapid eye movement (REM) sleep behaviour disorder. For the past few days, she had developed 'freezing' episodes of her hands and legs, which prompted her to go to the emergency department.

Her neurological examination revealed normal orientation, language and cranial nerves. She was unable to recall basic facts about her life and had difficulty recalling her symptoms. She had difficulty carrying on a conversation, and at times she would say things that were out of context. Her strength was mildly decreased symmetrically in proximal muscle groups with diminished reflexes throughout; sensation was intact. She had a bilateral low-amplitude high-frequency postural hand tremor without dysmetria or ataxia. Her gait was narrow based and shuffling, and she was unable to perform tandem gait.

At the outside hospital, her oxcarbazepine and duloxetine used for neuropathic pain were held because of mild hyponatraemia. Sodium returned to 133 by arrival to our institution. Urine toxicology screen and alcohol level were negative. She was febrile to 101.3°F (38.5°C) on admission and was placed on empiric ceftriaxone, but all cultures returned negative. Brain MRI was normal. Cervical

© BMJ Publishing Group Limited. No commercial re-use. See rights and permissions. Published by BMJ.

To cite: Stevens JM, Levine MR, Constantino AE, et al. *BMJ Case Rep* Published Online First: [please include Day Month Year]. doi:10.1136/bcr-2018-225155

and thoracic spine MRI with and without contrast showed myelomalacia at C5–C6 levels consistent with her history of prior transverse myelitis. A lumbar puncture was performed revealing normal white cell count (WCC), red cell count (RCC), glucose and protein.

An extensive workup revealed normal thyroid-stimulating hormone, T4, T3, B₁₂, thiamin, and ceruloplasmin, negative HIV and rapid plasma reagin, neuromyelitis optica antibody, paraneoplastic panel and anti-N-methyl-D-aspartate (NMDA) receptor antibody; antinuclear antibodies was positive with a homogeneous pattern and titre of 1:160, but further rheumatological labs were unremarkable (including dsDNA, anti-Sjögren's-syndrome-related antigens A and B, RF, extractable nuclear antigen panel, C3, C4). Anti-TPO antibodies were elevated at 459 and anti-Tg antibodies were elevated at 180. Long-term video-electroencephalography (EEG) monitoring over 4 days revealed a normal baseline EEG with no epileptiform activity. Her lower extremity myoclonus and episodes of hallucinations were captured on EEG, with no correlating epileptiform activity. Given continued progression of symptoms, a repeat brain MRI was done that was normal. A repeat lumbar puncture was performed that showed normal WCC, RCC, glucose and protein, as well as negative cerebrospinal fluid (CSF) paraneoplastic panel, angiotensin converting enzyme level, anti-NMDA, Epstein-Barr virus, Varicella zoster virus, Herpes Simplex Virus, Venereal Disease Research Laboratory, West Nile Virus and Lyme antibodies. The CSF 14-3-3 protein was elevated at 6.5 (upper limit of normal <2). A genetic test for PRNP protein was sent to a specialised laboratory (Fulgent Diagnostics, Temple City, California, USA).

TREATMENT

Given the elevated TPO and Tg antibodies, the reported previous negative genetic test for FFI and the elimination of

other autoimmune and infectious causes from the differential, a diagnosis of HE was considered. She was started on 1 g intravenous methylprednisolone daily for 5 days, then transitioned to 60 mg prednisone daily to be tapered over 6 months.

During her hospitalisation, her insomnia continued to dramatically worsen. Despite some relief with melatonin, quetiapine and trazadone, she slept only a few hours at night. She did begin to show some mild improvement in duration and quality of sleep, cognitive function and tremor and leg movements after starting intravenous corticosteroids and was discharged home.

OUTCOME AND FOLLOW-UP

Following discharge, the results of her genetic test returned positive for a heterozygous variant in the PRNP gene, NM_000311.3:c.532G>A (p.Asp178Asn; also called D178N, a single mutation at codon 178 resulting in the substitution of asparagine for aspartic acid) (figure 1). PRNP is the gene encoding the major prion protein PrP in human which is predominantly expressed in the nervous system.^{5 6} Autosomal dominant mutations in PRNP have been associated with PRNP-related cerebral amyloid angiopathy, Gerstmann-Straussler disease, Creutzfeldt-Jakob disease (CJD), Huntington disease-like 1, FFI and prion disease. This variant, p.Asp178Asn, is a well-documented mutation found in multiple families with CJD, and FFI. According to American College of Medical Genetics guidelines, the laboratory considered this variant to be pathogenic, consistent with the patient's family history and clinical course pointing towards FFI.

A month after discharge, the results of the test were discussed with the patient and her family and despite her family's report of some improvement in motor skills, cognition and sleep while taking corticosteroids, she was tapered off corticosteroids as it was felt that her symptoms were solely due to FFI rather than HE, and a more dramatic response to corticosteroids would have

Figure 1 Family tree. No. 11 indicates the patient. A heterozygous variant in the PRion Protein (PRNP) gene, NM_000311.3:c.532G>A (p.Asp178Asn), was identified. This variant is located in the PRNP/Doppel protein, beta-ribbon domain and has not been reported in the broad ExAC dataset (with >60 000 individuals without severe childhood onset disease). It has been reported that the p.Asp178Asn variant and wild type p.Met129 variant cosegregate with fatal familial insomnia, whereas the p.Asp178Asn and p.Met129Val variants cosegregate with Creutzfeldt-Jakob disease. In our patient's specimen, a wild type p.Met129 variant was found. However, the phenotypic expression of the p.Asp178Asn variant could be influenced by environmental or unknown genetic factors.^{1 13–17}

been expected with the latter. The patient's symptoms continued to progress over the next several months, and she passed away 6 months after her initial presentation.

DISCUSSION

Our patient's initial presentation of confusion, hallucinations, tremor and gait disturbance, along with elevated anti-TPO and anti-Tg antibodies as well as a reportedly negative previous genetic test for FFI, led us to treat the patient for HE as the potential aetiology of her symptoms.^{3 4 7} Further, she initially had some improvement with intravenous corticosteroid in conjunction with symptomatic relief with melatonin, quetiapine and trazodone. She also met the diagnostic criteria proposed by Krasnianski *et al* for FFI, that is, sleep disturbances, hallucination and myoclonus, and hyperthermia.⁸ Ultimately, the patient's PRNP gene testing was positive for the previously reported D178N variant, which, in context of the patient's known family history of FFI led us to the final diagnosis of FFI (with wild type p.Met129 variant, that may cosegregate with FFI) (figure 1).⁹

HE, also known as steroid-responsive encephalopathy associated with autoimmune thyroiditis, is characterised by encephalopathy associated with anti-TPO or anti-Tg antibodies, in the absence of alternative causes.¹⁰ FFI and HE characteristically have differing presenting symptoms. Common initial symptoms in FFI include psychological manifestations (anxiety, nervousness, depression and apathy), gait ataxia and insomnia.¹ The most typical presenting symptoms for HE include cognitive impairment and behavioural changes, transient aphasia and tremor. Previous studies^{6 7} that have analysed symptom frequency for HE confirm that the initial presentation of our patient would not be unusual for HE, with confusion as one of the characteristics in 46%, tremor in 80% and gait disturbance in 27%–65% of patients. Phenotypic studies of prion diseases have been undertaken that demonstrate a great deal of variability in initial symptoms of prion diseases including FFI.¹

During the patient's treatment with corticosteroids for the alternative diagnosis of HE, we found that the patient had an initial improvement in her insomnia, cognition and tremor. There are no other case reports about the beneficial effects of corticosteroids in FFI. In fact, a previous report by Jang *et al* described a patient with suspected HE before CJD was confirmed, who had symptomatic aggravation, with the patient deteriorating into a transient akinetic mute state with no response to pain or visual response 2 days after administration of pulse corticosteroids.¹¹ The role of corticosteroids in prion disease is currently under investigation with previous studies¹² suggesting that corticosteroids might play a role in the pathogenesis of neurodegenerative disorders in general. The discrepancy between our patient having initial symptomatic improvement with corticosteroids and the CJD patient reported by Jang *et al*, with severe deterioration, could be due to pathophysiological differences between CJD and FFI.^{13–17} A weakness of this case is the absence of polysomnography data as Wu *et al* have reported abnormalities in sleep architecture and REM sleep intrusion in wakefulness in five Chinese patients with FFI.¹⁸

Learning points

- Our patient points at the complicated and variable clinical picture of fatal familial insomnia (FFI) in the setting of a prior negative genetic test and how alternate phenotypes in conjunction with elevated antithyroid peroxidase and antithyroglobulin antibodies can mimic Hashimoto's encephalopathy (HE).
- It also shows the importance of obtaining, or repeating, genetic testing in experienced laboratories in highly suspected cases. In addition, a transient symptomatic improvement following corticosteroid treatment may not confirm HE nor rule out FFI.

Contributors All authors have contributed to patient care, obtaining history, examining the patient, manuscript preparation, data interpretation and discussion. They also contributed in terms of planning, conduct, reporting, conception and design, acquisition of data, data interpretation and manuscript writing.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests None declared.

Patient consent Next of kin consent obtained.

Provenance and peer review Not commissioned; externally peer reviewed.

REFERENCES

- 1 Zarranz JJ, Dagon A, Atarés B, *et al*. Phenotypic variability in familial prion diseases due to the D178N mutation. *J Neurol Neurosurg Psychiatry* 2005;76:1491–6.
- 2 Goldfarb LG, Petersen RB, Tabaton M, *et al*. Fatal familial insomnia and familial Creutzfeldt-Jakob disease: disease phenotype determined by a DNA polymorphism. *Science* 1992;258:806–8.
- 3 Graus F, Titulaer MJ, Balu R, *et al*. A clinical approach to diagnosis of autoimmune encephalitis. *Lancet Neurol* 2016;15:391–404.
- 4 Yoneda M. [Hashimoto's encephalopathy and autoantibodies]. *Brain Nerve* 2013;65:365–76.
- 5 Liao YC, Lebo RV, Clawson GA, *et al*. Human prion protein cDNA: molecular cloning, chromosomal mapping, and biological implications. *Science* 1986;233:364–7.
- 6 Prusiner SB. Shattuck lecture—neurodegenerative diseases and prions. *N Engl J Med* 2001;344:1516–26.
- 7 Castillo P, Woodruff B, Caselli R, *et al*. Steroid-responsive encephalopathy associated with autoimmune thyroiditis. *Arch Neurol* 2006;63:197–202.
- 8 Krasnianski A, Sanchez Juan P, Ponto C, *et al*. A proposal of new diagnostic pathway for fatal familial insomnia. *J Neurol Neurosurg Psychiatry* 2014;85:654–9.
- 9 Mastrianni JA. The genetics of prion diseases. *Genet Med* 2010;12:187–95.
- 10 Laurent C, Capron J, Quillerou B, *et al*. Steroid-responsive encephalopathy associated with autoimmune thyroiditis (SREAT): Characteristics, treatment and outcome in 251 cases from the literature. *Autoimmun Rev* 2016;15:1129–33.
- 11 Jang JW, Park SY, Park YH, *et al*. Symptomatic aggravation after corticosteroid pulse therapy in definite sporadic Creutzfeldt-Jakob disease with the feature of Hashimoto's encephalopathy. *BMC Neurol* 2014;14:179.
- 12 Voigtlander T, Unterberger U, Touma C, *et al*. Prominent corticosteroid disturbance in experimental prion disease. *Eur J Neurosci* 2006;23:2723–30.
- 13 Medori R, Tritschler HJ, LeBlanc A, *et al*. Fatal familial insomnia, a prion disease with a mutation at codon 178 of the prion protein gene. *N Engl J Med* 1992;326:444–9.
- 14 Tateishi J, Brown P, Kitamoto T, *et al*. First experimental transmission of fatal familial insomnia. *Nature* 1995;376:434–5.
- 15 Spacey SD, Pastore M, McGillivray B, *et al*. Fatal familial insomnia: the first account in a family of Chinese descent. *Arch Neurol* 2004;61:122–5.
- 16 Dauvilliers Y, Cervena K, Carlander B, *et al*. Dissociation in circadian rhythms in a pseudohypersomnia form of fatal familial insomnia. *Neurology* 2004;63:2416–8.
- 17 Saitoh Y, Ogawa M, Naito Y, *et al*. Discordant clinicopathologic phenotypes in a Japanese kindred of fatal familial insomnia. *Neurology* 2010;74:86–9.
- 18 Wu L, Lu H, Wang X, *et al*. Clinical Features and Sleep Analysis of Chinese Patients with Fatal Familial Insomnia. *Sci Rep* 2017;7:3625.

Copyright 2018 BMJ Publishing Group. All rights reserved. For permission to reuse any of this content visit <http://group.bmj.com/group/rights-licensing/permissions>.
BMJ Case Report Fellows may re-use this article for personal use and teaching without any further permission.

Become a Fellow of BMJ Case Reports today and you can:

- ▶ Submit as many cases as you like
- ▶ Enjoy fast sympathetic peer review and rapid publication of accepted articles
- ▶ Access all the published articles
- ▶ Re-use any of the published material for personal use and teaching without further permission

For information on Institutional Fellowships contact consortiasales@bmjgroup.com

Visit casereports.bmj.com for more articles like this and to become a Fellow