CASE REPORT

A Case of Familial Creutzfeldt-Jakob Disease Presenting with Dry Cough

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ABSTRACT: ***Background:*** Clinical diagnosis of Creutzfeldt-Jakob disease (CJD) is based on the classical triad of rapidly progressive dementia, myoclonus and abnormal EEG. The 200k mutation within the gene encoding *PrP*, located on the short arm of chromosome 20, accounts for more than 70% of families with CJD worldwide. ***Case Report:*** Herein, we report a patient who developed persistent dry cough and classical signs of CJD, including severe cognitive decline, cerebellar signs, and myoclonic jerks, leading to death a few weeks after disease onset. Mutation screening showed that he had the 200k point mutation in the *PRNP* gene. His mother had died twenty years earlier with neuropathologically confirmed CJD. She had presented a rapidly progressive ataxia with myoclonus, dementia, visual hallucinations, and the same persistent dry cough. ***Conclusions:*** The clinical presentation of this familial CJD case with persistent dry cough is quite unusual. Therefore, a neurological etiology should be sought when confronted with an unexplained persistent cough.

RÉSUMÉ: Une observation de maladie de Creutzfeldt-Jakob familiale ayant comme manifestation initiale une toux sèche. ***Contexte:*** Le diagnostic clinique de maladie de Creutzfeldt-Jakob (MCJ) est fondé sur la triade classique d'une démence progressant rapidement, de myoclonus et d'anomalies de l'ÉEG. La mutation 200k du gène codant le PrP, situé sur le bras court du chromosome 20, est en cause chez plus de 70% des familles atteintes de MCJ dans le monde. ***Observation:*** Nous rapportons l'observation d'un patient qui a présenté une toux sèche persistante et les signes classiques d'une MCJ, soit un déclin cognitif sévère, des signes cérébelleux et des secousses myocloniques avec décès en quelques semaines. Le dépistage de mutations dans le gène PRNP a mis en évidence la mutation ponctuelle 200k. La mère du patient était morte vingt ans auparavant et un examen neuropathologique avait confirmé qu'il s'agissait d'une MCJ. La maladie s'était manifestée chez elle par une ataxie progressant rapidement, des myoclonies, une démence, des hallucinations visuelles et la même toux sèche persistante. ***Conclusions:*** La toux sèche persistante comme manifestation d'une MCJ familiale chez ce patient est inusitée. Une étiologie neurologique devrait être recherchée si une toux persistante demeure inexpliquée.

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Creutzfeldt-Jakob disease (CJD) is usually characterized by rapidly progressive dementia, myoclonus, periodic sharp-wave electroencephalographic activity and spongiform degeneration. Although major variations in clinical presentation have consistently been observed, there is only one case in the literature of a CJD patient presenting with prodromal cough. Herein, we report a patient and his mother who both developed persistent dry cough prior to classical signs of CJD. Neurological etiologies of cough are discussed and relevant literature on its neurophysiology is reviewed.

Case presentation

A 52-year-old man came to our hospital because of recent onset of gait difficulties. He was born in Canada, but both his parents were born in Greece, being of Sephardim Jewish ancestry. His mother had died at 48 years of age with neuropathologically confirmed CJD. She had presented a rapidly progressive ataxia with myoclonus, dementia, visual hallucinations and dry cough. Four months prior to admission, our patient developed a flu-like syndrome with dry hacking cough. He began to complain of fatigue, tremulousness and intermittent diplopia. Two months after the onset of his chronic cough, he had some mild forgetfulness that did not compromise his ability to work as a teacher at

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graduate level. His spouse began to note at that time some memory lapses, slight confusion, mood changes, as well as rare myoclonic jerks. When he was first seen in our hospital, he was well alert. He was oriented to person, place, but not to time. The patient scored 27/30 on Mini Mental State Examination because he failed to recall three words after five minutes. Cranial nerves were unremarkable. Motor and sensory examinations were normal. His gait was somewhat narrow-based, and he could not perform tandem walking well.

Cerebral magnetic resonance imaging did not show any high signal on the T2-weighted images. Diffusion-weighted MRI, however, showed high signals in the caudate and putamen nuclei bilaterally (Figure). An electroencephalogram revealed high amplitude delta activity. The characteristic periodic sharp complexes were lacking but a diagnosis of CJD could not be rejected for that sole reason.[1] A lumbar puncture showed clear fluid with no white blood cells and a normal protein content. Viral and bacterial cultures of the cerebrospinal fluid were negative, while the 14-3-3 protein immunoassay - performed by slight modifications of the Western blot as previously described[2] - was positive.

During the hospitalization, the patient's cough persisted. Five days after admission, he started to present frank visual hallucinations with time-space disorientation. When alert, he would report palinopsia, polyopia or metamorphopsia. A neuropsychological evaluation revealed visual symptoms compatibles with Balint's syndrome. His myoclonic jerks became more obvious and his verbal output was reduced dramatically. He died 17 days after admission.

A brain autopsy was performed that confirmed the diagnosis of CJD. Antibodies to 6H4 were used, which are known to be reliable tools for the specific immunolabeling of the abnormal form of PrP.[3] The occipital and parietal neocortices showed microvacuolation, gliosis and neuronal loss. In the 6H4 stain, there was in some areas of the cortex and of the basal ganglia, a synaptic staining pattern indicative of pathologic accumulations of PrP. Neither microscopy nor immunohistochemical staining were performed on brainstem sections. Quantitative Western blot was carried out as previously described.[4] It was positive for PrP with a banding pattern consistent with the Methionine/Methionine-1 subtype of CJD.[5] We had access to the autopsy report of his mother, done 26 years earlier. Her autopsy demonstrated the same neuronal loss and microvacuolation of the occipital and parietal cortices. There was no mention of brainstem involvement.

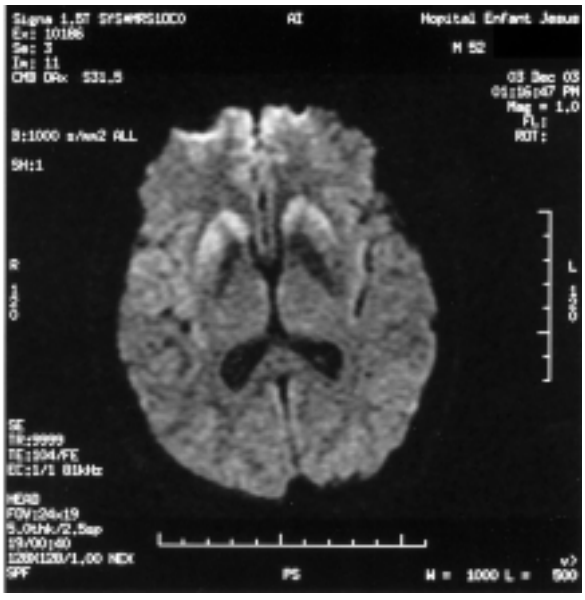

Figure: *Diffusion-weighted MRI. Hyperintensities in the caudate and putamen nuclei are present bilaterally.*

Genetic testing was performed on our patient. The protein-coding portion of *PRNP* was sequenced. Complete sequence was obtained for 250 of the total of 254 codons of exon 3 of *PRNP*, which covers the positions of all known disease-associated mutations and polymorphisms. Our patient was heterozygous for a G→A point mutation at codon 200 and homozygous for the "A" allele of the common A↔G polymorphism encoding methionine and valine respectively in codon 129 (M129V). This patient's genotype accounts for over 70% of cases of familial CJD worldwide.[6] Moreover, a single mutation within the gene encoding PrP is found in approximately 15% of CJD patients.[7]

Discussion

Both our patient and his mother reported a persistent dry cough months preceding their deaths. A large case-control study has identified prodromal upper respiratory infections in over 30% of patients.[8] Flu-like symptoms have also been noted prior to the clinical onset of CJD, in a review on clinical aspects of CJD,[9] but no correlation could be made with either allergy, hay fever or recent immunization. There are three cases reported in the literature in which influenza or tonsillitis preceded the onset of CJD symptoms[10] but only one case of a woman who developed an unexplainable cough prior to the diagnosis of CJD.[11]

There has always been considerable speculation about the possibility of a specialized neural "cough centre" in the brainstem.[12] Some researchers now prefer to believe that medullary Botzinger/rostral ventral respiratory group neurons implicated in generating the eupnoeic pattern of breathing are also involved in producing the central cough motor pattern.[13] Electrical stimulation of the motor cortex can cause movements of the vocal folds but cough itself has never been reported.[14] Unfortunately, the autopsy of our patient was performed several months after the onset of respiratory symptoms when the disease process had spread and thus could not aid the clinical localization. Creutzfeldt-Jakob disease patients who developed prodromal pruritus[15] or abnormal eye movements[16] have both been reported previously, suggesting an early involvement of their brainstem. However, the Diffusion-weighted MRI of our patient failed to show any high signal in the brainstem. Instead, hyperintensities were seen in the caudate and putamen nuclei. Prodromal cough has already been reported in patients with neurological diseases such as Parkinson's disease,[17] Wilson's disease[18] and Tourette's syndrome.[19] Interestingly, all these disorders are known to localize to those same subcortical regions. Despite this observation, we can only speculate on how the cortex communicates with the laryngeal motor neurones in the nucleus ambiguus.

The prevalence of the 200k variant of familial CJD is especially high among populations of Libyan Jews. Haplotypes studied among CJD families from different populations show that Libyan, Tunisian, Italian, Chilean and Spanish families share

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a major haplotype suggesting that this mutation may have originated from a single mutational event and spread to all these populations with Sephardim migrants expelled from Spain in the Middle Ages.[20]

In summary, our patient not only developed classical signs of CJD but he also developed a persistent dry cough. Therefore, a neurological etiology should be sought when confronted with an unexplained persistent cough. Finally, the present report constitutes the first published Canadian case of familial CJD. It reminds us of the importance of offering genetic testing in cases for whom the family history is positive.

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