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Case Report

Case Report- An Underreported Genetic Cause of Dementia- Familial CJD

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Abstract

A 59-year-old male with no comorbidity having a significant family history of similar symptomatology and demise, presented with ataxia for the last 1 year, tremors for the last 3 months, and one month of myoclonic jerks and cognitive decline. He had no headache, seizures, visual disturbance, constitutional symptoms, and toxin exposure. His 4 family members passed away in the 5th- 6th decade of life who had similar symptoms but did not seek any medical advice, and died within 1-2 years of disease onset. This patient was brought to medical attention and was worked up thoroughly. All metabolic and biochemical parameters were normal. CSF analysis showed mildly raised proteins and cells. CSF 14-3-3 levels were found to be raised by the immunoblot method. MRI changes were suggestive of CJD. EEG showed theta range slowing with no periodic discharges. Family members were advised for genetic analysis and counseled regarding the disease and risk of involvement of future generations but they were not willing for genetic workup and the patient was started on supportive therapy. There are case reports of sporadic CJD in literature but this highlights the familial CJD which was undiagnosed for years and family members continue to suffer from illness and finally succumb to it.

Keywords: Familial CJD; Ataxia; Dementia; Myoclonus

Introduction

CJD is one of the rare reported causes of rapidly progressive dementia. Few cases from India have been reported till now. The incidence of Genetic CJD is 5-15% of all CJD cases [1]. Genetic prion disease manifests with cognitive difficulties, ataxia, and myoclonus. The order of appearance and/or predominance of these features and other associated neurologic and psychiatric findings vary. The three major phenotypes of genetic prion disease are genetic Creutzfeldt-Jakob disease (gCJD), fatal familial insomnia (FFI), and Gerstmann-Sträussler-Scheinker (GSS) syndrome [2]. Here we report a case with unexplained deaths of family members presenting with similar symptomatology of ataxia, jerks, and dementia which made family members worried and brought him to health care services and proved to be a case of prion disease.

Case

A 59-year-old gentleman presented with a 1-year history of gait ataxia with swaying to either side followed by 3 months of bilateral hand action tremors. For the last 1 month, he started to have behavioral disturbances. He used to be a calm person but now started to have increased aggression. He would scold his sons over trivial issues. He lost interest in his daily activities and finances. He would not initiate talk with anyone and would only reply using minimal words. He had fragmented sleep with decreased total sleep duration. No h/o acting out dreams. Subsequently, he developed sudden involuntary transient jerky movement of the trunk and even hands along with tremors. He became so disabled because of illness that he was not able to do his routine chores and was dependent on family members for the same. He had no history

of headache, seizures, and hemiparesis. No history of constitutional symptoms. He quit alcohol twenty years ago and earlier used to consume alcohol occasionally. He had a significant family history of similar complaints of ataxia and the demise of four family members because of a similar symptomatology. His 3 generations in the family were affected. He also had a twin brother who was currently asymptomatic. On examination, he had MMSE score of 10 /30. Spontaneous eye movements were normal. He had rigidity in bilateral upper limbs. Bilateral coarse action tremors with superimposed myoclonic jerks were present. He had significant gait ataxia requiring two-person support on either side. Power and sensory examination were confounded by cognitive impairment.

He was worked up on lines of rapidly progressive dementia with myoclonus. On investigations, his hemogram and biochemistry were within normal limits. HbA1c was 5.2%. Serum PSA levels were 0.4 ng/ml. The thyroid profile was normal. CSF analysis showed 7 cells with 83 mg/dl protein and 62 mg/dl sugar. Cryptola antigen, India ink, MTB gene xpert, and malignant cytology were negative. CSF VDRL was non-reactive. His CSF 14-3-3 report was positive by immunoblot methodology up to 1.4 ng/ml (Normal < 1 ng/ml). EEG done showed theta range slowing with no periodic discharges (Figure 1). MRI Brain showed diffusion restriction in bilateral basal ganglia (Figure 2). NCS was suggestive of sensory-motor axonal neuropathy. Sural nerve biopsy showed chronic axonopathy with no evidence of abnormal prion proteins (no prionopathy). FDG PET whole body was normal. Autoimmune paraneoplastic panels were also reported normal.

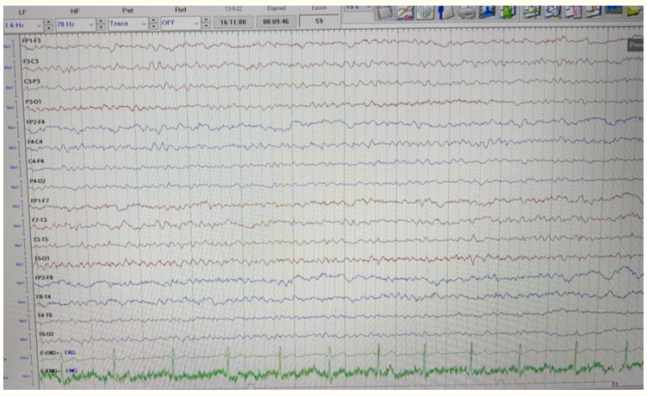

Figure 1: Showing generalized slowing with no periodic discharges.

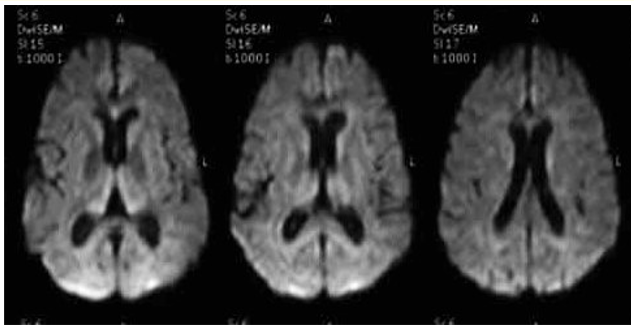

Figure 2: Showing diffusion restriction in bilateral basal ganglia and pulvinar nucleus of thalamus sparing globus pallidus.

The patient's family members explained about the disease and prognosis and advised genetic testing of the patient/patient's son for further risk in the family though they denied it. The patient was started on symptomatic therapy for tremors with beta-blockers (propranolol) and given Donepezil and thiamine trial.

Discussion

CJD is the most common prion disease and occurs in sporadic, familial, iatrogenic, and genetic forms [3]. The first case of familial CJD (fCJD) was recorded in 1924. There are more than 50 mutations described, and the disease is transmitted in an autosomal dominant pattern with high penetrance, and with an incidence that increases with age. fCJD has similar clinical, radiographic, and test findings as sCJD.

CJDE200K-129M is the most common form of familial CJD [4]. The mean age at onset is 58 years (range, 33-84 years), and the mean duration of illness is 6 months (range, 2-41 months). Presentation includes cognitive and mental abnormalities (80-83% of patients), cerebellar signs (43-55%), visual signs (19%), and myoclonus (12%) [4].

The sensitivity of positive 14-3-3 protein in CSF for classic sCJD is 92%-96% [5]. Positive 14-3-3 results are seen in viral encephalitides, recent stroke, subarachnoid hemorrhage, hypoxic brain damage, metabolic encephalopathy, glioblastoma, carcinomatous meningitis, paraneoplastic disorders, and corticobasal degeneration [6]. Real-time quaking-induced conversion (RT-QuIC) is a recently described laboratory technique that provides a definitive diagnosis of CJD from CSF samples by detecting PrPSc [7].

A CJD surveillance unit in Germany found that Periodic Sharp Wave Complexes (PSWC) have 37.5% sensitivity and 100% specificity [8]. Not all patients with sCJD develop PSWCs; these complexes are typically found in patients who have the MV1 and MM1 genotypes and not in those with valine homozygous variant at codon 129 [9]. Patterns of FLAIR/DWI hyperintensity and restricted diffusion have also been shown to differentiate sporadic CJD from other causes of rapidly progressive dementia [10]. PNS involvement has been considered a preclinical part of the disease and in one study 88% of patients showed peripheral neuropathy [11]. The mainstay of treatment is symptomatic and supportive. Future targets of therapy involve preventing the conversion of PrPC to PrPSc [12].

Summary

Elderly male with a history of three generational unexplained deaths of family members with rapidly progressive dementia with ataxia and myoclonus. On evaluation was found to have prion disease. Family members were informed about the future risk of disease in the family and the likely cause of the previous unexplained demise of family members.

Conclusion

CJD is a rare cause of rapidly progressive dementia. Once treatable causes of rapidly progressive dementia are ruled out, the workup for slow virus disease becomes the next step in the presence of elderly patients with myoclonus and ataxia with dementia. No proven therapeutic strategy has been beneficial till now.

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