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Case Report

Phenotypic Variability and Anticipation in a Family of D178N-Familial Creutzfeldt-Jakob Disease

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Abstract

Familial Creutzfeldt-Jakob disease (fCJD) is caused by mutation in *PRNP* gene. The D178N variant of CJD is known to have phenotypic variability and can often mimic other neurological disorders. In this article, we report a family with D178N variant of PRNP mutation with phenotypic variability and anticipation phenomenon.

Keywords: Anticipation; Creutzfeldt-Jakob Disease; D178N; CJD: Phenotype Variability

Abbreviations

fCJD: Familial Creutzfeldt-Jakob Disease; AAO: Age at Onset; MRI: Magnetic Resonance Imaging; FLAIR: Fluid Attenuated Inversion Recovery; PSWC: Periodic Slow Wave Complex; CSF: Cerebrospinal Fluid

Introduction

Familial Creutzfeldt-Jakob disease (fCJD) is a rare entity and accounts for 10% of all CJD [1]. More than 40 different variants of the *PRNP* gene are known to cause familial CJD [1]. These are mostly nonsense, missense, octapeptide repeat insertion or deletion mutations [1]. Anticipation in the age at onset (AAO) has never been conclusively proven nor refuted in CJD. However, the D178N variant of CJD is known to be associated with phenotypic variability in the age at onset, clinical symptoms, and investigation findings [1,2]. In this article, we report a family with D178N-fCJD with apparent anticipation.

Case Report

The proband is a 38 year-old gentleman who presented with rapidly progressive memory disturbance, slurred speech, slowness in activities, seizures, decreased sleep, emotional lability, anxiety and depression of two months duration. On clinical examination, he had generalized bradykinesia, dysarthria, asymmetrical postural tremor of the upper limbs, and cognitive impairment (Montreal Cognitive Assessment score: 19/30).

An initial blood screen, including routine haematology, biochemistry, thyroid function, vitamin B12, serology for neurosyphilis, paraneoplastic antibodies, genetic analysis for trinucleotide disorders (SCA1,2,3,6,7,10,17) were normal. MRI brain revealed T2 and FLAIR hyperintense signals in the bilateral basal ganglia and thalamus. The DWI sequences demonstrated the characteristic hyperintense 'cortical ribbon sign' (Figure 1). Electroencephalogram showed slowing and periodic discharges with triphasic sharp wave

complexes (PSWC). Exome sequencing revealed heterozygous, missense variation (c.532G>A, p.D178N) in the exon 2 of the *PRNP* gene (ENSG00000171867) with 129MV polymorphism. This variant has previously been reported as a pathogenic variation in CJD [3]. Sanger sequencing also confirmed the presence of the variant in the proband and his asymptomatic younger brother. CSF test was not performed due to a lack of consent. A final diagnosis of fCJD was established.

Figure 1a to 1c: Demonstrates the MRI changes in proband IIIa. Figure 1(a) demonstrates hyperintense signals in bilateral caudate and putamen in axial T2 sequence. Figure 1(b) demonstrates hyperintense signals in bilateral caudate, putamen and thalamus in axial FLAIR sequence. Figure 1(c) demonstrates hyperintense signals predominantly in the right frontal, parietal and occipital cortices (cortical ribboning sign) in axial DWI sequence. Figure 1(d) demonstrates the autosomal dominant inheritance pattern of the disease in the family. Square = male; circle = female; diagonal blackline = deceased; grey filled symbol = affected; light grey symbol = presymptomatic; empty symbol = clinically healthy relative; black arrow = proband; AAO = age at onset of symptoms; AAD = age at demise.

Family history of neurological symptoms was present in the father, paternal grandfather, aunt, and cousin. The medical records of these individuals was evaluated for their symptoms and AAO. Significant heterogeneity was present in clinical features and their provisional diagnosis of different family members (Table 1). The provisional diagnosis considered included familial dementia, spinocerebellar ataxia, and Huntington's disease. The symptoms were rapidly progressive and was invariably fatal in all subjects within a span of one to two years.

Discussion and Conclusion

Clinical variability has been previously reported in patients with D178N-fCJD [1,3]. It is known that on the basis of polymorphism at codon 129, patients may present either as familial fatal insomnia or fCJD [1,2]. Variable symptoms such as cognitive impairment, cerebellar signs, extrapyramidal symptoms, pyramidal signs, autonomic dysfunction, seizures, and psychiatric symptoms are known in D178N-fCJD variant [1,2]. Supplementary table 1 highlights the phenotypic variability in different members of the family. The imaging, EEG, and CSF 14-3-3 protein positivity is also variable in the D178N-fCJD variant [1,2].

Another notable observation was the presence of apparent anticipation in the AAO across three generations. A cursory review of previous reports on D178N-fCJD also demonstrates variability and an apparent anticipating trend in the AAO [2,3]. However, anticipation has never been truly established in the D178N-fCJD variant. Interestingly, anticipation was previously reported in terms of AAO and AAD (age at death) in the E200K-fCJD. However, Minikel., *et al*. demonstrated that the detected anticipation in the AAD of E200K-fCJD was most likely due to statistical ascertainment bias [4]. One of the major reasons for the disrepute of anticipation in CJD is probably due to the traditional view that anticipation is either due to the expansion of unstable repeats or telomere shortening [5]. The absence of such a genetic phenomenon in CJD may portend the possibility of anticipation in CJD. The role of epigenetic factors underlying the molecular mechanisms of the onset of disease at a specific age is now recognized and apparent anticipation has been described in a multitude of disorders [5].

Notwithstanding the absence of absolute proof of genetic anticipation in CJD, many pedigrees demonstrate a trend of apparent anticipation. Although this may be due to a reporting or documentation bias, it still has a significant implication on genetic counselling in at-risk and asymptomatic individuals. Furthermore, in the absence of the typical CJD features, the presence of apparent an-

	Ia	IIa	IIb	IIIa	IIIb	IIIc
Age at onset	73 years	50 years	53 years	38 years	Asymptomatic	40 years
Age at demise	75 years	52 years	55 years	-	-	41 years
Duration of disease	18 months	20 months	13 months	2 months (not deceased)	-	11 months
Cognitive impairment[1]	Dementia MMSE = 18	Dementia MMSE = 9	Forgetfulness#	Dementia MOCA = 19	No impairment MOCA = 30	Forgetfulness#
Psychiatric symptoms	-	Hallucination Depression	Hallucination Delusion Depression	Irritability Emotional lability Depression, Anxiety	-	-
Sleep disturbance	Insomnia	Insomnia	-	Insomnia	-	
Extrapyramidal signs	-	-	-	Myoclonus Postural tremor Bradykinesia		Tremor/ Myoclonus Bradykinesia
Seizures	-	-	-	Generalized tonic-clonic seizure	-	-
Cerebellar signs	-	-	Ataxia Incoordination	-	-	-
Provisional diagnosis	Alzheimer's disease	Familial dementia	Spinocerebellar ataxia? type	Creutzfeldt Jakob disease	Creutzfeldt Jakob disease	Genetic parkinsonism

Table 1: Phenotypic variability and apparent anticipation in the members of the family.

[1]: Formal neuropsychological test data was available only in subjects IIIa (proband) and IIIb (asymptomatic brother). Patient IIIa had impairment in executive function, complex attention, perceptual motor function, learning and memory domains. Proband IIIb had no cognitive impairment in detailed neuropsychological evaluation. # No formal testing done.

ticipation in the pedigree may lead the diagnostic process astray as portrayed by the provisional diagnosis of the family members in this case report.

Hence, further research should clarify the molecular mechanisms responsible for the determination of AAO and anticipation. Clinicians should also keep this conundrum in mind while evaluating patients with rapidly progressive cognitive disorder associated with abnormal movement disorders.

This manuscript was prepared following the ethical norms after written consent from subjects.

Conflict of Interest

The authors report no conflicts of interest.

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