Fatal familial insomnia

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Abstract:

The genetic scope of diseases is getting wider every day. With the advancement of knowledge and the ever growing entanglement between different branches of science, the diagnosis of prion-caused diseases is becoming easy. However, the devastating outcome of these diseases such as the eventual death in the case of FFI is not. Rare as it may be, FFI is just as dangerous as any other disease; this is mainly due to its fatal outcome. FFI is an autosomal dominant prion disease; the mutation is in the protein gene (PRNP) D178N/129.According to our knowledge, no cases have been reported in Sudan. This may be explained by the misdiagnosis as the symptoms are shared by many neurological diseases.

Key words: Fatal familial insomnia, prion diseases, neurodegenerative disorders, D178N mutation, transmissible spongiform encephalopathies

I. Introduction

The myth surrounding nervous system disorders has been around for a significant amount of time. They ranged from the unknown to theory of being possessed by evil spirits; fatal familial insomnia was and still is no exception. The disease is rare and it usually strikes victims in a familial pattern. Two cases were described in 1986 and they displayed a familial pattern of inheritance and an untreatable insomnia with motor disturbances. (1) More cases have been discovered later and the number rose to 29 across five generations and the symptoms became more severe and included additional set, such as hallucinations and hormonal imbalances. (1)

Several families in America and Italy were detected, in fact, these cases were first to investigate the symptoms and eventually name the disease. As time passes, more and more patients are being accounted for around the globe, China, Netherland and many more.

Sven Rupprecht and colleagues from Germany reported a case 2013, in which the disease has developed early in life at the age of 23. They described a female with a family history of death due to a suspected prion disease. After a genetic analysis, they reported that the young female had *PRNP* mutation at codon 178 and homozygote methionine polymorphism at codon 129. [2] This did support their assumption that the disease could present at early age due to a certain polymorphism in young patients with unclear neuropsychiatric disturbances. [2]

II. Clinical aspects of the disease

Introduction

Clinically, the disease is extremely difficult to diagnose due to the differences in presentations as well as the disease not being fully understood. As aforementioned, the mutation leading to the disease occurs in chromosome 20p12. Here, we shall go over some of the expected presentations of the disease as well as detection methods and an introduction to the epidemiology of the disease. Clinically speaking, human prion diseases are (in no particular order) 1.CJD 2 FFI 3.GSS 4.Kuru [3]. Here, we will focus on the clinical manifestations of FFI. Some divide human prion diseases into 1) those caused by internally originating prions and 2) those caused by infections of external prions [4]. FFI is a branch of the 1st division [4].

Background

The very first reported case we were able to come across dated back to 1986, they were 2 cases and were the reason of naming of the disease [1].This was followed by a research paper published in 1992 with highly similar signs and symptoms [1]. We believe that these 2 reports were the “eye-opener” of this disease. We hope our paper exhibits a similar effect in regards to the disease in Sudan in particular and Africa in general

Signs and symptoms

Here, we will cover the most common signs and symptoms as well as mention some that might encounter physicians, it is crucial we note that these will vary depending on the genotype of patients as well as lifestyle, socioeconomic status, age of onset etc. Some of the earliest signs and symptoms include sleep disorders, dysautonomia, loss of weight and motor signs [5]. The type of polymorphism is most likely a determinant of the phenotype and thereby the signs and symptoms of the disease [6]. Genotypes, as aforementioned are divided into MM and MV [6]. Depending on the genotype, the phenotype will vary. MV patients suffer more from vegetative disturbances and nystagmus, but no hallucinations (i.e. these are more prominent in them) [6]. MM

patients initially complain of sleep disturbances as well as huskiness and visual deficits [6]. Both genotypes express loss of temporal and spiral orientations, followed by dysarthria and ataxia and finally Myoclonus and pyramidal signs [6]. Spongiform changes are no exception to this rule (i.e. they differ between MM and MV patients) [6]. MV patients develop more prominent spongiform changes than their counterparts [6]. MM patients are also noticeably younger than MV patients [6]. The following table summarizes similarities and differences between the signs and symptoms of MM and MV patients [6]. Chinese patients present with signs and symptoms similar to those of Caucasians [7].

Table 1

MM	MV
Weight loss	Weight loss
Higher frequency of myoclonus	Vegetative disturbances
Early-stage hallucinations	Late-stage hallucinations
Less prominent changes as compared to MV	Extrapyramidal signs
Myoclonus	Ataxia
	Nystagmus
	More prominent spongiform changes
Onset at a noticeably younger age than MV	

Given these signs and symptoms, some would believe that they would be easily capable of diagnosing FFI patients and their genotypes based on their presentations only. However, there has been a reported case of a female who exhibited FFI and CADASIL at the same time [8]. This helps us reach the conclusion that presentations can be of two genetic abnormalities at once [8]. The aforementioned case's diagnosis was confirmed using gene sequencing [8]. This case also proves that prion diseases should always be a differential diagnosis of patients presenting with rapid dementia and related diseases [8].In later stages, patients exhibit endocrine disturbances, movement disorders and cognitive dysfunction [8]. All complications of insomnia are also prominent in FFI patients.

III. Affected areas and their complications

In FFI, the deposition of PRPsc is mainly focused on the DM and AV thalamic nuclei, cortical areas are affected in later stages of the disease. Significantly reduced REM sleep and slow wave sleep are some of the earliest presentations of patients [8]. Vivid dreams are usually a rare occurrence for normal individuals, however FFI patients exhibit them as well as complex

hallucinations in an alarming rate, it is important that we note that these episodes cannot be relieved by common hypnotics [8]. There has been a case report which the patient suffered from a TGA episode [8]. To the extent of our knowledge, only one case has been reported to suffer from both FFI and CADASIL [8]. When atypical presentations take place, physicians should immediately consider the possibility of 2 or even more genetic abnormalities [8]. One of the first case reports on the topic also mentioned tremor and quick deterioration of the patient [9]. The same case report also mentioned the patient was awakened by light stimuli [9]. Since initial reports of the disease, over 100 pedigrees have been reported [8]. We expect more reported pedigrees in the future.

IV. Epidemiology of the disease

On a yearly basis, human prion diseases (which include FFI) affect 1-2 persons per million worldwide [4]. According to the latest data we can come across from the CJD International Surveillance Network (formerly Euro CJD), countries with the highest mortality rates from sCJD are Switzerland and France, respectively [4]. ***No accessible data for SsCJD cases in South Asia or Africa*** (4). FFI is dominant in certain European countries (e.g. Spain and Germany) (4). It is also of high importance that the disease is common amongst the Han Chinese population (4). Death rates differ amongst the Japanese [4].

Laboratory tests

Routine laboratory tests and technical investigations usually turn out normal and cannot be used as tools of diagnosis. CSF is usually negative for 14-3-3 protein; however there has been a reported case with elevated levels of this protein [8].

Detection of the disease

Until recently, detection of the disease depended on matching of clinical signs and symptoms with PRNP sequencing since MRI, CT and IHC abnormalities are not apparent till late stages of the disease. However, recent studies proved that the OM of FFI patients contains amounts of PRPsc which can be detected by PMCA and RT-QuIC [5]. PMCA analysis concluded concentrations of PRPsc in FFI patients to be $\sim 1x10$-14 g/ml, while it was unable to detect amounts of PRPsc in controls or patients with other neurodegenerative disorders (e.g. Alzheimer's disease) [5].

Treatment

No treatments/cures are available as of the publication of this paper. Active surveillance is currently the practiced standard in an attempt to find a cure for this disease [4].

V. Conclusion

As medical personnel, it is our duty to study, diagnose, prevent and treat diseases. FFI is no exception to this rule. Unfortunately, we were unable to come across any reported cases in the Republic of the Sudan based on our research. It is a culture of beliefs of supernatural powers being the main causative agents of many nervous and psychological anomalies, this maybe the reason that cases may have gone undocumented. This review is to be considered a start to track down the disease in the Republic of Sudan and come out with better understanding and eventually a better diagnosis and hopefully, treatment.

VI. Recommendation

We recommend immediate efforts are put forward towards the teaching of prion diseases and immediate research into the topic and drag it to the priority lists of the WHO and MOH. We, without doubt, believe many cases have gone unreported due to misguided beliefs of individuals. This goal can only be achieved when we first understand the mutations related to the disease and causative agents.

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