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Rapidly progressive Creutzfeldt-Jakob disease in patients with Familial Mediterranean Fever

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Abstract

Background—The largest cluster of familial Creutzfeldt-Jakob disease (fCJD) exists in Jews of Libyan origin. Familial Mediterranean fever (FMF) is an inflammatory disease also common in this population.

Objectives—We hypothesized that FMF, as a pro-inflammatory condition, may affect the course of CJD.

Methods—Three hundred and seventy two consecutive patients diagnosed clinically and genetically as CJD were included in the study. Two hundred and thirty six had fCJD and 136 had sporadic disease (sCJD). Review of the patient's records revealed three patients with FMF-CJD co-morbidity. In addition, 50 DNA samples of CJD patients were genotyped as homozygote, heterozygote and non carriers of the FMF mutation. The demographic and clinical variables of the groups were compared.

Results—The 3 FMF patients had an earlier age of onset and significantly shorter disease duration than the non-FMF patients. Heterozygote carriers did not differ in disease onset and duration from non-FMF patients.

Conclusions—The shorter disease duration of CJD patients with FMF may indicate the importance of pro-inflammatory factors in the disease.

Keywords

Creutzfeldt-Jakob Disease; Familial Mediterranean Fever

Introduction

Creutzfeldt-Jakob disease (CJD) is the most common prion disease in humans, caused by a conformational change of the normal prion protein (PrP^C) into the pathological state (PrP^{Sc}) [1] which aggregates mainly in the CNS. Several clinical patterns of CJD have been characterized including sporadic (sCJD), acquired and familial (fCJD) forms [2]. The largest

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cluster of fCJD exists in the North African Jewish community of Libyan and Tunisian ancestry [3], linked to the E200K mutation in the prion protein gene (*PRNP*) [4,5].

The exact pathogenesis of the disease is not understood and relatively few factors that influence the onset and course of the disease have been described. The first to be reported is the Valine/Methionine polymorphism at codon 129 of the *PRNP* gene. Homozygote trait (V/V or M/M) patients are more prone to have a more aggressive disease course in comparison to the heterozygote trait (V/M) [6]. Another disease modulating factor is the apolipoprotein E4 polymorphism which is associated with an earlier onset and a more rapid course of CJD [7]. Although inflammation was not considered as having a role in CJD, recent reports support the involvement of the inflammatory response in the pathogenesis of prion disease [8,9].

Familial Mediterranean fever (FMF) is an inflammatory disease characterized by episodes of fever accompanied by peritonitis and abdominal pain, pleuritis, arthritis and erysipelas-like rashes [10]. The defective gene in FMF is the *MEFV* gene [11] that encodes pyrin, an anti-inflammatory protein that regulates interleukin-1 β (IL-1 β) [12]. Several mutations in the *MEFV* were found and one of them, the M694V mutation, is especially common in Jews of Libyan and Tunisian origin [13,14].

We encountered a patient with FMF who had a very rapid course of CJD culminating in death within 6 weeks. This prompted us to carry out a systematic search for an association between the two diseases. We found and present 3 patients of Jewish Libyan ancestry with long standing FMF who developed CJD with an aggressive and fulminant disease course, dying within a few weeks of disease onset.

Methods

Patients were collected through the Israeli Register of Neurological Diseases [15]. Three hundreds and seventy two consecutive CJD patients that were investigated clinically and genetically between the years 1963-2008 were included in the analysis, 236 with fCJD and 136 with sCJD. We reviewed all records and found 3 patients with FMF-CJD co-morbidity. These were compared to the 369 patients without FMF for demographic and clinical variables using t-tests and the non parametric Mann Whitney U test. Disease duration was defined as the time interval between the first reported symptom and death. In addition, the DNA data base of the Israeli Register of Neurological Diseases was screened for DNA samples of the patients included in the study. 50 DNA were located and checked for the most common *MEFV* mutation (M694V) associated with FMF using PCR amplification and restriction enzyme digestion as previously described [16]. The study was approved by the ethic committee of Sheba Medical Center and the ethic committee of the Israeli Ministry of Health. Based on the genetic data, the patients were separated into 3 groups: 1. Homozygote for FMF mutation (all with clinical FMF). 2. Heterozygote healthy carriers and 3. Patients with no M694V *MEFV* mutation. The demographic and clinical variables of the groups were compared using t-tests and ANOVA or the non parametric Mann Whitney U test.

Results

I. Case reports

We present here three cases of patients of Jewish Libyan ancestry with long standing FMF who developed CJD with an aggressive and fulminant disease course, dying within a few weeks of disease onset.

Case I (index case)—A 41 year old patient of a Jewish Libyan origin with a negative family history of CJD was admitted to our department. He had a past medical history of FMF treated with colchicine and amyloid nephropathy secondary to FMF treated with angiotensin converting enzyme inhibitors. Two months prior to his admission, he developed headache and sleep disturbances that were related to new onset depression. Later, dysarthria, ataxia and rapid cognitive decline appeared as well. On examination, the patient was agitated, partially oriented (to date) with marked mental slowing. His Mini Mental Status Examination (MMSE) was 18/30. His horizontal and upward gaze was limited. No focal weakness was found, deep tendon reflexes were diminished and the plantar responses were flexor. A sensory gloves and stocking deficit was found and attributed to peripheral neuropathy. He had a bilateral limb ataxia with ataxic gait disturbance. Routine MRI scan (that did not include diffusion Tensor imaging (DTI)) was interpreted as normal. The CSF profile was normal with no cells or elevated protein levels but was positive for the 14-3-3 protein. EEG showed periodic spike and wave activity compatible with CJD. Genetic testing revealed a positive E200K mutation in the *PRNP* gene. During his hospitalization, the patient deteriorated rapidly in his cognitive and motor skills. Myoclonus and seizures appeared and he died six weeks after his admission, 3.5 months after the first symptom of his disease.

Case II—A 57 years old man of a Jewish Libyan origin was admitted to another hospital for observation due to mild hemiparesis and blurred vision which began a few days before his admission. His past medical history was remarkable for episodes of fever, vomiting and abdominal pain diagnosed as FMF attacks necessitating treatment with colchicine. Family history was negative for CJD. Examination revealed pronation drift, numbness and ataxia of the left hand. His gait was unstable due to ataxia. The CT scan was normal. Because of the acute appearance of the neurological deficits the working diagnosis was ischemic stroke and treatment with aspirin was initiated. Vascular evaluation that included carotid Doppler and cardiac echocardiogram was normal. During his hospitalization the gait ataxia constantly worsened, accompanied by myoclonic jerks. Lumbar puncture showed normal values of protein and sugar with no cells, and the CSF culture was sterile. EEG showed periodic slow activity of theta range and was compatible with CJD, and the patient was transferred to our department for further evaluation. On his admission to our department, the patient was bed ridden with marked and diffuse myoclonic jerks, general rigidity and severe dysarthria. EEG showed periodic triphasic sharp waves and the tau protein level in CSF was 900 pg/ml. Genetic evaluation was negative for the *PRNP* E200K mutation. MRI revealed a characteristic CJD pattern [17] including hyperintense signal at the caudate nucleus (bilaterally), putamen (right) and fronto-temporal (right) by DTI sequence. During his hospitalization seizures appeared and the patient died one month after onset of symptoms.

Case III—A 54 years old Jewish Libyan woman with a positive family history of CJD was admitted due to general deterioration and cognitive decline which began one month before admission. Her short term memory was affected and she forgot daily events and was not orientated in time or place. Her gait became ataxic and her speech became unclear. Her past medical history was remarkable for FMF of many years duration for which she was treated with colchicine, diabetes mellitus, hypertension and active ischemic heart disease. She also had myopathy for many years. Investigation had revealed low carnitine level (2.7) and mitochondrial disease was suspected but several biopsies were normal. The patient was treated with carnitine for the previous 10 years and was clinically stable. On admission she had an episode of generalized tonic clonic seizures. On examination, the patient was alert but disoriented to date and time. She had right facial nerve palsy with no other focal weakness. The muscle tone was increased with paratonia and diminished deep tendon reflexes, plantar response was extensor on the right leg. Diffuse myoclonic movements of

the limbs were noticed as well. Due to the clinical picture of rapid dementia, her familial history of CJD and the physical finding of pyramidal and extrapyramidal findings with diffuse myoclonus, the working diagnosis was CJD. The EEG that showed periodic discharge compatible with CJD and the positive result for *PRNP* E200K mutation supported the diagnosis. The patient died 2.5 months after onset of the disease.

II. Group analysis

Ila: Clinical classification—Of the 372 CJD patients included in the study, 236 had familial disease while 136 were sporadic cases. One hundred and eighty five (50%) of the patients were men. The mean± standard error (SE) duration of the disease was 9.8±0.6 months and the mean± SE age of presentation of the disease was 61.5±0.5 years. Among the 372 patients included in the study, 3 were previously diagnosed as having FMF, and were all of Libyan origin. This prevalence of 1.27% (3/236 patients) is similar to the known prevalence of FMF in the Libyan Jewish community (1%) [14].

A comparison of the disease course between the groups of CJD in the FMF patients to the non FMF patients is presented in the Table 1. As can be seen, disease duration was significantly shorter in the FMF patients compared to fCJD patients, sCJD patients and CJD patients in general (all P values < 0.001). The age of presentation was significantly earlier in the FMF patients compared to all CJD patients and sCJD patients but this comparison just failed to reach significance for the fCJD group (p=0.001, 0.002, 0.06 respectively). When we compared the sCJD group to the fCJD group we found significantly older age of presentation (65.3±0.8 years) in the sporadic compared to the familial cases (59.3±0.6 years, p<0.001), but no significant difference in the duration of disease (10.9±1.1 months in the sporadic and 9.2±0.8 months in the familial cases).

In order to examine other known disease modifying factors, we performed a regression analysis of age of onset and disease duration. In fCJD it was found that there was a trend to shorter disease duration with age (-0.088 months/years of age, p=0.27). In sCJD there was a significant (p=0.005) prediction of -0.3 months/years of age on disease duration. It is important to note that the FMF patients were significantly younger than the other CJD patients but had shorter duration of disease, in contrast to the expected effect of age. Analysis by t-test of the effect of gender on disease duration in both fCJD and sCJD did not find any significant differences although the mean age of female patients was 2 years older than males in both groups. Data on *PRNP* codon 129 was available for 51 fCJD and 22 sCJD patients. In the fCJD group there were 39 MM, 12 MV and as expected, no VV patients [18]. In the sCJD group there were 14 MM, 5 MV and 3 VV patients. Homozygosity (MM or VV) in comparison to MV at codon 129 affected duration of illness significantly in the sCJD group (16.9±4.5 versus 5.1±0.6 months, p=0.002). A similar but non significant trend (11.5±2.0 versus 7.2±1.6 months, p=0.08), was found in the fCJD group. No significant effect of M129V was found on the age of disease onset.

Ila: Genetic classification—Fifty DNA samples of the CJD patients were found. Two of the FMF patients were homozygous to the *MEFV* M694V mutation, as assumed. The DNA sample of the third patient was dry. In the remaining samples, 3 patients were heterozygous and in the rest of the 45 patients no FMF mutation was found.

A comparison of the disease duration showed significantly shorter duration in the homozygous patients (2.3±0.7 months) compared to both heterozygous patients (10.5±6.6 months) and the CJD patients with no mutation (10.6±13.9) by both t-test and Mann-Whitney comparisons (p<0.03). Disease onset was significantly earlier in the FMF homozygous patients (50.7±4.9 years) compared to the heterozygous (64.1±10.2) and no mutation (60.9±9.8) by t-tests (p<0.05).

Discussion

Our study describes an accelerated course and an earlier age of onset of CJD in three patients with FMF. These differences in disease duration and age of onset were found to be significant when the comparison was based on the clinical data and the genetic data. The FMF heterozygote state was not found to affect the disease course of CJD. As far as we know this is the first description of FMF as a disease modifying factor of CJD. The study analyzed a large group of fCJD patients which is unique for its size and for the high co-existence of FMF but we detected only 2 familial and one sporadic case but these groups are too small to perform separate sub analyses.

CJD is a neurodegenerative disease caused by conformational change of the normal neural protein PrP^C to the pathologic conformation of the isomer PrP^{Sc}. This pathologic isomer is thought to induce a conformational change in the normal PrP^C protein that switches to the PrP^{Sc} form. This reaction was thought to evoke no immune response and it was accepted for a long time that inflammation plays no role in the pathogenesis of CJD. This concept was supported by the histological studies in spongiform encephalopathies that observed no inflammatory cells infiltrating the brain. Recently however, several studies suggested a possible role for inflammation in the pathogenesis of CJD. Increased numbers of astrocytes, microglia and apoptotic neurons are found in the brains of CJD patients [8]. Human models show that microglia, the antigen presenting cells of the brain, are activated soon after PrP^{Sc} infection [20]. The role of the immunomodulatory molecules in the pathogenesis of CJD was examined in several studies [21]. Microglia cell isolated from infected brains were found to express increased mRNA level of inflammatory agents including IL-1 β [22]. In vivo, increased levels of pro inflammatory cytokines include tumor necrosis factor alpha and IL-1 β were found in the brain tissue of infected mice [23] and in the CSF of CJD patients [8,24], although other studies failed to confirm this [25]. Gabizon et al [26] have demonstrated the influence of the inflammatory process on the disease course of prion disease. They showed a shorter survival of mice with co-morbidity of scrapie and experimental autoimmune encephalomyelitis (EAE) compared to mice with scrapie only. Flupirtine, a non-steroidal anti inflammatory agent, has shown to protect neuronal cell from apoptosis induced by prion [27] and in a placebo controlled clinical study of CJD patients it slowed the cognitive decline, although didn't effect the survival [28].

The pyrin protein, encoded by the *MEFV* gene, is involved in IL-1 β regulation and acts as an anti inflammatory molecule. A mutation in the *MEFV* gene removes the inhibition from IL-1 β formation and causes uncontrolled inflammation of the serosal tissues that characterizes FMF. Our observation of an aggressive course of CJD in patients with concomitant inflammatory disease reinforces the notion that the immune system can play a role in the pathogenesis of CJD. The heterozygote state, which is not expressed by clinical symptoms and is not associated with uncontrolled inflammatory response, is not associated with an aggressive disease course. We suggest that the rapidly progressive CJD course seen in FMF patients may be caused by the uncontrolled immune response due to their reduced ability to suppress the immune cascade resulting in formation of IL-1 β . This concept supports the therapeutic potential of anti inflammatory treatment that may reduce the formation of cytokines such as IL-1 β and therefore prevent its harmful effect on the brain [29].

It is interesting to note that there have been conflicting reports on the effect of M129V on disease duration in E200K patients. Data on *PRNP* codon 129 in Israeli E200K patients has been previously published [18]. All Libyan Jewish CJD patients with the E200K mutation encode a Met129 on the mutant allele. Homozygosity for Met129 was not found to correlate with age at disease onset or the duration of illness. The frequency of the Met129 allele was

higher in the affected pedigrees than in a control population of Libyan Jews with a frequency of 90% Met129 alleles. This is in contrast to data from the Slovakia E200K cluster in which homozygosity for Met129 was associated with a significantly shorter disease duration [19], but in agreement with the present study, in the group of Jewish Libyan origin M129V status does not seem to offer a strong possible confounding factor which would explain the effect of FMF.

In conclusion: This shorter disease duration of CJD patients with FMF may indicate the importance of pro-inflammatory factors in the disease.

Acknowledgments

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Table 1

Demographic and Clinical Characteristics

Group	N	Gender (% male)	Age of presentation in years (mean±se)	Duration of disease in months (mean±se)
Total CJD	372	50	61.5±0.5	9.8±0.6
fcJD	236	48	59.3±0.6	9.2±0.8
sCJD	136	53	65.3±0.8	10.9±1.1
FMF+CJD	3	67	50.7±4.9	2.3±0.7
Non FMF CJD	369	50	61.6±0.5	9.9±0.6