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Review

Familial adult myoclonic epilepsy: A new expansion repeats disorder

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ABSTRACT

Familial adult myoclonic epilepsy (FAME), also described with different acronyms (ADCME, BAFME, FEME, FCTE and others), is a high-penetrant autosomal dominant condition featuring cortical hand tremors, myoclonic jerks, and occasional/rare convulsive seizures. Prevalence is unknown since this condition is often under-recognized, but it is estimated to be less than 1/35,000. The disease usually starts in the second decade of life and has been genetically associated with at least 4 different loci (8q24, 2p11.1-q12.2, 5p15.31-p15 and 3q26.32 – 3q28). Recently, the expansion of non coding TTTTA and TTTCA repeats has been identified as the causative mutation in Japanese families linked to the 8q24. The diagnosis is supported by clinical features and electrophysiological investigations as jerk-locked back averaging, C-reflex, and somatosensory-evoked potential. Photic stimulation, emotional stress, and sleep deprivation may trigger both tonic-clonic and myoclonic seizures. FAME has a slow but progressive clinical course occurring with intellectual disability and worsening of both tremor and myoclonus although with a less severe decline compared to other progressive myoclonic epilepsies. Valproate, levetiracetam, and benzodiazepines are considered the first-line treatments.

1. Introduction

The first description of a family showing tremulous movement associated with myoclonic jerks and generalized seizures was provided by Uyama and colleagues in 1985 [1]. In this description, no other neurological nor neuroradiological abnormalities were identified and all the patients showed a cortical reflex myoclonus as demonstrated by the electrophysiological assessment. Subsequently, four additional unrelated families, including a total of 27 individuals, with similar symptoms were described [2]. In 1990, Ikeda et al. introduced the term "cortical tremor" to describe the postural and action-induced shivering movement, that was in fact a variant of cortical reflex myoclonus [3] with distinctive electrophysiological features, namely [1], electromyographic burst lasting more than 50 msec [2]; no definite synchronisation or reciprocity in the antagonist muscles [3]; a positive-negative biphasic EEG spikes at the jerk-locked back averaging and [4] enlarged EEG response to somatosensory-evoked potentials (SEPs) [4,5]. In 1991, this condition was renamed "Familial Myoclonic Epilepsy (FAME)" [6]. We herein review the main clinical features, the diagnostic work-up, and the genetic background of this condition (Fig. 1).

2. Clinical features

Familial Adult Myoclonic Epilepsy is mainly characterized by cortical tremor, myoclonus, and occasional tonic-clonic seizures. Cortical tremor, the most remarkable feature of this condition, arises as a continuous and arrhythmic shivering-movement with the semiology of an essential tremor and the electrophysiological signatures indicative of cortical myoclonus [7]. The hands are the most affected part however, involvement of more proximal muscles, especially the eyelids, is also possible [8]. Even though it has a variable age of onset, first symptoms usually begin in the second decade of life, between 11–50 years of age [9,10]. Myoclonus is typically action- and posture-induced but it can occur also at rest. Moreover, despite the variable onset, it usually starts contemporary to cortical tremor at around the same age as the other relative affected within the family [11].

Generalized seizures are rare, from 5 to 10 episode during life, however, tonic-clonic seizures are occasionally reported. They normally appear later than tremor, between 12 and 67 years with a peak around the age of 30 and they are usually not preceded by any aura, despite myoclonus might occur immediately before. Drug-resistant focal seizures with focal EEG abnormalities may rarely arise [12]. Emotion, fatigue but also sleep deprivation and photic stimulation are notable

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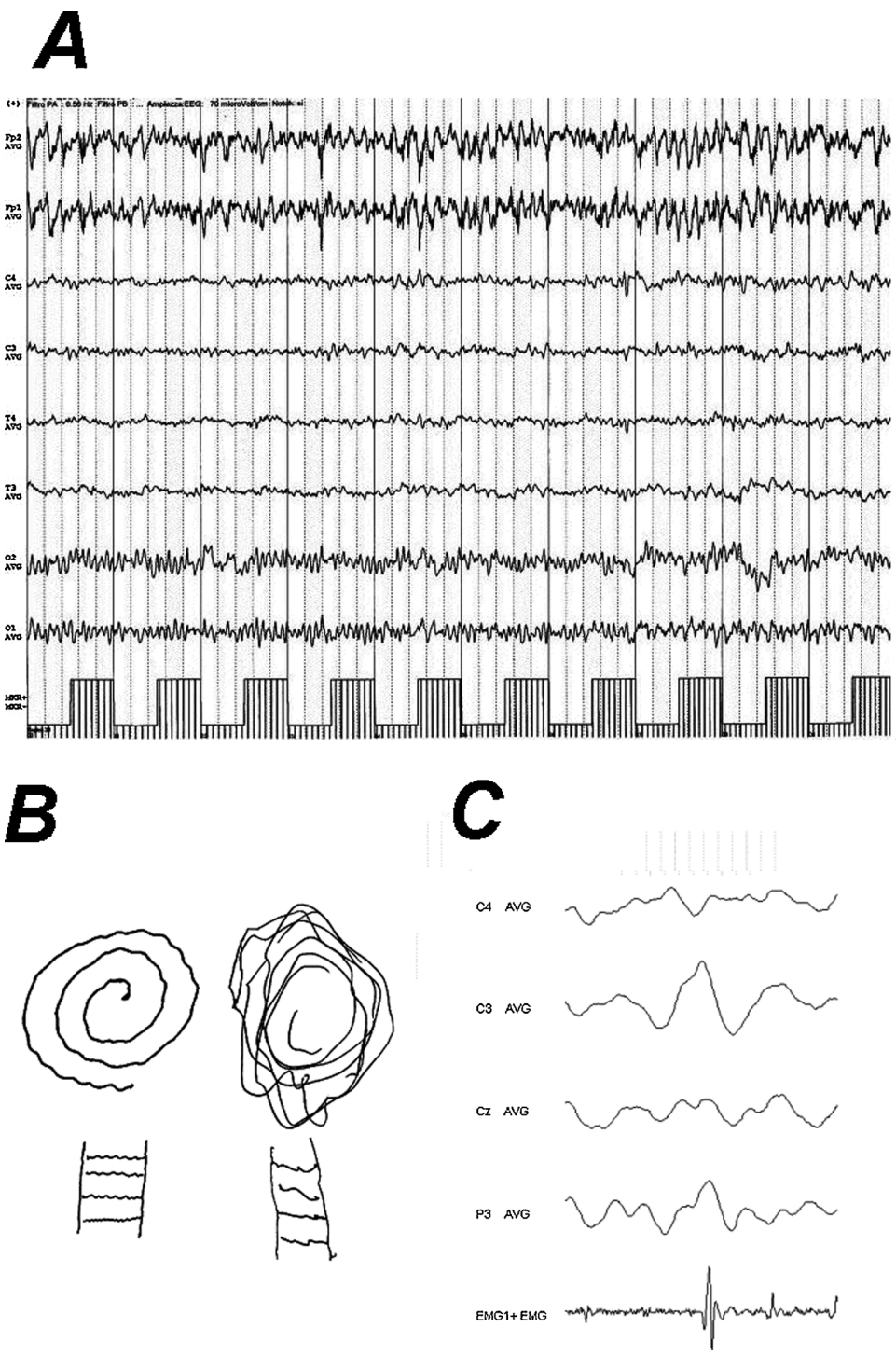

Fig. 1. Electroclinical features of Familial adult myoclonic epilepsy. A: EEG of a patient (with closed eyes) showing a myoclonic response to photic stimulation that mainly regards the anterior regions of the brain. The myogenic potentials appear strictly related to light stimuli and present an increasing trend. **B**: Archimedes spiral and ladder test showing the differences between essential (left) and cortical (right) tremor. Cortical tremor is irregular and characterized by sudden smudges provoked by the jerks. Essential tremor whereas, is regular and unidirectional. **C**: electromyography (EMG) of reciprocally antagonist muscles (EMG1: right wrist extensor; EMG2: right wrist flexor) with extended arms: irregular, high frequency, short-lasting EMG bursts without any definite synchronisation or reciprocity in the antagonist muscles. *Reproduced from Striano and Zara, 2010, with permission.*

triggers for seizures [13].

Psychiatric comorbidities, especially anxiety and depression, along with pathological traits of personality, i.e., paranoid and schizophrenia, are observed with higher frequency compared to the other epileptic syndrome [14]. Migraine, intellectual disability [15], and night blindness have been also reported in some patients from Japan and Turkey [16,2]. The natural history of the disease is usually characterized by a slow but inevitable worsening of the cortical tremor resulting with the impairment of fine movement as writing, buttoning, and picking up small objects [17]. Slow-progressive dementia, ataxia and worsening of myoclonus combined with drug-resistant epilepsy is observed in older patients [18].

3. Diagnostic procedures

Electrophysiological investigations, in particular EEG, EMG and SEPs, are essential for the diagnostic work-up of FAME. EEG background is usually normal for many years. However, long-term EEG evolution is characterized by progressive slowing of background activity in parallel with the gradual worsening of myoclonus. In contrast, paroxysmal activity and photosensitivity were particularly evident during the intermediate phases of the disease. Furthermore, the EEG pattern may be influenced by antiepileptic drugs as demonstrated by the more frequent occurrence of generalized paroxysmal and photoparoxysmal abnormalities in patients not receiving treatment [16,19].

Focal epileptiform discharge, despite rare, have been reported in patients with drug-resistant focal seizures [12]. EMG, is one of the core technique used for the diagnosis of FAME and it helps to better define the cortical tremor distinctive of this syndrome and, not rarely, the demonstration of the myoclonus cortical origin is often required for the differential diagnosis. EMG pattern in patients affected by FAME is normally characterized by a burst duration of less than 50 ms, unlike myoclonus of subcortical region which have a longer latency. Moreover, cortical myoclonus typically shows a contemporary activation of both agonist and antagonist muscles combined with an arrhythmic occurrence. EMG discharge are triggered by sensitive stimulus as tendon tap, small voluntary movement or change of posture, as well as by emotional stress.

Cortical tremor is indeed characterized by: a positive-negative, biphasic spike or a more complex pattern representing the cortical activation preceding the myoclonic discharge at EMG and confirming their temporal and spatial relationship. Other typical EMG features are: irregular, arrhythmic and high-frequency (around 10/s) myoclonic jerks, EMG burst of less than 50 ms; no definite synchronization or reciprocity in the antagonist muscles (in essential tremor whereas, the regular alternation between agonist and antagonist is respected) [20,4]. Back-averaging EEG time-locked to the myoclonic EMG discharge is often mandatory to confirm the diagnosis.

Since 1946, when Dawson and colleagues demonstrated an exaggerated EEG response (P25-N33 amplitude larger than 8.5–15 μV) to electrical stimuli applied to the peripheral nerve in patients with myoclonic epilepsy, somatosensory evoked potentials (SEPs) have been extensively used for the diagnostic workup of myoclonus [21]. At surface EMG indeed, the reflex jerk evoked by the sensory stimulus usually appears as an enhanced, long-latency reflex in response to the stimulus, referred to as a C reflex [22,23]. In cortical reflex myoclonus, the enhanced EMG response is mediated by a transcortical reflex pathway; other “long loops” are possible in other types of myoclonus. Finally, no haematological, biochemical or MRI alterations have been reported in FAME. In particular, no pathognomonic pattern are described at MRI, however, nonspecific alteration as enlargement of the subarachnoid spaces of the lateral ventricles are occasionally reported. Moreover, an MRI spectroscopy study showed an elevated choline/creatine ratio in the cerebellum cortex of patients compared with controls [24–26].

4. Pathophysiology

Among the first pathophysiological hypothesis, the increased cortical hyperexcitability should be mentioned. At this regards, Striano et al. hypothesized that the pathogenesis of FAME might be attributed to the impairment of the cerebello-thalamo-corticalprojections which would cause the decreased cortical inhibition normally applied by the cerebellum [27,16]. These findings were also confirmed by the evidence of cerebellar pathology in sporadic post-mortem histological studies, and by a few imaging investigations [28]. In particular, MRI spectroscopy reported an elevated choline/creatine ratio in the cerebellum cortex of patients compared to controls [26,24]; and a MR-DTI study demonstrated reduced mean fractional anisotropy (i.e., microstructural damage of the cerebellar white matter) in patients affected by FAME compared to patients with essential tremor [29]. Neuro-pathological findings revealed the formation of RNA foci containing repeats in the nucleus of cortical neurons (as reported in other neurodegenerative disease with expanded RNA repeats, i.e. ALS, FTLD-TDP), and a mild loss of Purkinje cell, although the last was described only in patients with homozygous mutations [30]. Some of the pathogenic hypothesis are the hypermethylation of the promoter and the consequent silencing of the gene; the trapping of vitals proteins by the RNA foci, that are therefore unable to function properly; or the translation of the expanded repeat into an abnormal protein [31].

5. Differential diagnosis

The diagnosis of FAME is based on patient’s clinical history and seizure semiology however, not rarely the demonstration of the cortical origin of the tremor by EMG is mandatory for differential diagnosis [32]. In particular, essential tremor and juvenile myoclonic epilepsy (JME) are the conditions mainly confused with FAME [33]. JME can be distinguished from FAME for the proximal involvement of limbs, the typical occurrence of seizures at awakening and the absence of cortical tremor. Moreover, the adult onset with a less severe prognosis and the absence of a rapidly progressive deterioration helps to differentiate FAME from progressive myoclonus epilepsies [34]. Finally, essential tremor can be differentiated by FAME due to the distinctive EMG pattern of these two conditions and because normally no seizures occur with essential tremor.

6. Treatment and evolution

Valproate, levetiracetam, and benzodiazepines are the first line treatment, obtaining the most effective controls on both epilepsy and myoclonus [35,36]. Cortical tremor usually is not responsive to alcohol or l-dopa/carbidopa, and in some cases drug-resistance is reported [3,16,19]. As for juvenile absence epilepsy (JAE) and juvenile myoclonic epilepsy (JME), carbamazepine or gabapentin may worsen myoclonus or precipitate a status epilepticus. In such cases, a correct diagnosis and prompt discontinuation of the drug may reverse this potentially life-threatening condition [37].

7. Genetics

FAME is characterized by a broad genetic heterogeneity which consists of at least four different identified loci including 8q24 (FAME1), 2p11.1-q12.2 (FAME2), 5p15.31-p15.1 (FAME3), and 3q26.32 − 3q28 (FAME4) with a worldwide distribution [38]. The first genetic locus associated with FAME was mapped in a Japanese family to chromosome 8q24 (FAME1) by Mikami et al. [39]. The same locus of FAME1 was also found in a Chinese family and in 1 large and 4 small pedigrees from Japan. The same linkage analysis on chromosome 8q24 was found negative in a cohort of European patients [40,28] affected by the same clinical condition. In 2001 Guerrini et al. reported a linkage to chromosome 2p11.1-q12.2 in a group of 8 patients with a slightly different phonotype (characterized by focal seizures of frontotemporal origin) and previously classified negative to 8q24linkage. Later on, Striano and colleagues confirmed the same results (maximum lod score = 5.9) in a 5-generation Italian family both in affected individuals presenting cortical tremor, myoclonus, and epilepsy [16], and in 3 presymptomatic members showing giant somatosensory-evoked potentials and enhanced long loop reflex who developed FAME 1.5 years later. The confirmation of the chromosome 2p11.2-q11.2 founder effect was then provided by Heden et al. in 2016 [34] in a cohort of 10 European and 1 Australian/New Zealander families, proving the allelic heterogeneity of FAME with at least 4 distinct founders. Additional loci have been mapped on 5p15.31-p15 and 3q26.32-q28 in French, Thai, and Chinese families [41–44]. In April 2018, Ishiura and colleagues made a crucial contribution to the identification of the causative mutation of FAME (remained unknown so far), reporting the expansion of TTTCA and TTTTA repeats in intron 4 of SAMD12 as the causative mutation of FAME linked to chromosome 8q24 (FAME1). These repeat expansions were detected in 49 out of 51families studied. TTTCA expansion whereas, was absent in more than 1000 controls and TTTA reported in less than 3,1% controls, confirming their causative role. Moreover, in some of the negative families, similar expansions of TTTCA and TTTTA repeats were found in TNRC6A and RAPGEF2 genes, suggesting that the expansion of these motifs are involved in the pathogenesis of FAME regardless of the gene involved. Ishiura et al. also showed that the length of the expanded repeats tended to be unstable

over successive generations and it appears inversely correlated with age of onset of both epilepsy and cortical tremor [45]. These findings have been confirmed by Lei and colleagues in five Chinese families, demonstrating the presence of TTTTA and TTTCA expansion repeats involving the SAMD12 and RAPGEF2 genes. These data indicate that a core haplotype containing the (TTTCA)n can be considered the founder effect between FAME pedigrees across China and Japan linked to the FAME1 locus [46]. Similar findings are being confirmed for the FAME 2 and FAME 3 loci (in publication).

8. Conclusions

FAME is a distinct and well-characterized condition that, however, is not included yet in ILAE classification. Moreover, the slow but inevitable progression of the disease requires a strict follow-up of the affected patients. Finally, further investigation and comparison with other repeat expansion diseases, such as spinocerebellar ataxia type 36 (SCA36) [47], is recommended to better define the underlying pathological mechanisms.

Declarations of interest

None.

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