Familial adult myoclonus epilepsy

Dubbioso, Raffaele; Suppa, Antonio; Tijssen, Marina A.J.; Ikeda, Akio

Published in:
Epilepsia

DOI:
10.1111/epi.17553

Publication date:
2023

Received: 4 December 2022 | Revised: 14 February 2023 | Accepted: 16 February 2023

DOI: 10.1111/epi.17553

Epilepsia®

SPECIAL ISSUE ARTICLE

Familial adult myoclonus epilepsy: Neurophysiological investigations

Raffaele Dubbioso[1] | **Antonio Suppa**[2,3] | **Marina A. J. Tijssen**[4,5] | **Akio Ikeda**[6]

[1]Department of Neuroscience, Reproductive Sciences and Odontostomatology, Federico II University of Naples, Napoli, Italy

[2]Department of Human Neurosciences, Sapienza University of Rome, Rome, Italy

[3]IRCCS Neuromed, Pozzilli, Italy

[4]Department of Neurology, University of Groningen, University Medical Centre Groningen (UMCG), Groningen, The Netherlands

[5]Expertise Centre Movement Disorders Groningen, University Medical Centre Groningen (UMCG), Groningen, The Netherlands

[6]Department of Epilepsy, Movement Disorders and Physiology Kyoto University Graduate School of Medicine Shogoin, Kyoto, Japan

Correspondence
Raffaele Dubbioso, Department of Neuroscience, Reproductive Sciences and Odontostomatology, Federico II University of Naples, Via Pansini 5, 80131 Napoli, Italy.
Email: rafdubbioso@gmail.com

Abstract

Familial adult myoclonus epilepsy (FAME) also described as benign adult familial myoclonus epilepsy (BAFME) is a high-penetrant autosomal dominant condition featuring cortical myoclonus of varying frequency and occasional/rare convulsive seizures. In this update we provide a detailed overview of the main neurophysiological findings so far reported in patients with FAME/BAFME. After reviewing the diagnostic contribution of each neurophysiological technique, we discuss the possible mechanisms underlying cortical hyperexcitability and suggest the involvement of more complex circuits engaging cortical and subcortical structures, such as the cerebellum. We, thus, propose that FAME/BAFME clinical features should arise from an "abnormal neuronal network activity," where the cerebellum represents a possible common denominator. In the last part of the article, we suggest that future neurophysiological studies using more advanced transcranial magnetic stimulation (TMS) protocols could be used to evaluate the functional connectivity between the cerebellum and cortical structures. Finally, non-invasive brain stimulation techniques such as repetitive TMS or transcranial direct current stimulation could be assessed as potential therapeutic tools to ameliorate cortical excitability.

KEYWORDS

cortical excitability, cortical tremor, giant SEP, JLA, TMS

1 | INTRODUCTION

Familial adult myoclonus epilepsy (FAME), also described as benign adult familial myoclonus epilepsy (BAFME), is a high-penetrant autosomal dominant condition characterized by the clinical combination of varying frequency of cortical myoclonus, and tonic–clonic seizures. The main frequencies of cortical myoclonus may overlap with those seen in specific tremors.

In the first description in 1990, Ikeda et al.[1] reported an action and postural tremor originating from the cerebral cortex, which was thus defined as a cortical tremor. Cortical tremor was then recognized to be a remarkable feature of the disease, often in association with generalized tonic–clonic seizures.

Over time, neurophysiological findings have clarified that cortical tremor and myoclonus shared pathophysiological features suggesting the existence of a continuum.[2]

Raffaele Dubbioso and Antonio Suppa contributed equally as first authors.

Indeed FAME/BAFME patients can display rhythmic and highly frequent jerks of small amplitude and involving the distal upper limb during posture and action and/or less frequent and arrhythmic jerks affecting the legs, head, trunk, proximal upper limbs, and facial muscles, especially around the mouth and the eyelids. Cortical myoclonus can be spontaneous or stimulus sensitive, namely provoked by sensory inputs (i.e., somatosensory, visual stimulation).[2]

The aim of this update is to provide a detailed description of the main neurophysiological findings reported so far in FAME/BAFME patients, discussing the possible pathophysiological mechanisms underlying aberrant cortical hyperexcitability. In the last section of the article, we consider more advanced neurophysiological techniques to get new neurobiological insight of the disease and their use as innovative therapeutic approaches to ameliorate cortical hyperexcitability.

Key Points

- A detailed neurophysiological study remains the main tool for the diagnosis of familial adult myoclonus epilepsy/benign adult familial myoclonus epilepsy (FAME/BAFME).
- Neurophysiological studies have consistently demonstrated marked and diffuse hyperexcitability of several cortical areas, likely due to an imbalance between facilitation and inhibition.
- We propose that FAME/BAFME clinical features should arise from an "abnormal neuronal network activity" between cortical and subcortical structures, such as the cerebellum.
- Future neurophysiological studies using more advanced protocols could be used to evaluate functional connectivity between the cerebellum and cortical structures.

2 | THE CONTRIBUTION OF NEUROPHYSIOLOGY TO FAME/BAFME

Electrophysiological investigations are essential for the diagnostic workup of FAME/BAFME, since neurophysiological tools may help to confirm the cortical origin of myoclonus. An adequate neurophysiological study should include:

(i) Electroencephalography (EEG).
(ii) The occurrence of cortical spikes preceding myoclonic jerks, demonstrated by jerk-locked back averaging (JLA).
(iii) Polymyographic recording demonstrating the classic electromyography (EMG) pattern consistent with irregular, arrhythmic (or semi-rhythmic), and high-frequency myoclonic jerks occurring in bursts lasting 50–100 ms.
(iv) Somatosensory evoked potentials (SEPs) with enlarged cortical components (i.e., giant SEPs).
(v) An enhanced long-loop reflex (C-reflex) evoked by the stimulation of the peripheral nerve.
(vi) Strong cortical and intermuscular coherence in an 8–30 Hz range.

Table 1 summarizes the articles on FAME/BAFME with the main neurophysiological findings.

3 | STANDARD EEG RECORDINGS

EEG recordings of patients with FAME/BAFME have been characterized by non-epileptic background activity and epileptic activity. The posterior dominant rhythm (PDR) was commonly reported as mildly abnormal because of slight slowing at the time of occurrence of symptoms in middle age.[18,33] Initially, gradual and progressive slowing of the PDR with age was reported in European patients with FAME/BAFME based on EEG.[18] Following this report, the statistical analysis compared with the control data was performed, and the effect of antiseizure medications (ASMs) was also investigated in 19 Japanese patients with FAME/BAFME (50.6 ± 15.7 years).[33] PDR frequency in the patient group (9.1 ± 0.7 Hz) was significantly slower than that of age-matched 38 control subjects (50.1 ± 14.5 years) (10.4 ± 1.1 Hz; $p < .0001$).

Controls were gathered from an EEG database of normal EEG judgment blind to clinical information with the same age range as patients with FAME/BAFME. Their diagnosis was then disclosed as idiopathic generalized epilepsy, focal epilepsy, syncopal attack, movement disorders, and other various kinds of etiology (e.g., sleep disorders, psychiatric disorders, and so forth). Of 38 control subjects, 24 were on ASMs. PDR frequency was also significantly lower in the 19 FAME/BAFME patients than in the age-matched control subjects taking anticonvulsants (24 subjects; 10.6 ± 0.9 Hz; $p < .0001$) or not taking ASMs (14 subjects; 10.0 ± 1.2 Hz, $p = .0068$). Both findings are consistently suggestive of slowly progressive diffuse encephalopathy, but its degree was very mild compared with other so-called progressive myoclonus epilepsy.

TABLE 1 Neurophysiological studies on FAME/BAFME patients.

Articles	No. of patients	ASMs	Abnormal C-reflex	Giant SEP	EEG abnormalities	Presence of JLA	Cortico-muscular coherence range (Hz)	EMG- tremor frequency range (Hz)
Ikeda et al., 1990[1]	2	2/2	2/2	2/2	2/2	2/2	-	-
Okuma et al., 1998[3]	4	4/4	4/4	4/4	4/4	4/4	-	8–10
Elia et al., 1998[4]	4	3/4	4/4	4/4	4/4	4/4	-	8–10
Mikami et al., 1999[5]	17	-	17/17	17/17	17/17	-	-	9–10
Guerrini et al., 2001[6]	8	6/8	7/7	6/7	7/7	9/9	8–25 (Rolandic area)	8–15
Labauge et al., 2002[7]	15	5/5	5/5	3/5	1/5	3/3	-	10–13
Van Rootselaar et al., 2002[8]	13	6/13	4/5	4/5	2/4	Absent	-	12–16
De Falco et al., 2003[9]	15	8/15	12/15	10/15	9/15	7/7	-	High frequency
Striano et al., 2004[10]	5	5/5	5/5	3/5	5/5	5/5	-	-
Striano et al., 2005[11]	11	9/11	11/11	9/11	10/11	11/11	-	-
Van Rootselaar et al., 2006[12]	7	5/7	4/5	4/5	3/5	Absent	8–30 (C3 and FC3)	13–20
Gardella et al., 2006[13]	7	1/7	2/7	1/7	2/7	Present	-	
Carr et al., 2007[14]	17	-	11/11	7/8	12/12	7/8	-	8–10
Van Rootselaar et al., 2007[15]	10	7/10	4/6	4/6	4/10	-	-	-
Van Rootselaar et al., 2008[16]	8	5/8	5/6	4/6	2/5	-	Present	-
Suppa et al., 2009[17]	7	-	0/7	0/7	7/7	7/7	-	8–12
Coppola et al., 2011[18]	14	12/14	-	-	8/14	-	-	-
Hitomi et al., 2011[19]	16	9/16	-	13/16	-	-	-	-
Licchetta et al., 2013[20]	16	13/16	3/3	2/3	10/11	3/3	-	7–15
Yeetong et al., 2013[21]	13	7/13	11/11	7/11	9/10	2/2	-	-
Buijink et al., 2013[22]	7	5/7	5/5	3/5	2/5	-	-	-
Cen et al., 2016[23]	55	29/55	29/31	28/32	26/35	-	-	-
Gao et al., 2016[24]	6	5/6	1/1	1/1	5/5	-	-	-
Mahadevan et al., 2016[25]	48	48/48	-	33/48	48/48	-	-	-
Latorre et al., 2018[26]	3	-	2/3	3/4	-	0/3	-	-
Kobayashi et al., 2018[27]	101	88/95	35/41	55/67	64/94	8/11	-	-
Liu et al., 2020[28]	12	6/12	-	12/12	-	-	-	-
Demura et al., 2020[29]	3	1/3	1/3	3/3	1/3	-	-	-
Matsubara et al., 2021[30]	5	5/5	5/5	4/5	5/5	-	-	-
Tojima et al., 2021[31]	16	15/16	-	16/16	-	-	-	-
Dubbioso et al., 2022[32]	26	21/26	21/26	20/26	15/24	18/18	-	6–11.25

Note: EEG abnormalities include nonepileptic background activity and/or epileptic activity. Note that ratios refer to the number of patients manifesting the specific neurophysiological abnormality over the total number of patients examined with the same technique in each study.

Abbreviations: ASMs, antiseizure medications; SEP, somatosensory evoked potential; JLA, jerk-locked back averaging. -, Not performed.

Concerning epileptiform discharges, generalized spike/polyspike and wave complexes have been recorded frequently in BAFME patients, and with a higher frequency than those observed in patients affected by idiopathic generalized tonic–clonic seizures (4.3 ± 1.0 vs 3.2 ± 0.8 Hz).[34] Moreover, in a subsequent sleep study,[1] epileptiform discharges have been reported more frequently in awake patients rather than during sleep periods, suggesting a relative reduction in cortical irritability during sleep in BAFME.[35]

Finally, several studies have demonstrated that patients with FAME/BAFME may frequently manifest the photoparoxysmal response, especially when not receiving therapy. Moreover, during intermittent photic stimulation, patients may also show a photomyogenic response in cranial and/or limb muscles time-locked with visual inputs. The photomyogenic response might be considered as the neurophysiological correlate of reflex myoclonus induced by visual stimuli.

4 | JERK-LOCKED BACKWARD AVERAGING (JLA)

Jerk-locked backward averaging (or JLA) may help to demonstrate the cortical origin of myoclonus. By averaging at least 50–200 trials of scalp EEG, JLA can reveal cortical spikes preceding and time-locked to individual myoclonic jerks recorded from intrinsic hand muscles (i.e., the extensor indicis muscle or the first dorsal interosseous muscle). The time interval between the cortical spike preceding the onset of the EMG discharge recorded from hand muscles was compatible with the cortico-muscular transmission.[1] Because JLA can directly demonstrate a causal relationship between cortical activity and EMG discharge, its specificity is thought to be high. Recently, a study investigating 44 patients who manifested cortical myoclonus clinically and instrumentally using EMG, demonstrated that JLA disclosed cortical spikes preceding and time-locked to individual myoclonic jerks in only 22% of participants. It is relevant to report, however, that half of the patients were not investigated because of technical limitations (i.e., the high frequency of myoclonic jerks, major EEG artifacts, or neuropathy). An improved method seems to be warranted such as time-frequency analysis for JLA. Indeed, the time-frequency analysis might provide more information of a wider frequency range than those obtained by single waveform analysis by JLA, and thus possibly supplement, endorse, or replace JLA.

5 | MYOCLONUS ANALYSIS

In patients with FAME/BAFME, most of the studies examining surface EMG recordings to extract the dominant peak frequency found increased power in the range of 8–15 Hz (see Table 1). This observation points to a rather homogeneous frequency of myoclonus in patients with FAME/BAFME typically occurring in the beta range. Of interest, patients with a longer disease duration have a higher power of tremor associated with a lower frequency.[32] The dominant peak frequency of jerky EMG activity in patients with FAME/BAFME differs from that commonly observed in patients with Parkinson's disease (PD) (i.e., 4–6 Hz); it significantly overlaps with the frequency of essential tremor (ET). However, the peak in FAME/BAFME is much broader because it reflects myoclonus rather than tremor. Concerning the neurophysiological difference between FAME/BAFME and ET, it is relevant to consider that ET is usually characterized by alternating EMG bursts in agonist and antagonist muscles, whereas myoclonic activity occurs synchronously in antagonist and agonist muscles in patients with FAME/BAFME.

6 | SOMATOSENSORY EVOKED POTENTIALS

Since the first description of cortical myoclonus in FAME/BAFME patients, giant SEPs have been considered the neurophysiological signature of somatosensory cortical hyperexcitability in response to peripheral electric stimuli.[1] Patients usually display a cortical amplitude's enlargement of P25 (e.g., >8.6 μV) and N33 components (e.g., >8.4 μV),[36] whereas the early negative component, N20, seems to be unaffected or in some cases even reduced.[32] However, the absence of giant SEPs does not exclude the diagnosis of FAME/BAFME, since its occurrence in previous studies ranges from 0% to 100% (Table 1). This would also reflect the influence of ASMs on reducing somatosensory cortex excitability. For instance, Striano et al. reported the beneficial effect of levetiracetam on six FAME/BAFME patients demonstrating improvement in myoclonus severity as well as the significant reduction of SEP amplitudes in all patients for P25 component and in 4 of 6 patients for N30 wave.[37]

More recently, some authors have shown that perampanel (PER),[38] an α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid-receptor antagonist, reduces the amplitude of early cortical components of giant SEPs. In addition, the decrease of P25 and N33 amplitudes was associated with prolonged latencies, especially for the N33 component. The amount of SEP prolongation scaled positively with blood PER concentration, suggesting that the drug reduced the degree of synchronized discharges in the postsynaptic neurons in the motor efferent pathways.[38]

Somatosensory hyperexcitability, indexed by giant SEPs, seems to be associated with a more severe myoclonus[23] and older age.[39] However, such results were not entirely confirmed by the other two studies,[32,37] raising the question that not only cortical circuits but also subcortical networks might play a role in disease severity.

In this direction, a recent study with paired-pulse SEPs, applied at interstimulus intervals of 5, 20, and 40 ms, has shown that the physiological suppression of the second response is less evident in patients with FAME. Such results indicated that in addition to intracortical hyperexcitability, as indexed by short interstimulus intervals (ISIs) (i.e., 5 ms), the lack of suppression at longer ISIs (i.e., 20 and 40 ms) may also reflect the concomitant involvement of subcortical networks, such as the dorsal column nuclei and the ventral posterolateral nucleus of the thalamus.[40,41] The same study has confirmed the involvement of subcortical structures, by using the early component of the high-frequency oscillations (e-HFOs) evoked by electrical nerve stimulation and overlapping the earliest part of the N20. Indeed, the

authors have demonstrated a significant reduction of the area of e-HFOs that likely represents the activity of thalamocortical fibers directed to the somatosensory cortex.[32] On the other hand, a Japanese study[31] has demonstrated that the presence of the late HFO component (i.e., overlapping P25 component) might differentiate BAFME from other forms of cortical myoclonus, with a sensitivity and specificity higher than enlarged P25 and N33 components. The authors, therefore, speculated that the presence of late HFOs may reflect cortical hyperexcitability partly due to paroxysmal depolarizing shifts in epileptic neuronal activities and higher degrees of rhythmic tremulousness than those observed in other neurological diseases denoted by cortical myoclonus.[31]

7 | C-REFLEX

Among the typical neurophysiological features of patients with cortical myoclonus, the enhanced C-reflex is thought to provide robust evidence of cortical hyperexcitability. The C-reflex is commonly elicited in the thenar muscle following percutaneous electric stimulation of the median nerve at the wrist.[42] The afferent neuronal pathway that is thought to mediate the C-reflex includes electric activation of Ia afferents with action potentials traveling through the lemniscal pathway, and finally reaching the primary somatosensory cortex (S1) in about 20 ms. Conversely, the efferent neuronal pathway likely responsible for the C-reflex implies the activation of the primary motor cortex (M1) and descending signals traveling through the corticospinal tract and in turn activating anterior horn alpha motor neurons projecting to thenar muscles, again in about 20 ms. Typically an expected latency of 45–55 ms for a C-reflex recorded from thenar muscles would reflect the time required for activation of S1 (about 20 ms) + the transcortical polysynaptic transmission of signals from S1 to ipsilateral M1 (5–15 ms) + the time required for signals generated in M1 to elicit thenar muscle activation (about 20 ms). Accordingly, the observation of enhanced C-reflex in a patient manifesting myoclonus is thought to support the hypothesis of sensory-motor cortex hyperexcitability.[36] The enhanced C-reflex would be, therefore, considered the neurophysiological counterpart of cortical reflex myoclonus induced by somatosensory stimulation. Finally, in FAME/BAFME patients, enhanced C-reflex is a common neurophysiological observation being observed even more frequently than giant SEPs (see Table 1). This would in theory be explained considering the specific neurophysiological underpinning of enhanced C-reflex that, differently from SEP, also reflects the hyperexcitability of M1.

8 | CORTICOMUSCULAR COHERENCE

EEG–EMG corticomuscular coherence consists of a commonly used method allowing the assessment of the functional coupling between the sensorimotor cortex activity and the (voluntary or involuntary) contraction of contralateral upper limb muscles.[43] Specifically, EEG–EMG corticomuscular coherence allows the examination of the functional coupling between neural signals generated from the sensorimotor cortex (i.e., through surface EEG recordings) and EMG signals recorded from contralateral upper limb muscles. Accordingly, abnormal corticomuscular coherence (mainly in the beta band) may help to demonstrate a cortical drive for involuntary muscle activity, especially in patients with cortical myoclonus without evidence of cortical potentials preceding myoclonus at the EEG back-averaging technique.[42] This specific scenario would likely occur in patients with cortical myoclonus manifesting continuous/subcontinuous muscular activity, leading to low-amplitude myoclonic jerks (i.e., polymyoclonus or cortical tremor). Moreover, the abnormally increased EEG–EMG corticomuscular coherence in patients with cortical myoclonus would be considered the neurophysiological counterpart of postural/action myoclonus. Only a few studies (see Table 1) have examined EEG–EMG corticomuscular coherence in patients with FAME/BAFME, demonstrating that coherence analysis can provide additional information compared with back-averaging EEG alone. For instance, van Rootselaar and colleagues[12] showed a strong cortical and intermuscular coherence in the 8- to 30-Hz range in FAME/BAFME, whereas healthy subjects and ET patients displayed normal weak coherence around 20 Hz. In addition, ET patients showed coherence at tremor frequency (6 Hz), suggesting that coherence analysis could be an easy and useful method to differentiate ET from FAME/BAFME.

9 | MOTOR EVOKED POTENTIALS

Four studies[6,15,17,32] evaluated M1 excitability by using single and paired-pulse TMS paradigms. Specifically, these studies demonstrated a reduction of motor thresholds[6,17,32] along with a significant decrease of short intracortical inhibition (SICI)[15,17,32] and a shorter cortical silent period.[6,17,32] These results put forward a significant excitatory-inhibitory imbalance within M1 characterized by increased facilitation and/or decreased inhibition of the primary motor cortex involving both glutamatergic as well as γ-aminobutyric acid (GABA) ergic networks.

A direct comparison of diagnostic accuracy of neurophysiological techniques, such as SEP and TMS, has been performed recently.[32] Specifically, the authors demonstrated that specific TMS variables such as SICI and long-interval intracortical inhibition, predicted FAME/BAFME with much higher diagnostic usefulness than the conventional SEP variables (i.e., P25 and N33 amplitudes) and supported the implementation of TMS protocols in the neurophysiological workup before genetic testing.

In summary, data from SEP and TMS suggest that pathological cortical excitability affecting FAME/BAFME patients might be composed of hyperexcitability of both the primary somatosensory and motor cortex.

10 | VISUAL EVOKED POTENTIALS

Besides sensory-motor cortex hyperexcitability, FAME/BAFME patients might also display a significant increase of primary visual cortex excitability. The neurophysiological correlate is the significant enlargement of visual evoked potentials (VEPs).[6] In a recent study on BAFME patients carrying the intronic expansions in the *SAMD12* gene,[29] the authors have found giant VEPs as a reliable measure to detect photosensitive myoclonus elicited during flash stimulation.[29] Of interest, in these patients, the authors have observed a clinically overt reflex myoclonus induced by visual stimuli.

11 | CONCLUSION AND OUTLOOK

Despite relevant advances in the genetic investigation of FAME/BAFME, the detailed neurophysiological study remains the main tool to demonstrate the cortical origin of myoclonus.

So far, neurophysiological studies have consistently demonstrated marked and diffuse hyperexcitability of cortical areas, such as somatosensory, motor, and visual areas, likely due to excessive facilitation along with decreased inhibition of cortical excitability only partially attenuated by current ASMs. However, such cortical hyperexcitability is not strictly associated with disease severity and the size of expanded repeats.[39] The lack of correlation among cortical hyperexcitability measures and phenotypes as well as genotype would point to the intrinsic heterogeneity in clinical (i.e., phenotypic variability due to different ethnic origins), genetic (i.e., the site of the intronic expansion), as well as neurophysiological features of the disease (i.e., complex pathophysiological interaction between cortical and subcortical structures).[2]

We suggest that FAME/BAFME clinical features should arise from "an abnormal neuronal network" activity. Among putative pathophysiologic theories, a fascinating hypothesis is that the decreased cortical inhibition is driven by a dysfunction of the cerebellar-thalamocortical loop secondary to primary cerebellar pathology. Indeed, cerebellar clinical signs as well as structural and functional cerebellar alterations have been demonstrated by postmortem studies, magnetic resonance imaging (MRI) spectroscopy data, and brain MR diffusion tensor imaging (DTI).[44] Therefore, future neurophysiological studies using more advanced TMS protocols should focus on evaluating functional connectivity between the cerebellum and cortical structures (i.e., cerebellar brain inhibition[45]). Future therapeutic approaches based on repetitive cerebellar-TMS or cerebellar-transcranial direct stimulation would in theory ameliorate the abnormal excitability of sensory-motor cortex[46] in FAME/BAFME patients.

AUTHOR CONTRIBUTIONS

Raffaele Dubbioso: study concept and design; drafting of the manuscript; acquisition of data; administrative, technical, or material support; analysis and interpretation of data; and critical revision of the manuscript. **Antonio Suppa:** drafting of the manuscript; acquisition of data; administrative, technical, or material support; and critical revision of the manuscript. **Maria AJ Tijssen:** analysis and interpretation of data and critical revision of the manuscript. **Akio Ikeda:** study drafting of the manuscript; acquisition of data; administrative, technical, or material support; and critical revision of the manuscript.

ACKNOWLEDGMENTS

This communication was part of the International Workshop on Familial Adult Myoclonic Epilepsy, held in Naples (Italy) on May 27–28, 2022. This networking event has received funding from the European Union's Horizon 2020 research and innovation programme under the EJP RD COFUND-EJP N° 825575. Open Access Funding provided by Universita degli Studi di Napoli Federico II within the CRUI-CARE Agreement.

FUNDING INFORMATION

This study received no specific funding.

CONFLICT OF INTEREST STATEMENT

None of the authors have any conflicts of interest to disclose.

PATIENT CONSENT

All data used in this study had been previously published and deidentified.

PERMISSION TO REPRODUCE MATERIAL FROM OTHER SOURCES

No figures/tables/excerpts were reproduced in this text and all data is appropriately cited.

CLINICAL TRIAL REGISTRATION

No clinical trial registration was needed for this review.

DISCLAIMER

None.

ORCID

Raffaele Dubbioso https://orcid.org/0000-0003-2487-4741
Antonio Suppa https://orcid.org/0000-0001-9903-5550
Marina A. J. Tijssen https://orcid.org/0000-0001-5783-571X
Akio Ikeda https://orcid.org/0000-0002-0790-2598

REFERENCES

1. Ikeda A, Kakigi R, Funai N, Neshige R, Kuroda Y, Shibasaki H. Cortical tremor: a variant of cortical reflex myoclonus. Neurology. 1990;40(10):1561–5.
2. Latorre A, Rocchi L, Magrinelli F, Mulroy E, Berardelli A, Rothwell JC, et al. Unravelling the enigma of cortical tremor and other forms of cortical myoclonus. Brain. 2020;143(9):2653–63.
3. Okuma Y, Shimo Y, Shimura H, Hatori K, Hattori T, Tanaka S, et al. Familial cortical tremor with epilepsy: an under-recognized familial tremor. Clin Neurol Neurosurg. 1998;100(1):75–8.
4. Elia M, Musumeci SA, Ferri R, Scuderi C, del Gracco S, Bottitta M, et al. Familial cortical tremor, epilepsy, and mental retardation: a distinct clinical entity? Arch Neurol. 1998;55(12):1569–73.
5. Mikami M, Yasuda T, Terao A, Nakamura M, Ueno SI, Tanabe H, et al. Localization of a gene for benign adult familial myoclonic epilepsy to chromosome 8q23.3-q24.1. Am J Hum Genet. 1999;65(3):745–51.
6. Guerrini R, Bonanni P, Patrignani A, Brown P, Parmeggiani L, Grosse P, et al. Autosomal dominant cortical myoclonus and epilepsy (ADCME) with complex partial and generalized seizures: a newly recognized epilepsy syndrome with linkage to chromosome 2p11.1-q12.2. Brain. 2001;124(Pt 12):2459–75.
7. Labauge P, Amer L, Simonetta-Moreau M, Attané F, Tannier C, Clanet M, et al. Absence of linkage to 8q24 in a European family with familial adult myoclonic epilepsy (FAME). Neurology. 2002;58(6):941–4.
8. van Rootselaar F, Callenbach PMC, Hottenga JJ, Vermeulen FLMG, Speelman HD, Brouwer OF, et al. A Dutch family with "familial cortical tremor with epilepsy": clinical characteristics and exclusion of linkage to chromosome 8q23.3-q24.1. J Neurol. 2002;249(7):829–34.
9. De Falco FA, Striano P, De Falco A, Striano S, Santangelo R, Perretti A, et al. Benign adult familial myoclonic epilepsy: genetic heterogeneity and allelism with ADCME. Neurology. 2003;60(8):1381–5.
10. Striano P, Chifari R, Striano S, de Fusco M, Elia M, Guerrini R, et al. A new benign adult familial myoclonic epilepsy (BAFME) pedigree suggesting linkage to chromosome 2p11.1-q12.2. Epilepsia. 2004;45(2):190–2.
11. Striano P, Madia F, Minetti C, Striano S, Zara F. Electroclinical and genetic findings in a family with cortical tremor, myoclonus, and epilepsy. Epilepsia. 2005;46(12):1993–5.
12. van Rootselaar AF, Maurits NM, Koelman JHTM, van der Hoeven JH, Bour LJ, Leenders KL, et al. Coherence analysis differentiates between cortical myoclonic tremor and essential tremor. Mov Disord. 2006;21(2):215–22.
13. Gardella E, Tinuper P, Marini C, Guerrini R, Parrini E, Bisulli F, et al. Autosomal dominant early-onset cortical myoclonus, photic-induced myoclonus, and epilepsy in a large pedigree. Epilepsia. 2006;47(10):1643–9.
14. Carr JA, van der Walt P, Nakayama J, Fu YH, Corfield V, Brink P, et al. FAME 3: a novel form of progressive myoclonus and epilepsy. Neurology. 2007;68(17):1382–9.
15. van Rootselaar A, van der Salm S, Bour LJ, Edwards MJ, Brown P, Aronica E, et al. Decreased cortical inhibition and yet cerebellar pathology in 'familial cortical myoclonic tremor with epilepsy'. Mov Disord. 2007;22(16):2378–85.
16. van Rootselaar A, Maurits NM, Renken R, Koelman JHTM, Hoogduin JM, Leenders KL, et al. Simultaneous EMG-functional MRI recordings can directly relate hyperkinetic movements to brain activity. Hum Brain Mapp. 2008;29(12):1430–41.
17. Suppa A, Berardelli A, Brancati F, Marianetti M, Barrano G, Mina C, et al. Clinical, neuropsychological, neurophysiologic, and genetic features of a new Italian pedigree with familial cortical myoclonic tremor with epilepsy. Epilepsia. 2009;50(5):1284–8.
18. Coppola A, Santulli L, del Gaudio L, Minetti C, Striano S, Zara F, et al. Natural history and long-term evolution in families with autosomal dominant cortical tremor, myoclonus, and epilepsy. Epilepsia. 2011;52(7):1245–50.
19. Hitomi T, Ikeda A, Kondo T, Imamura H, Inouchi M, Matsumoto R, et al. Increased cortical hyperexcitability and exaggerated myoclonus with aging in benign adult familial myoclonus epilepsy. Mov Disord. 2011;26(8):1509–14.
20. Licchetta L, Pippucci T, Bisulli F, Cantalupo G, Magini P, Alvisi L, et al. A novel pedigree with familial cortical myoclonic tremor and epilepsy (FCMTE): clinical characterization, refinement of the FCMTE2 locus, and confirmation of a founder haplotype. Epilepsia. 2013;54(7):1298–306.
21. Yeetong P, Ausavarat S, Bhidayasiri R, Piravej K, Pasutharnchat N, Desudchit T, et al. A newly identified locus for benign adult familial myoclonic epilepsy on chromosome 3q26.32-3q28. Eur J Hum Genet. 2013;21(2):225–8.
22. Buijink AWG, Caan MWA, Tijssen MAJ, Hoogduin JM, Maurits NM, Van Rootselaar AF. Decreased cerebellar fiber density in cortical myoclonic tremor but not in essential tremor. Cerebellum. 2013;12(2):199–204.
23. Cen Z, Huang C, Yin H, Ding X, Xie F, Lu X, et al. Clinical and neurophysiological features of familial cortical myoclonic tremor with epilepsy. Mov Disord. 2016;31(11):1704–10.
24. Gao L, Li L, Ye J, Zhu X, Shen N, Zhang X, et al. Identification of a novel mutation in PLA2G6 gene in a Chinese pedigree with familial cortical myoclonic tremor with epilepsy. Seizure. 2016;41:81–5.
25. Mahadevan R, Viswanathan N, Shanmugam G, Sankaralingam S, Essaki B, Chelladurai RP. Autosomal dominant cortical tremor, myoclonus, and epilepsy (ADCME) in a unique south Indian community. Epilepsia. 2016;57(3):e56–9.

26. Latorre A, Rocchi L, Berardelli A, Rothwell JC, Bhatia KP, Cordivari C. Reappraisal of cortical myoclonus: a retrospective study of clinical neurophysiology. Mov Disord. 2018;33(2):339–41.
27. Kobayashi K, Hitomi T, Matsumoto R, Watanabe M, Takahashi R, Ikeda A. Nationwide survey in Japan endorsed diagnostic criteria of benign adult familial myoclonus epilepsy. Seizure. 2018;61:14–22.
28. Liu C, Song Y, Yuan Y, Peng Y, Pang N, Duan R, et al. TTTCA repeat expansion of SAMD12 in a new benign adult familial myoclonic epilepsy pedigree. Front Neurol. 2020;11:1–7.
29. Demura A, Demura Y, Ota M, Kondo T, Kinoshita M. Clinical significance of the long-loop reflex and giant evoked potentials in genetically proven benign adult familial myoclonic epilepsy. Clin Neurophysiol. 2020;131(4):978–80.
30. Matsubara T, Ahlfors SP, Mima T, Hagiwara K, Shigeto H, Tobimatsu S, et al. Bilateral representation of sensorimotor responses in benign adult familial myoclonus epilepsy: an MEG study. Front Neurol. 2021;12:1–15.
31. Tojima M, Hitomi T, Matsuhashi M, Neshige S, Usami K, Oi K, et al. A biomarker for benign adult familial myoclonus epilepsy: high-frequency activities in Giant somatosensory evoked potentials. Mov Disord. 2021;36(10):2335–45.
32. Dubbioso R, Striano P, Tomasevic L, Bilo L, Esposito M, Manganelli F, et al. Abnormal sensorimotor cortex and thalamo-cortical networks in familial adult myoclonic epilepsy type 2: pathophysiology and diagnostic implications. Brain Commun. 2022;4(1):1–15.
33. Hitomi T, Kobayashi K, Sakurai T, Ueda S, Jingami N, Kanazawa K, et al. Benign adult familial myoclonus epilepsy is a progressive disorder: No longer idiopathic generalized epilepsy. Epileptic Disord. 2016;18(1):67–72.
34. Toyota T, Akamatsu N, Tanaka A, Tsuji S, Uozumi T. Electroencephalographic features of benign adult familial myoclonic epilepsy. Clin Neurophysiol. 2014;125(2):250–4.
35. Hitomi T, Inouchi M, Takeyama H, Kobayashi K, Sultana S, Inoue T, et al. Sleep is associated with reduction of epileptiform discharges in benign adult familial myoclonus epilepsy. Epilepsy Behav Case Reports. 2019;11:18–21.
36. Shibasaki H, Yamashita Y, Neshige R, Tobimatsu S, Fukui R. Pathogenesis of giant somatosensory evoked potentials in progressive myoclonic epilepsy. Brain. 1985;108(Pt 1):225–40.
37. Striano P, Manganelli F, Boccella P, Perretti A, Striano S. Levetiracetam in patients with cortical myoclonus: a clinical and electrophysiological study. Mov Disord. 2005;20(12):1610–4.
38. Oi K, Neshige S, Hitomi T, Kobayashi K, Tojima M, Matsuhashi M, et al. Low-dose perampanel improves refractory cortical myoclonus by the dispersed and suppressed paroxysmal depolarization shifts in the sensorimotor cortex. Clin Neurophysiol. 2019;130(10):1804–12.
39. Neshige S, Hitomi T, Tojima M, Oi K, Kobayashi K, Matsuhashi M, et al. A role of aging in the progression of cortical excitability in benign adult familial myoclonus epilepsy type 1 patients. Mov Disord. 2021;36(10):2446–8.
40. Eccles J. In: Purpura DP, Yahr MD, editors. Properties and functional organization of cells in the ventrobasal complex of the thalamus. New York: Thalamus New York Columbia Univ Press; 1966. p. 129–41.
41. Lueders H, Lesser RP, Hahn J, Dinner DS, Klem G. Cortical somatosensory evoked potentials in response to hand stimulation. J Neurosurg. 1983;58:885–94.
42. Shibasaki H, Hallett M. Electrophysiological studies of myoclonus. Muscle Nerve. 2005;31(2):157–74.
43. Mima T, Hallett M. Corticomuscular coherence: a review. J Clin Neurophysiol. 1999;16(6):501–11.
44. Striano P, Coppola A, Dubbioso R, Minetti C. Cortical tremor: a tantalizing conundrum between cortex and cerebellum. Brain. 2020;143(10):e87.
45. Ugawa Y, Uesaka Y, Terao Y, Hanajima R, Kanazawa I. Magnetic stimulation over the cerebellum in humans. Ann Neurol. 1995;37(6):703–13.
46. Manto M, Argyropoulos GPD, Bocci T, Celnik PA, Corben LA, Guidetti M, et al. Consensus paper: novel directions and next steps of non-invasive brain stimulation of the cerebellum in health and disease. Cerebellum. 2022;21:1092–122.

How to cite this article: Dubbioso R, Suppa A, Tijssen MAJ, Ikeda A. Familial adult myoclonus epilepsy: Neurophysiological investigations. Epilepsia. 2023;64:S39–S46. https://doi.org/10.1111/epi.17553