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FULL-LENGTH ORIGINAL RESEARCH

Clinical and neurophysiologic features of progressive myoclonus epilepsy without renal failure caused by *SCARB2* mutations

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Summary

Purpose: Mutations of the *SCARB2* gene cause action myoclonus renal failure syndrome (AMRF), a rare condition that combines progressive myoclonus epilepsy (PME) with severe renal dysfunction. We describe the clinical and neurophysiologic features of PME associated with *SCARB2* mutations without renal impairment.

Methods: Clinical and neurophysiologic investigations, including wakefulness and sleep electroencephalography (EEG), polygraphic recording (with jerk-locked back-averaging and analysis of the EEG–EMG (electromyography) relationship by coherence spectra and phase calculation), multimodal evoked potentials, and electromyography were performed on five Italian patients with *SCARB2* mutations.

Key Findings: The main clinical features were adolescent–young adulthood onset, progressive action myoclonus, ataxia, absence of cognitive deterioration and, in most cases, epilepsy. The severity of the epilepsy could vary from uncontrolled seizures and status epilepticus in patients with adolescent onset to absent or rare seizures in patients with adult onset. Relevant neurophysiologic findings were a pronounced photosensitivity and massive action myoclonus associated with rhythmic myoclonic jerks at a frequency of 12–20 Hz, clinically resembling a postural tremor. The cortical origin of rhythmic myoclonus was demonstrated mainly by coherence and phase analysis of EEG–EMG signals indicating a significant EEG–EMG coupling and a direct corticospinal transfer.

Significance: Our patients with *SCARB2* mutations showed the clinical and neurophysiologic phenotype of PME, in which epilepsy could be extremely severe, extending the spectrum reported in the typical AMRF syndrome. Patients with PME of unknown origin of adolescent or young adult onset, with these neurophysiologic features, should be tested for *SCARB2* mutations, even in the absence of renal impairment.

KEY WORDS: Progressive myoclonus epilepsy, SCARB2, Myoclonus, Renal failure, Cortical tremor.

The progressive myoclonus epilepsies (PMEs) comprise a heterogenous group of inherited disorders characterized by myoclonus, epileptic seizures, and variable degrees of neurologic dysfunction, particularly dementia and ataxia (Berkovic et al., 1986; Marseille Consensus Group, 1990). Recently, mutations in the gene encoding for the lysosomal protein SCARB2 were shown to cause action myoclonus renal failure (AMRF) syndrome (Berkovic et al., 2008), a rare, recessively inherited condition that combines the clinical picture of PME with progressive renal dysfunction sufficiently severe as to lead rapidly to death (Andermann et al., 1986; Badhwar et al., 2004). Five additional PME cases associated with *SCARB2* mutations, all of Italian origin, with a phenotype at the onset reminiscent of Unverricht-Lundborg disease (ULD) were subsequently reported. At variance with classical AMRF syndrome, these patients never had renal failure, even in the terminal stage of their disease (Dibbens et al., 2009). In this article, we describe the clinical and neurophysiological characteristics of these five patients.

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Materials and Methods

All patients presented with a PME that previously resulted negative for assays tests for sialidosis, celiac

disease, Gaucher disease, and for genetic tests for the most common forms of PME in Italy (ULD, Lafora disease, mitochondrial encephalomyopathies); skin and muscle biopsies were inconclusive. The genetic study leading to the proper diagnosis was performed only recently, when four of the five patients were already dead (Dibbens et al., 2009); preliminary genetic findings on one patient were also reported by Dardis et al. (2009). In four deceased patients, clinical or laboratory evidence of renal impairment was never detected.

The patients underwent repeated neurologic evaluations and neurophysiologic investigations that included waking and sleep electroencephalography (EEG), polygraphic recordings, multimodal (motor, brainstem, somatosensory) evoked potentials, and electromyography (EMG).

Brain computed tomography/magnetic resonance imaging (CT/MRI) scans were unremarkable in all but Patient 2, in which MRI showed mild cerebellar and bulbopontine atrophy.

Local ethical committees approved the study; the only living patient provided informed consent.

Neurophysiologic methods

The EEG was recorded by silver/silver chloride electrodes applied to the scalp according to the 10–20 International System and ear lobe electrodes. The polygraphic EMG signals were recorded with pairs of surface electrodes with standard belly-tendon placement. The signals were digitally acquired (sampling frequency: 512 Hz; band pass filters: 1.6–210 Hz; MicroMed System, Mogliano Veneto, Italy; NeuroScan system, Herndon, VA, U.S.A.). The relationship between the EEG and EMG bursts was analyzed by applying jerk-locked back-averaging (JLBA) and by estimating the autospectra, coherence, and phase functions using a bivariate nonparametric (AR) model, as described previously (Panzica et al., 2003).

Long-loop reflexes (LLRs) by median nerve stimulation at the wrist were studied, by evaluating the abnormal presence of LLR at rest and by calculating the onset latency of short-loop reflex responses (SLRs) and LLRs, and the SLR-LLR amplitude ratio in preactivated condition.

Somatosensory evoked potentials (SEPs), checkerboard pattern-reversal visual evoked potentials (VEPs), and brainstem auditory evoked potentials (BAEPs) were recorded by standard laboratory procedures.

Needle EMG and conduction velocities studies with F-wave assessment were performed.

Results

Clinical features

Patient 1

The parents of this male patient were first cousins. At the age of 14 years, he started to experience sudden falls and jerks, particularly when performing movements, with a progressive course. At 17 years, while viewing television, he had his first tonic–clonic seizure preceded by massive jerks. At first examination in our center at the age of 19 years, his neurologic examination showed dysarthria, nystagmus, hypotonia, severe action myoclonus, and ataxia (see Video S1). Since the age of 20, the patient presented with weekly generalized myoclonic seizures or tonic–clonic seizures that were sometimes triggered by TV viewing or other light sources. At the age of 22 years he started to suffer from repeated convulsive status epilepticus, requiring admissions to the intensive care unit (ICU). Following these episodes, he was bedridden, with tetraparesis and severe spontaneous and reflex myoclonus triggered by movement as well as by auditory, visual, and tactile stimuli, often evolving into severe tonic–vibratory seizures. Several antiepileptic drugs (AEDs) including valproate, piracetam, vigabatrin, phenobarbital, lamotrigine, and benzodiazepines had a limited effect on seizures and myoclonus. To avoid external stimuli triggering myoclonus, he spent the last stage of his disease in a dark room, bedridden. Despite the severity of his condition, his mental status was preserved until death, which occurred at 29 years of age because of pneumonia.

Patient 2

The parents of this male patient were from a small village but they were not known to be related. Action myoclonus and ataxia began at the age of 15 years, rapidly associated with mild hypoacousia and peripheral neuropathy. At 16 years of age, two convulsive seizures occurred. In about 3 years, the patient became severely disabled due to marked movement-induced myoclonus and to recurrent myoclonic seizures elicited by eye closure (Fig. 3) (see Video S2) or other light stimuli. At the age of 21 years, he was admitted to the ICU because of convulsive status that was stopped by intravenous phenytoin. After this episode, he was bedridden, unable to speak because of myoclonia, and had tetraparesis and severe peripheral neuropathy. Photosensitivity was extremely pronounced, forcing him to live in almost complete darkness. Valproate, phenobarbital, piracetam, lamotrigine, and topiramate, in various combinations had poor effect on seizures and myoclonus. After several episodes of aspiration pneumonia, he underwent tracheostomy and percutaneous endoscopic gastrostomy. His mental status was grossly preserved until death. He died at 29 years of age from pneumonia.

Patient 3

The parents of this female patient were second cousins. At the age of 23 years, she had two nocturnal convulsive seizures and she started to complain of myoclonic jerks triggered by abrupt changes in environmental light. Two years later, a movement disorder interpreted as postural tremor at

the upper limbs and a rapidly progressive generalized action myoclonus appeared. At the age of 30 she was wheelchair-bound. Treatment with risperidone and olanzapine, started because of psychotic symptoms, was soon discontinued because of worsening of myoclonia. At the age of 31 years, she was bedridden, with severe myoclonus either at rest or triggered by movements, poorly responsive to valproate, zonisamide, and levetiracetam in various combinations. Neuropsychological testing did not detect any cognitive impairment. She died when she was 33 years old due to convulsive status epilepticus.

Patient 4

The parents of this female patient were unrelated but both originated from a restricted area in Northern Italy. She started to have falls without loss of consciousness at the age of 25 years. A few years later, she started to complain of movement-induced focal jerks while performing fine motor tasks. Action myoclonus worsened over the years, and was refractory to treatment with valproate and benzodiazepine. She also reported subjective uneasiness associated with forced blinking when exposed to intense light. Paroxysmal episodes of ''diffuse tremors, fear, and dyspnea,'' triggered by stressing events, were interpreted as panic attacks. She never had obvious epileptic seizures. Due to action myoclonus, at 34 years she was unable to walk and at 36 years she started to have repeated aspiration pneumonia, which led to tracheostomy and percutaneous gastrostomy. Repeated neuropsychological tests showed IQ values at the lower limits of the normal range until she died at the age of 40 years.

Patient 5

This female patient, born from a nonconsanguineous marriage, was in good health until the age of 26, when she started to complain of tremor of the voice and at the upper limbs, and of episodes of motor arrest associated with anxiety and panic. In a few months, jerks at the upper limbs, ataxic gait, and discomfort when exposed to intense light appeared, with a slowly progressive course. At the age of 27 years, she had her only tonic–clonic seizure. At the age of 32 years, the neurologic examination showed voice tremor, diffuse hypotonia, action myoclonus, and postural tremor at the upper limbs (see Video S3), ataxia, and unstable walking that required assistance. Neuropsychological testing was normal but the patient showed marked anxiety and behavioral disturbances. Biochemical investigations showed a slight reduction of the creatinine clearance (50 ml/min), mild proteinuria (21 mg/dl; normal value <15 mg/dl), and microalbuminuria (64.7 mg/L; normal value <25 mg/L). The patient declined renal biopsy. She is on levetiracetam and clonazepam; she did not tolerate valproate or zonisamide.

Neurophysiologic features

EEG and polygraphic findings

At disease onset, EEG studies showed a preserved alpha background activity, with rare generalized or focal (central or posterior) epileptiform discharges (Fig. 1). Over the years, the EEG background activity progressively slowed, with irregular theta and delta activity intermixed with alpha activity.

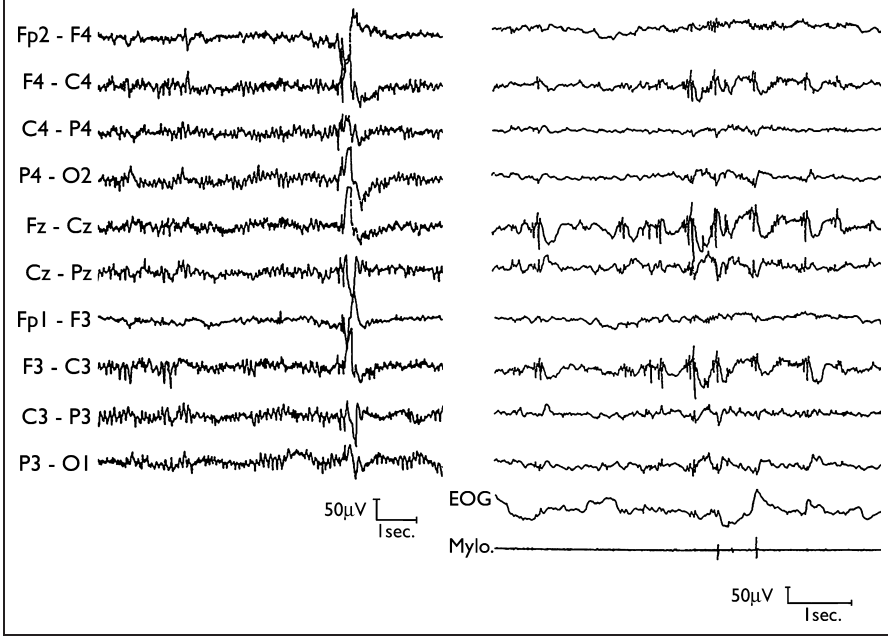

Figure 1.
Wakefulness and sleep EEG. EEG recording in Patient 1, one year after the onset. Left panel: during wakefulness EEG showed preserved background activity and sporadic generalized spike-and-wave discharges. Right panel: during REM sleep, brief runs of fast spikes or polyspikes over the vertex leads, spreading bilaterally to central regions were observed. EOG, electrooculogram; Mylo: mylohyoideus. *Epilepsia* © ILAE

Intermittent photic stimulation triggered bursts of generalized spike-polyspike-wave discharges, outlasting the train of light stimuli (Fig. 2). In Patients 1 and 2, polygraphic recordings of massive myoclonic seizures elicited by eye closure showed a pattern of generalized spike-polyspike-wave bursts associated with myoclonic jerks at the upper limbs that resolved with eyes opening (Fig. 3).

Overnight sleep recordings performed in Patients 1 and 2 revealed during rapid eye movement (REM) sleep, fast spikes on the vertex leads spreading to bilateral frontocentral regions, occasionally associated with myoclonic jerks (Fig. 1).

Continuous EEG monitoring, performed in Patient 2 during an episode of epileptic status lasting several hours, showed a pattern of recruiting fast EEG rhythmic discharge starting in the frontocentral regions, corresponding to a tonic–vibratory seizure that recurred every few minutes, without recovery of consciousness, followed by irregular slow activity during which the patient was stuporous (Fig. 4).

Polygraphic recordings consistently revealed action myoclonus during motor tasks or posture maintenance and erratic myoclonic jerks at rest, rarely associated with contralateral central spikes. In Patients 3, 4, and 5, when they maintained a posture at the upper limbs, surface EMG revealed quasirhythmic EMG bursts, each lasting <50 ms, at a frequency of 12–20 Hz, that clinically resembled a postural tremor (Fig. 5A,B). The brief EMG bursts involved synchronously antagonist muscles couple, whereas asynchronous EMG bursts were observed only occasionally.

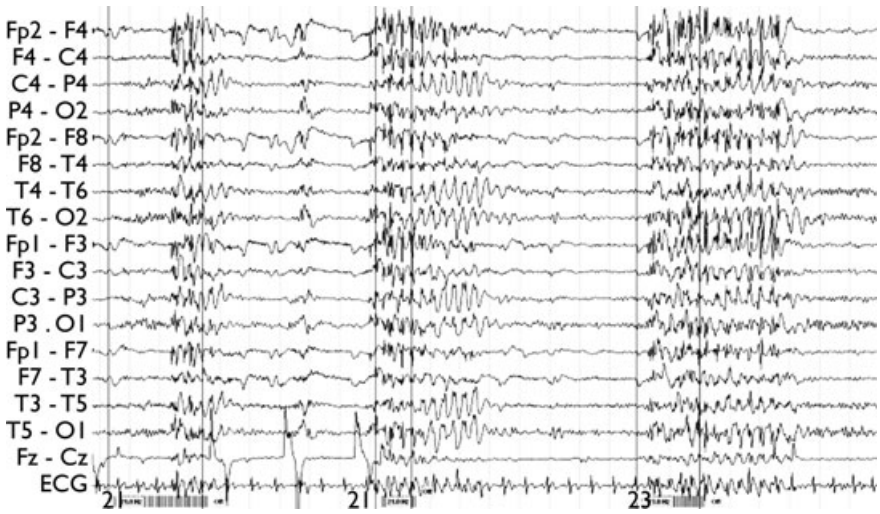

Figure 2.
Photoparoxysmal response triggered by intermittent photic stimulation. Spike-polyspike wave discharges outlasting the trains of stimuli elicited by intermittent photic stimulation in Patient 3 (flash stimuli are illustrated in the bottom lead; the numbers indicate the stimulus frequencies).
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Figure 3.
Myoclonic seizure triggered by eye closure. Eye closure (arrow on the top left) elicited diffuse spike-wave, polyspike-wave bursts associated with myoclonic jerks at the upper limbs that resolved with eyes opening (arrow on the top right) (shown in Video S2). EEG recorded with both earlobes reference. L., left; R., right; Delt, deltoid.
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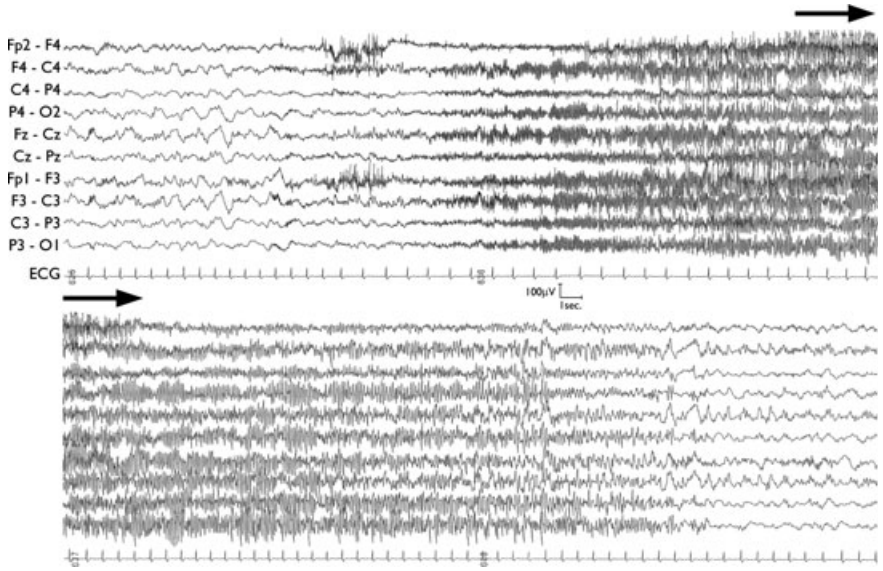

Figure 4.
EEG recording of a tonic–vibratory seizure during status epilepticus. The tonic–vibratory phase was associated with a recruiting fast EEG rhythmic activity starting in the frontocentral regions, which was followed by irregular slow activity, clinically corresponding to stupor.
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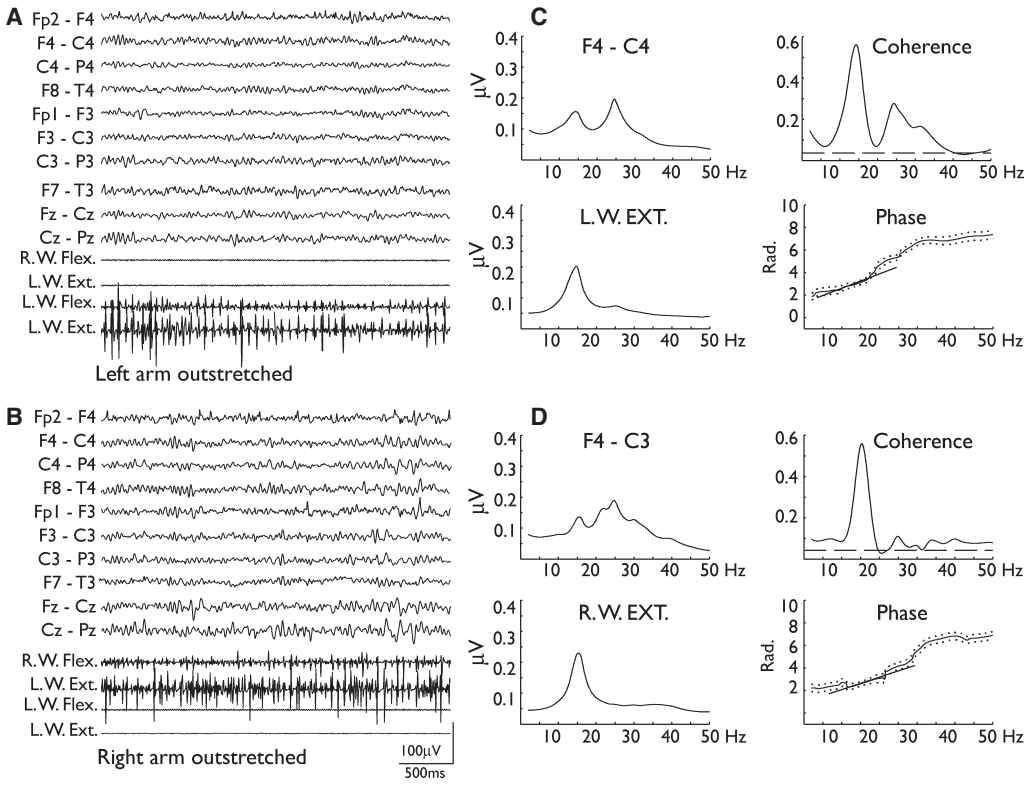

Figure 5.
Polygraphic recordings and EEG–EMG correlations by autospectra, coherence, and phase analysis. (**A**, **B**) EEG–EMG recordings performed in Patients 3 and 5, maintaining, respectively, the left and the right arm raised and outstretched. Note the recurrent myoclonic jerks at the wrist flexors and extensors (clinically resembling a tremor) without obvious EEG correlates. (**C**, **D**) spectral properties on EEG and EMG (left panels), coherence, and phase analysis (right panels). The amplitude spectra show prominent peaks around 15 Hz, associated with other peaks in β or γ band (traces are the mean of 39 and 25 samples). A significant EEG–EMG coherence (54 ± 17; 48 ± 7.8) at the frequency of the main peaks indicates a consistent relationship between EEG oscillations and the myoclonic jerks allowing to calculate a corticomuscular delay (ranging from 12.7–13.1 ms and consistent with a corticospinal transfer). W., wrist; Flex., flexor; Ext., extensor; R., right; L., left.
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Analysis of the EEG–EMG relationship by coherence spectra showed significant EEG peaks in the β band at a frequency ranging from 14.4 to 17.6 Hz (mean values 16.4 ± 1.6 Hz); phase calculation on significantly coherent frequency peaks indicated that EEG activity (at F4-C4 and F3-C3 electrode) preceded the EMG activity in right wrist flexor/extensors by 12.7–13.1 ms (mean 12.8 ± 0.4 ms) (Fig. 5C,D).

In Patients 3, 4, and 5, jerk-locked back-averaging analysis of EEG triggered from myoclonic jerks revealed a clear cortical spike at the centroparietal electrodes only in Patient 3.

Multimodal evoked potentials and short- and long-loop reflexes

SEP results were heterogenous. The amplitude of cortical components was moderately enlarged in Patients 1 and 2, whereas it was slightly decreased in Patients 3 and 4; in Patient 5, the amplitude was normal. Latencies were slightly increased only in Patient 4. VEPs performed in Patients 3, 4, and 5, were enlarged only in Patient 5 (N75-P100 = 33 uV). Brainstem-evoked potentials were unremarkable in all patients but for a prolonged conduction time in Patient 2.

LLR evaluated in Patients 3 and 5 was normal at rest, whereas it was slightly facilitated during muscular contraction in Patient 4.

EMG findings

Conduction velocities were investigated in Patients 2, 3, and 5: only Patient 2 showed slowed conduction velocities and prolonged F-waves, consistent with a mixed, mainly demyelinating, neuropathy that remained unchanged over several years, and worsened markedly after intensive care unit (ICU) admission for epileptic status, treated with phenytoin. Needle EMG, performed only in Patient 5, was normal.

Discussion

There are few clinical and neurophysiologic descriptions of AMRF syndrome (Horoupian & Ross, 1977; Andermann et al., 1986; Rothdach et al., 2001; Badhwar et al., 2004; Vadlamudi et al., 2006; Balreira et al., 2008; Berkovic et al., 2008). In this article, we describe the clinical and neurophysiologic features of five Italian patients with *SCARB2* mutations and *without* renal failure. They presented with a PME phenotype characterized by prominent action myoclonus, epilepsy, ataxia, photosensitivity, and preserved cognitive functions thus being especially reminiscent of the presentation of ULD, which is the most common PME in Europe (Kalviainen et al., 2008). The most obvious discrepancies between our *SCARB2* patients and ULD are the more variable age of onset and much more severe course. Indeed, in three of our *SCARB2* patients the onset was in the third decade of life, whereas ULD consistently begins between 6 and 18 years (Kalviainen et al., 2008). As to the disease course, four of our patients were extremely disabled after a few years of disease and died within 10–15 years from the onset from complications of unrelenting myoclonus and seizures, similar to that reported in AMRF syndrome (Badhwar et al., 2004; Balreira et al., 2008), but in the absence of renal failure. On the contrary, patients with ULD commonly show limited progression, reaching an almost stationary state in middle age (Magaudda et al., 2006; Genton, 2010).

Severe action myoclonus appeared in our *SCARB2* patients between 14 and 26 years (mean: 20.6 years), an age similar to AMRF syndrome but significantly older than in ULD, in which it appears between 6 and 18 years of age (Kalviainen et al., 2008). In two patients, at the onset, action myoclonus was mixed with a fine tremor of the hands, which is one of the early detected symptom in AMRF syndrome (Andermann et al., 1986; Badhwar et al., 2004; Vadlamudi et al., 2006). With the progression of the disease, obvious action myoclonus became progressively more intense and disabling.

Difference in epilepsy severity is one of the most relevant features of intersubject variability in our *SCARB2* patients. Severe and frequent epileptic seizures recurred in fact throughout the disease course in the two patients with adolescent onset, often as convulsive status occurring spontaneously or as severe myoclonic status triggered by light sources. In the other three patients, showing an adult disease onset, seizures were rare or lacking, albeit in one of them an epileptic status was the terminal event. The extreme seizure severity appears to be a remarkable feature, unusual in ULD (Kalviainen et al., 2008; Genton, 2010), and not reported in the previously described AMRF patients (Badhwar et al., 2004; Balreira et al., 2008), who generally showed no or rare seizures, responsive to antiepileptic drugs.

As in other PMEs (Koskiniemi et al., 1974; Tassinari et al., 1974, 1978; Berkovic et al., 1986; Mervaala et al., 1986; Rubboli et al., 1999), photosensitivity was consistently or transiently present in all our patients. In our two patients with severe epilepsy, photosensitivity was markedly pronounced and extremely disabling, obliging them to live in almost complete darkness.

As in AMRF syndrome, we did not observe any evidence of intellectual deterioration or dementia, even in the last stages of the disease. In PME beginning in adolescence or adulthood, absence of dementia helps to clinically differentiate this condition from Kufs' disease (Berkovic et al., 1988), late-onset Lafora disease, and neuroserpinopathy.

Neurophysiologic features of our patients resembled those of other forms of PME. Indeed, preserved EEG background activity at the onset, with sporadic generalized spike-and-wave discharges has been described in ULD (Ferlazzo et al., 2007) and, in the earliest disease stages of Lafora disease (Tassinari et al., 1978), as well as in rarer PMEs. Over the years, a progressive slowing of EEG background activity in four of five patients paralleled the worsening of the clinical condition; in the fifth, still alive,

patient, after 5 years from the onset, the EEG background activity is still within normal limits.

Cortical myoclonus is a common feature of all PMEs, characterized by time-locked contralateral premyoclonic spike in sensory-motor regions, often unveiled by jerk-locked back-averaging (Shibasaki & Kuroiwa, 1975; Shibasaki et al., 1978), and associated with the so-called C-reflex (or enhanced long-loop reflex, LLR) (Sutton & Mayer, 1974; Canafoglia et al., 2004) and with abnormally enlarged SEPs (Shibasaki et al., 1985), indicating hyperexcitable loops sustaining reflex myoclonus. Action myoclonus was the most striking feature in our patients, although erratic, fragmentary myoclonus at rest, often without an overt EEG correlate, was observed as well. Jerk-locked back-averaging gave inconsistent results. SEPs were moderately enlarged only in patients with severe epilepsy. This latter finding is in agreement with evidence showing an increased sensorimotor cortex excitability in ULD with severe epilepsy as compared to ULD with milder epilepsy (Silen et al., 2002). Although the possibility of either a cortical or a subcortical origin of myoclonus in PME has been demonstrated (Cantello et al., 1997; Tassinari et al., 1998), in our patients a cortical origin of myoclonus is supported by the presence, even if inconsistent, of premyoclonic spike in at least one of them, and by the more consistent results of the coherence and phase analysis indicating a significant EEG–EMG coupling and a direct corticospinal transfer. The rhythmic jerks in the β-band found during active movements are reminiscent of the so-called "cortical tremor" (Ikeda et al., 1990; Regragui et al., 2006) and of the rather rhythmic myoclonus found in some PMEs associated with rare storage diseases (Brown et al., 1999; Panzica et al., 2003; Canafoglia et al., 2006). The lack of associated signs of cortical hyperexcitability (such as increased SEPs and enhanced LLR) suggests that, in some *SCARB2* patients, the sensorimotor cortex is unable (or rapidly loses the ability) to respond with sufficient synchronization to incoming stimuli (leading to enhanced LLR and SEPs) and to generate clear cortical spikes, whereas pathologic oscillatory activity, as demonstrated by the detection of EEG–EMG coupling, persists and plays a major role in sustaining myoclonus.

In one patient (Patient 2) we observed clinical and electrophysiologic evidence of a mild hearing impairment and of a mixed peripheral, predominant demyelinating, neuropathy. The involvement of the auditory system has not been reported in AMRF patients, whereas peripheral neuropathy, with mixed features (either predominantly axonal or demyelinating) was occasionally observed (Rothdach et al., 2001; Badhwar et al., 2004; Berkovic et al., 2008; Dibbens et al., 2011) and may be more common than reported to date. Interestingly, deafness and peripheral neuropathy occur in LIMP-2 deficient mice, the animal model of AMRF syndrome (Gamp et al., 2003).

As previously reported (Dibbens et al., 2009), our cases showed novel *SCARB2* mutations, not previously reported in classical AMRF patients. Four of our patients were homozygotes, two of them were from known consanguineous union, and one (the still living patient) was a compound heterozygote. All were Italian, but were unrelated, and the mutations were different in all five patients. The product of the *SCARB2* gene is a glycoprotein expressed in brain and kidney, located in the lysosomal membranes, probably involved in the biogenesis and maintenance of the endosomal/lysosomal compartments. Interference with posttranslational modification of proteins in the endosomal/lysosomal compartments is emerging as a common mechanism in many forms of PME (Ramachandran et al., 2009; Corbett et al., 2011).

So far we are unable to make *SCARB2* genotype–phenotype correlations. Inspection of the *SCARB2* mutations found to date shows no clear distinction between the class (e.g., missense or nonsense) or position of the mutation and the phenotype seen in the patient. The phenotypic heterogeneity encompasses a wide range of tissues and we are yet to understand why some patients with mutation of *SCARB2* will develop PME with or without renal failure and why others develop hearing loss or peripheral neuropathy.

In conclusion, distinctive clinical features of *SCARB2* mutated patients without renal failure are the following: an adolescent–young adulthood onset, severe action myoclonus and ataxia with a progressive course, absence of mental deterioration and, in most cases, epilepsy. Epilepsy severity varies from uncontrolled seizures or status epilepticus in patients with adolescent onset to infrequent or no major seizures in patients with a more delayed onset. Cortical tremor, common in typical AMRF cases, and peripheral neuropathy may be inconstantly observed. The neurophysiologic picture is consistent with PME, characterized by a relatively preserved EEG background activity, photosensitivity, and cortical myoclonus. *SCARB2* mutations might represent an underdiagnosed cause of PME and in cases showing the above clinical and neurophysiologic features, careful evaluation of renal function should be performed, although absence of proteinuria even in advanced stages of the condition does not exclude the diagnosis. Future research aimed to explore the function of *SCARB2* gene, and its role in cerebral and renal function is warranted.

Disclosure

None of the Authors has any conflict of interest to disclose. We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

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Supporting Information

Additional Supporting Information may be found in the online version of this article:

Video S1. Severe and disabling action myoclonus in Patient 1.

Video S2. Massive myoclonic seizure triggered by eye closure in Patient 2.

Video S3. Fine postural tremor at the upper limbs in Patient 5.

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