

# Myoclonic status epilepticus in juvenile myoclonic epilepsy

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**ABSTRACT** – *Background.* Myoclonic status epilepticus (MSE) is rarely found in juvenile myoclonic epilepsy (JME) and its clinical features are not well described. We aimed to analyze MSE incidence, precipitating factors and clinical course by studying patients with JME from a large outpatient epilepsy clinic. *Methods.* We retrospectively screened all patients with JME treated at the Department of Neurology, Medical University of Innsbruck, Austria between 1970 and 2007 for a history of MSE. We analyzed age, sex, age at seizure onset, seizure types, EEG, MRI/CT findings and response to antiepileptic drugs. *Results.* Seven patients (five women, two men; median age at time of MSE 31 years; range 17-73) with MSE out of a total of 247 patients with JME were identified. The median follow-up time was seven years (range 0-35), the incidence was 3.2/1,000 patient years. Median duration of epilepsy before MSE was 26 years (range 10-58). We identified three subtypes: 1) MSE with myoclonic seizures only in two patients, 2) MSE with generalized tonic clonic seizures in three, and 3) generalized tonic clonic seizures with myoclonic absence status in two patients. All patients responded promptly to benzodiazepines. One patient had repeated episodes of MSE. Precipitating events were identified in all but one patient. Drug withdrawal was identified in four patients, one of whom had additional sleep deprivation and alcohol intake. Two patients received inappropriate treatment (carbamazepine, phenytoin). *Conclusions.* MSE is a rare event in JME. Precipitating factors are commonly identified and for such cases the treatment response and outcome are excellent, in contrast to other cases with unknown causes.

**Key words:** juvenile myoclonic epilepsy, nonconvulsive status epilepticus, idiopathic generalized epilepsy, myoclonic status epilepticus

Juvenile myoclonic epilepsy (JME) is one of the most common age related idiopathic generalized epilepsies (IGEs; Janz, 1997). The syndrome is characterized by myoclonic seizures (MS), generalized tonic clonic seizures (GTCS) and absence seizures (AS). MS appear as shock-like jerks, affecting mainly

shoulders and arms. They may occur as a single myoclonic jerk or repetitively with irregular frequency and varying intensity. Although they are usually bilateral, some asymmetries may be observed. Patients may be fully conscious or experience some impairment of consciousness to a

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variable degree (Janz, 1957a; Christian, 1980). Seizures are clearly related to the sleep/waking cycle and occur predominantly in the morning hours after awakening or in drowsy state during the day. MS may present frequently as repeated jerks lasting for minutes with or without transition to a GTCS. Very rarely, they may last for more than 30 minutes fulfilling the formal criteria (Walker *et al.*, 2005) for myoclonic status epilepticus (MSE), termed “impulsive-petit mal status” in the original descriptions.

The occurrence of MS and MSE is mostly provoked by trigger factors such as sleep deprivation, alcohol intake, non-compliance with or inappropriate antiepileptic drugs (AEDs) (Thomas *et al.*, 2006; Panayiotopoulos *et al.*, 1994). However, MSE is seemingly a rare event in JME. Available literature is limited to single case reports or small series (Badhwar *et al.*, 2002; Terzano *et al.*, 1978; Grüneberg and Helmchen, 1969; van Leeuwen *et al.*, 1969; Schneemann *et al.*, 1969). We aimed to analyze incidence, precipitating factors and clinical course of MSE by studying a cohort of patients with JME from a large outpatient epilepsy clinic.

## Patients and methods

In this retrospective hospital based study we reviewed all patients with JME ( $n = 247$ ) for a history of MSE. Patients were treated at the outpatient epilepsy clinic, Department of Neurology, Medical University Innsbruck, Austria between 1970 and 2007.

The diagnosis of JME was based on the criteria of the International League against Epilepsy (ILAE) (Commission on Classification and Terminology of ILAE, 1989). MSE was diagnosed if myoclonic jerks lasted for at least 30 minutes (Walker *et al.*, 2005). In six of seven patients the EEG during MSE was available for re-evaluation. For one patient only, a written report with a clear description of ongoing ictal activity was available.

We analyzed sex, age at time of MSE, age at seizure onset, seizure types, EEG and CT/MRI findings. Seizure outcome refers to the last visit at the outpatient clinic. We extracted all available data from patients' charts and reviewed available EEGs during MSE and the responsiveness to AEDs, as well as the course of the disease after the MSE.

## Statistical analysis

Data processing and analysis was performed with SPSS 12.0 and EXCEL for Windows 11.0. We used descriptive methods (average values and standard deviations). Incidence rate in person years was calculated in relation to the total number of patients at risk observed over time.

## Results

### Study population

Seven of 247 JME patients (five women and two men) had a history of MSE, yielding a percentage of 3% or an incidence of 3.2/1,000 patient years. The median age at the time of MSE was 31 years (range 17-73). The mean duration of epilepsy before MSE was 26.4 ( $\pm 17$ ) years and median was 26 years (range 10-58). The median age at seizure onset was 14 years (range 3-35). Four out of seven patients had three seizure types (MS, AS, GTCS). Three patients had only MS and GTCS. Demographic data are summarized in *table 1*.

### Semiology of MSE

According to the observed seizure semiology, we distinguished three types of MSE:

- Type (1) *only MS* ( $n = 2$ ): in one patient upper and lower extremities were affected, only upper extremities were affected in the other patient. Consciousness was not impaired in these two patients;
- Type (2) *MSE with GTCS* ( $n = 3$ ): in three patients MSE was observed immediately after termination of a GTCS. It was impossible to determine whether the GTCS preceded MS since consciousness was impaired in these patients. In one of the patients, myoclonic jerks involved upper and lower extremities and in the other two cases only upper extremities were affected. In all patients consciousness was impaired;
- Type (3) *GTCS with myoclonic absence status* ( $n = 2$ ): consciousness was clearly impaired in a discontinuous way. In both cases, the jerks were limited to the upper extremities without involvement of head or lower extremities.

### Ictal EEG patterns

An EEG during MSE was available in six out of seven patients (*figures 1-3*). Generalized polyspike-wave activity and spike-wave activity was recorded in all EEGs. In three patients, generalized epileptiform discharges presented repeatedly throughout the whole recording with changes in intervals and morphology (*figure 1*). The EEG during myoclonic absence status was characterized by bursts of generalized 3-4 Hz spikes and waves as well as polyspikes and waves during the whole recording time (*figure 2*). In one patient, epileptiform activity occurred periodically with short interruptions (*figure 3*). One patient's EEG exhibited an asymmetry of generalized epileptiform discharges with the higher amplitude over the left hemisphere.

### Treatment

At the time of MSE, chronic AED treatment consisted of valproic acid (VPA) for two patients, and topiramate (TPM), phenytoin (PHT) and carbamazepine

**Table 1.** Clinical characteristics and treatment of MSE.

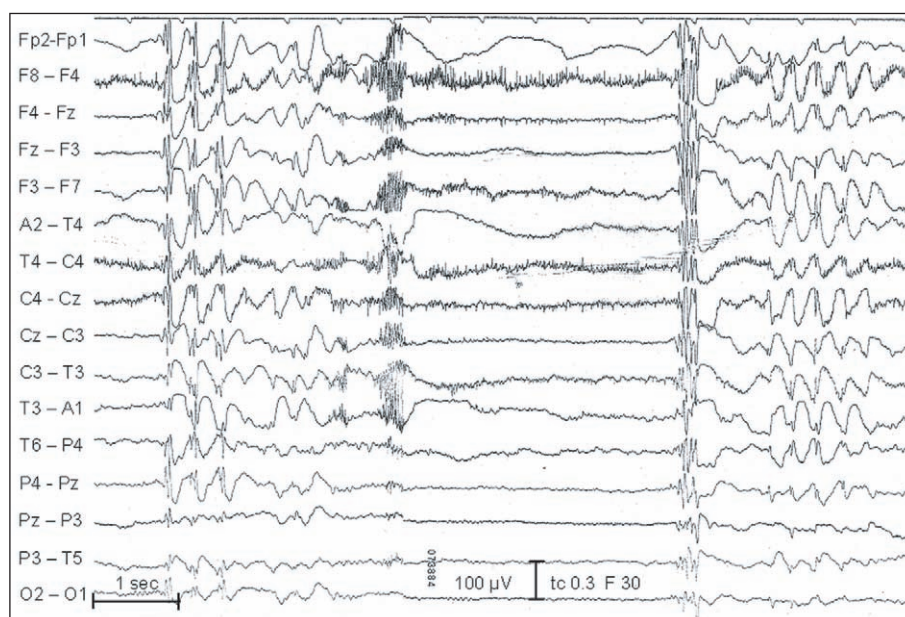
Patient No (sex, age at time of MSE)	Age at seizure onset	Seizure types	AED at time of MSE (mg/day)	Semiology of MSE	Precipitating factors	Treatment of MSE (mg/day)	AED after MSE (mg/day)	Repeated MSE
1 (M, 31)	14	MS, GTCS, AS	None	MS with GTCS	AED withdraw	CLZ (4) IV	VPA (900)	Lost for FU
2 (W, 62)	35	MS, GTCS, AS	PHT (750)	GTCS with myoclonic absence status	Inappropriate treatment (PHT)	DZP (20) IV	VPA (900)	No
3 (W, 54)	17	MS, GTCS, AS	CBZ (600)	MS with GTCS	Inappropriate treatment (CBZ)	DZP (20) IV	VPA (1500)	No
4 (W, 17)	7	MS, GTCS	None	MS only	AED withdraw	DZP (20) IV	VPA (1000)	No
5 (W, 29)	3	MS, GTCS, AS	VPA (2000) PRM (750)	GTCS with myoclonic absence status	-	CLZ (4) PO	VPA (2500) PRM (750)	No
6 (W, 73)	15	MS, GTCS	None	MS with GTCS	AED withdraw	LZP (2) IV	VPA (1500)	No
7 (M, 23)	13	MS, GTCS	TPM (400)	MS only	AED withdraw Alcohol intake	LZP (2) IV	TPM (500)	Yes (same clinical type)

M: man; W: woman; GTCS: generalized tonic clonic seizure; MS: myoclonic seizure; AS: absence seizure; AED: Antiepileptic drug; VPA: sodium valproate; PHT: phenytoin; CBZ: carbamazepine; PRM: primidone; CLP: clonazepam; DZP: diazepam; LZP: lorazepam; NSF: not-seizure-free; SF: seizure-free; SE: status epilepticus; IV: intravenous; PO: *per os*.

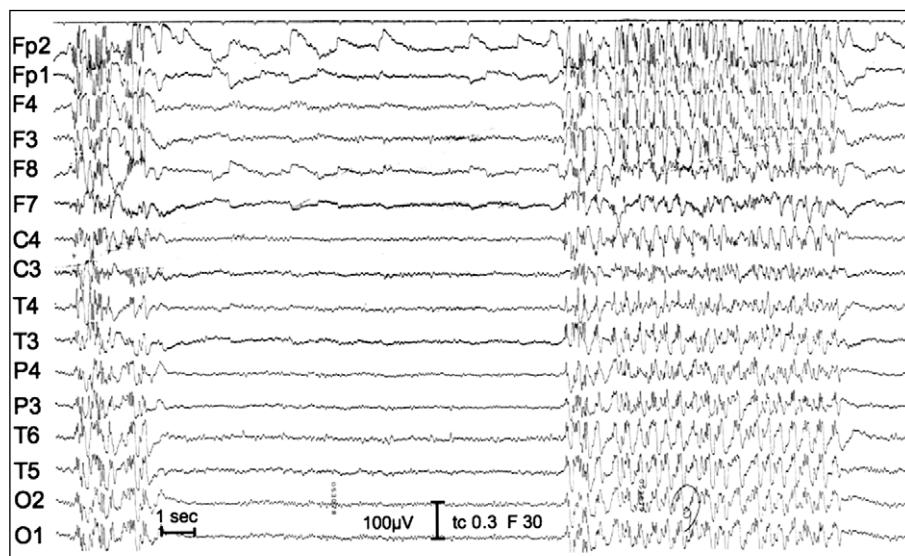
(CBZ) for three other patients, respectively. PHT and CBZ treatments were started several months before first admission to our institution. For two of the seven patients, drugs were withdrawn three and four years, respectively, before the occurrence of MSE.

MSE ceased in six patients treated with intravenous benzodiazepines (diazepam, clonazepam and lorazepam); in one patient oral treatment with clonazepam was sufficient. After MSE, six patients were treated with VPA and one with TPM.

Details of treatment are given in *table 1*.



**Figure 1.** Patient 1, 31 years, male. The patient had myoclonic seizures since the age of seven years and rare GTCS after awakening. He presented with irregularly repeated bilateral myoclonic jerks and time-locked generalized polyspikes and waves on EEG. Note the intermingled 3 Hz spikes and waves.



**Figure 2.** Patient 2, 62 years, female. She had her first seizure at the age of 35 years, but had questionable absence seizures during childhood. She was admitted to the hospital after a GTCS in a confusional state with absence seizures occurring every 10 seconds with prominent myoclonic jerks in upper extremities. EEG showed 3 to 4 Hz polyspikes and waves in trains lasting up to 10 seconds. Note the normal alpha rhythm in between the paroxysmal abnormalities.

### Precipitating factors

In six out of seven patients, precipitating events were identified. Two out of six patients deliberately discontinued chronic antiepileptic treatment due to non-compliance, and for one of these patients, additional triggers, aside from AED discontinuation, were alcohol intake and sleep deprivation.

Two other patients stopped medication despite ongoing seizures and medical advice for three and four years prior to MSE, respectively. In these last two cases, an immediate triggering factor was not evident.

The other two patients received inappropriate treatment (CBZ, PHT) at the time when MSE occurred.

### Course of epilepsy after MSE

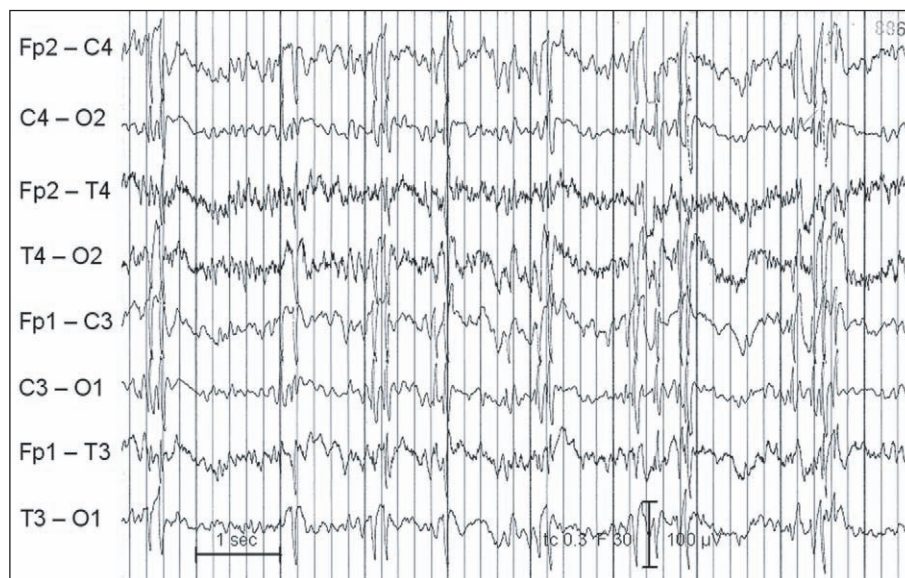
For one of the seven patients, follow-up was discontinued six months after MSE. The other six patients had a median follow-up of 10 years (range 2-19). Only one patient had multiple episodes of MSE over the years. Two of six patients were free of seizures at the last follow-up. Four had recurrent GTCS and MS. In two cases this was presumably due to non-compliance. The remaining two patients had rare GTCS and MS. After MSE, none of the patients had any neuropsychiatric disorders during the follow-up time.

### Discussion

MSE was observed in 3% of our population with JME. The incidence was comparatively low with a rate of 3.2/1,000 patient years. Precipitating factors were

identified in six out of seven patients. AED withdrawal, inappropriate treatment with CBZ and PHT, as well as sleep deprivation, were the most important factors. MSE was readily controlled in all patients with low doses of intravenous benzodiazepines and none of them experienced a deterioration in the course of the seizure disorder or related psychiatric disturbances after MSE. In contrast to postanoxic myoclonic status, which is most often refractory, MSE in the context of JME is easy to treat. In addition to benzodiazepines, intravenous valproate or levetiracetam are treatment options which have been used successfully in open uncontrolled series (Trinka, 2007; Trinka and Dobesberger, 2009). Previous studies on MSE in patients with JME report a widely varying frequency ranging from 1.4% (Dziewas *et al.*, 2002; Panayiotopoulos *et al.*, 1994) to 42% of patients (Asconape and Penry, 1984). These discrepancies might be explained by several factors such as small sample size or selection bias. The occurrence of MSE is clearly associated with trigger factors. In the present study, two out of seven patients were each treated with either CBZ or PHT which are considered as inappropriate AEDs for the treatment of JME. In other retrospective series, 19 out of 28 (68%) patients with JME who were treated with CBZ and six out of 16 (38%) who were treated with PHT, experienced seizure aggravation, which resulted in two patients with MSE (Genton *et al.*, 2000). Another retrospective series reported 14 patients with absence status epilepticus or MSE. Four JME patients in this series were treated with CBZ and lamotrigine (LTG), which may also aggravate seizures in IGE (Thomas *et al.*, 2006). In another small series, three patients developed absence status





**Figure 3.** Patient 6, 73 years, female. JME onset at age of 15 years. She was admitted to the hospital with “tremulousness and confusion” after a GTCS. Continuously repeated jerks in upper extremities were observed at admission. The EEG shows periodically repeated generalized polyspikes and waves.

epilepticus with mild myoclonic components after replacement of VPA with LTG. After reinstitution of VPA, the clinical course was favourable (Trinka *et al.*, 2002). Drug withdrawal is another important triggering factor. In a prospective study of patients with JME, only one out of 66 (1.5%) had MSE. This patient was among the seven who underwent discontinuation of treatment (Panayiotopoulos *et al.*, 1994). In our study, four out of seven patients did not take any AED at the time of MSE (two of them due to non compliance leading to acute withdrawal and two due to non-compliant withdrawal, years before MSE). Semiology of MSE can be variable and three types of MSE can be distinguished.

– Patients with bilateral myoclonic jerks synchronous with generalized polyspike-wave discharges on EEG and without impairment of consciousness represent the form of MSE designated as “impulsive petit mal status epilepticus” (SE) or “typical MSE” (Thomas *et al.*, 2006; Dzierwas *et al.*, 2002; Christian, 1980; Janz, 1957b). In the latest classification of SE, typical MSE is termed “myoclonic status epilepticus” (Engel, 2006). Preservation of consciousness is emphasized. In the recent definition of the ILAE, MSE can also occur in a variety of other epilepsy syndromes like Dravet syndrome or non-progressive myoclonic epilepsies in infancy. However, MSE definition by the ILAE does not include status myoclonicus in coma after cardiorespiratory arrest.

– MSE may be preceded, followed or interrupted by a GTCS. The consciousness of these patients is mostly impaired after GTCS. A condition with impairment of consciousness and mild myoclonic jerks after a GTCS can be misinterpreted as postictal confusion. A routinely

performed EEG can detect the ictal nature and govern parenteral AED treatment of SE (Bauer *et al.*, 1982; Bauer, 1975).

– Absence status with superimposed myoclonic jerks is another form of SE. Jerks can be very prominent in the eyelids with variable involvement of the upper extremities. Consciousness is moderately impaired in these patients. Myoclonic jerks are rarely time-locked with polyspike-wave discharges on EEG (Engel, 2006). The boundaries between MSE and myoclonic absence status and their relationship to different epilepsy syndromes are not well delineated and they may represent a biological continuum. A combination of type 2 and 3 of SE can also be observed and this has been referred as “atypical MSE” and might have important therapeutic consequences (Schneemann *et al.*, 1969; Thomas *et al.*, 2006).

There are limited data about sequelae of MSE in JME. Cerebral damage caused by non-convulsive SE is discussed controversially (Shorvon and Walker, 2005). In a case report, Grüneberg and Helmchen (1969) described the occurrence of paranoid psychosis after an untreated MSE which lasted for days. The patient had frequent MSE but recovered completely. In contrast, none of our patients had psychiatric problems or cognitive deficits after MSE.

In conclusion, MSE in JME is a rare event related most often to inappropriate drug treatment. MSE in JME is easily controlled by benzodiazepines without any following permanent sequelae. □

#### Disclosure.

None of the authors has any conflict of interest to disclose.

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