JUVENILE MYOCLONIC EPILEPSY – THE JANZ SYNDROME –

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Abstract

The juvenile myoclonic epilepsy is one of the most common epileptic syndromes, i.e. 5-10% of all epilepsies, but often misdiagnosed. The epilepsy begins at an age of about 12-18 years, with female predominance. It is a genetic determined epilepsy syndrome, with a polygenic mode of transmission.The predominant features are myoclonic jerks in 100% of the cases, generalised tonic-clonic or myoclonic tonic-clonic seizures in 90 – 95%, and absences in 30% of the patients, especially in the early morning after wake up, or after a nap in the afternoon. The seizures are often triggered by a lack of sleep mainly in combination with alcohol. The EEG is typical: generalised poly spike wave complexes and photosensibility in 30%. The MRT is normal. As for the therapy, a suitable life-style is most important. Antiepileptic drugs are valproate, the drug of first choice, lamotrigine, topiramate, levetiracetam and, if necessary, benzodiazepines. Carbamazepine or oxcarbazepine could aggravate the situation. Seizures can be controlled in 85%, but the risk for relapse after stopping the therapy being seizure free for 3-5 years is 90%, so, the therapy is in most cases is lifelong. The epidemiology of the syndrome, its diagnosis, course, and treatment are demonstrated and illustrated by examples.

Keywords: juvenile myoclonic epilepsy, Janz syndrome

The juvenile myoclonic epilepsy (JME) was first described by Janz and Christian in 1957. According to the International classification of epilepsies (1989), the JME belongs to the generalized idiopathic epilepsies and syndromes with age related onset. In older children and adolescents the most important syndromes are: the juvenile absence epilepsy, the juvenile myoclonic epilepsy and the epilepsy with grand mal on awakening. These epilepsies have common main seizure types: absences, myoclonic jerks and grand mal seizures. The main seizure type determinates the syndrome: the absences in juvenile absence epilepsy, the myoclonic jerks in juvenile myoclonic epilepsy, and the tonic-clonic seizures in epilepsy with grand mal on awakening.

These syndromes have a genetic background and belong together. The genetic background for the JME is heterogeneous, sometimes mutations in the alpha-1 subunit of the GABAA receptor (GABRA1) and point mutations in EFHC1 (Suzuki 2004, Ma 2006, Murai 2008, Medina 2008). The different types as the juvenile absence epilepsy, the juvenile myoclonic epilepsy, and the epilepsy with grand mal on awakening may be present in the same family.

The juvenile myoclonic epilepsy is one of the most common epileptic syndromes, about 5-10% of all epilepsies. The seizures usually occur shortly after awakening. They are often triggered by sleep deprivation (84%) or lack of sleep plus consumption of alcohol (51%) or lack of sleep plus stress. The combination of early morning myoclonic jerks as the most characteristic element, tonic-clonic seizures, rare absences, and the age of onset makes the diagnosis of JME comparatively easy. Nevertheless JME is often misdiagnosed or diagnosed with delay because the morning jerks are not mentioned by the patients. There is a paper from Atakli in 1998 who mentioned that 52,6% of the JME are not diagnosed at the initial interview, but with an average delay of 5,9 years.

In contrast to the former studies of Janz

and co-workers, which reported equal sex distribution, there is a female predominance. There is no preexisting neurological history, except simple febrile seizures in 5-10%.

Clinical symptoms:

1. **The myoclonic jerks** are the cardinal symptom of JME. They are spontaneous, brief, involuntary, sudden, synchronous and grossly symmetric, and of variable amplitude. There is no change of consciousness during the myoclonic jerks. They typically occur half an hour after morning awakening, but also after an afternoon nap, and only sporadically during daytime. Clusters of myoclonic jerks are possible, as well as myoclonic status (7,3% of the patients) with full preservation of consciousness. A myoclonic status is triggered by the fact that the patient does not stop his activity after a series of myoclonic jerks, but also facilitated by acute drug withdrawal or by intake of inadequate AED. The myoclonic jerks predominate in the upper limbs, with flexion of the forearms. They interfere with activities. So the patients drop or throw away things which they commonly hold during that daytime, e.g. coffee cup, tooth-brush. This clumsiness often leads to be subject of mockery. Asymmetric or even unilateral jerks are also possible, and the dominant arm is more involved. The amplitude of the myoclonic jerks is variable, so not all minimal jerks are seen by the onlookers, sometimes it is only an intense electrical inner vibration, as an intermittent tremulousness or an occasional clumsiness. The lower limbs may also be involved. Falls are possible by flexion of the knees, but only in special circumstances, for example when climbing or going down stairways. Traumatic falls are rare, preceded by an immediate short cry and followed by a brief sensation of fatigue, often mistaken as a loss of consciousness.

2. **Generalized tonic-clonic seizures (GTCS)** are seen in 80-95% of the patients. This is the symptom that causes the patient to see the doctor. They have the same daily distribution and trigger factors as myoclonic jerks, and typically occur after a longer cluster of myoclonic jerks with an increasing amplitude and frequence, so the sequence in total is a clonic-tonic-clonic seizure. The GTCS are not frequent (1-2 incidents per year). Clusters are possible during adolescence during a few weeks. They are more frequent in con-compliant or mistreated patients, especially when lifestyle is abnormal, i.e. sleep deprivation and alcohol abuse. GTCS follow myoclonic jerks in JME after a mean delay of 1-3 years.

3. **Typical absences** are not constant, neither very intense nor frequent. They are short, often ignored, often diagnosed only during the lead of an EEG. Absences occur only in 10% (Janz) to 38% (Panayiotopoulos) of the patients with JME. Absence status is very uncommon in JME.

4. **Perioral reflex myoclonias** are a more recent discovery. These are most single, flash-like oro-linguo-facial myoclonias, mostly only seen by video-EEG (23%), and regularly triggered by talking and less common by reading.

5. Another feature is the **clinical photosensitivity**, usually with myoclonic jerks, uncommon with GTCS, and only in 5% of the patients. The existence of atonic seizures in JME is controversially discussed.

The association of seizure types is typically in JME, 58% of the patients with JME have myoclonic jerks and rare GTCS. Only about 33% of the patients have myoclonic jerks, GTCS and typical absences, about 2,4% have myoclonic jerks and absences, and a very few ones only have myoclonic jerks. These patients often don´t see a doctor and may escape medical attention.

The psychological profile of patients shows no mental deterioration and no

neurological damage. However, Janz and Christian (1957, 1994) reported an “attractive but immature personality”, some difficulties of social integration, abnormal lifestyle, less perfect compliance. Similar findings are reported by Tsuboi (1977), Lund (1976), and Reintoft (1976). Devinsky (1977) suggested that features might be due to dysfunction of the prefrontal cortex. De Araújo Filho (2007) found more psychiatric disorders (49%), like anxiety, mood disorders, personality disorders; these findings are more frequent in patients with high seizure frequency. Piazzini (Epilepsia 2008) described a clear frontal cognitive dysfunction similar to that of patients with frontal lobe epilepsy, and not associated with other clinical factors, like duration of the disease, frequency or type of seizures, and treatment. He takes the hypothesis that this is due to some neuroanatomic changes. Non-epileptic seizures in JME are rare, but possible, often in response to particular psychological events.

The ictal EEG is characterised by polyspike-wave discharges, which are bilateral, synchronous and symmetric, immediately preceding a myoclonic jerk. The polyspike-wave discharges normally have 5-20 spikes with a frequency between 12 and 16 Hz and with an increasing amplitude, maximal over the frontal leads, up to 200-300 µV. The slow wave frequency is 3-4 Hz with an amplitude of 200-350 µV. The slow waves precede or follow the polyspikes. This results in a polyspike-wave complex, which lasts longer than the myoclonic jerk. The number of the spikes is correlated with the intensity of the myoclonic jerk. The conduction time between the apex of the spike and the onset of the myoclonic jerk is short, 20-30 ms and this is the characteristic of a cortical myoclonia.

Before starting the therapy, a 24 hours video-EEG is recommended. Alternatively an EEG with sleep and awakening, e.g. an afternoon nap, and an early morning EEG with hyperventilation and photostimulation is possible.

The interictal EEG background activity is normal. Interictal polyspike-wave complexes have a smaller number of spikes, sometimes localized only over the anterior portions, but they are not pathognomonic for JME.

Focal changes are present in 15-55%, as asymmetric ictal discharges, or focal slow waves that shift sides, from one recording to the other or in the same recording. Usui reported in his paper from 2005 that 54% of the patients with JME have focal semiology or focal EEG features or both. Focal epilepsy is excluded because of the association of these focal discharges with generalized SW and polyspike-wave complexes, and that these generalized discharges are activated during slow sleep and reduced or disappeared during REM sleep. Photoparoxysmal response with polyspike-waves is characteristic for JME, one of the most clearly associated epileptic syndromes with photosensitivity. Photosensitivity occurs in 30-48% of the patients, females twice as much as males, more in children than in adults, 56% in a paediatric cohort (Lu 2008).

Neuroimaging, MRI, is in general normal in JME. But recent quantitative MRI studies have shown controversial structural abnormalities in frontal and temporal cortical and thalamic grey matter. In 1999, Woermann described a thickening mesio-frontal, J.H. Kim (NeuroImage 2007) an increased thickness of the superior mesiofrontal bilateral regions as well as bilateral atrophy of thalamic grey matter, and W.S. Tae (J Neurol 2008) an atrophy of the precentral and medial orbital gyrus of right hemisphere which was negatively correlated with the duration of the disease.

Treatment

Most important for treatment is the lifestyle, i.e. regulated sleep/wake rhythm, no coffee and no tea in the later evenings, and alcoholic drinks only in small quantities.

As anticonvulsive drug, valproic acid (VPA) has a specific potency in JME. About 85% of the patients became seizure free. Lamotrigine (LTG) in association with VPA or as monotherapy can be very useful, especially if there are side effects of valproic acid, but you must be careful with LTG because of the possibility of activation of myoclonic jerks. Levetiracetam (LEV) in combination with VPA or as monotherapy can be recommended (Verrotti 2008: 1000-2500 mg/d), particularly in myoclonic jerks, also in photosensitivity. Topiramate (TPM) in mono- or as adjunctive therapy (Sousa Pda 2005: 200 mg/d). Zonisamide (ZNS) is also possible as mono- and adjunctive treatment. If there is drug resistance Clobazam (CLB) and Mesuximid (MSM) are further options.

Aggravating effect in JME have carbamazepine (CBZ) in 68%, but as well as oxcarbazepine (OXC), phenytoin (PHT), vigabatrin (VGB), particularly for myoclonic jerks.

Mostly a life long therapy is necessary because of relapses in about 90% after drug withdrawal. The prognosis is very good, in 80-90% of the patients seizure control is possible. Relapses occur during pregnancy or after delivery. Pharmacoresistance is found only in about 15%, and this is particularly in patients with poor compliance, with inadequate treatment and lifestyle.

Case report:

Carmen, born in 1987, has no family history of epilepsy. She is the 2nd child, her personal history is without any remarkable events. Her first seizure occurred in 1/2002, at an age of 14 ¾ years, a shivering of the left hand, myoclonic jerks. Afterwards the myoclonic jerks also happened on both sides, and with an increasing number.

In 3/2002, after a crescendo of myoclonic jerks in school, she had a first grand mal seizure during her period. MRI was normal, also EEG during daytime. By that she received no medication.

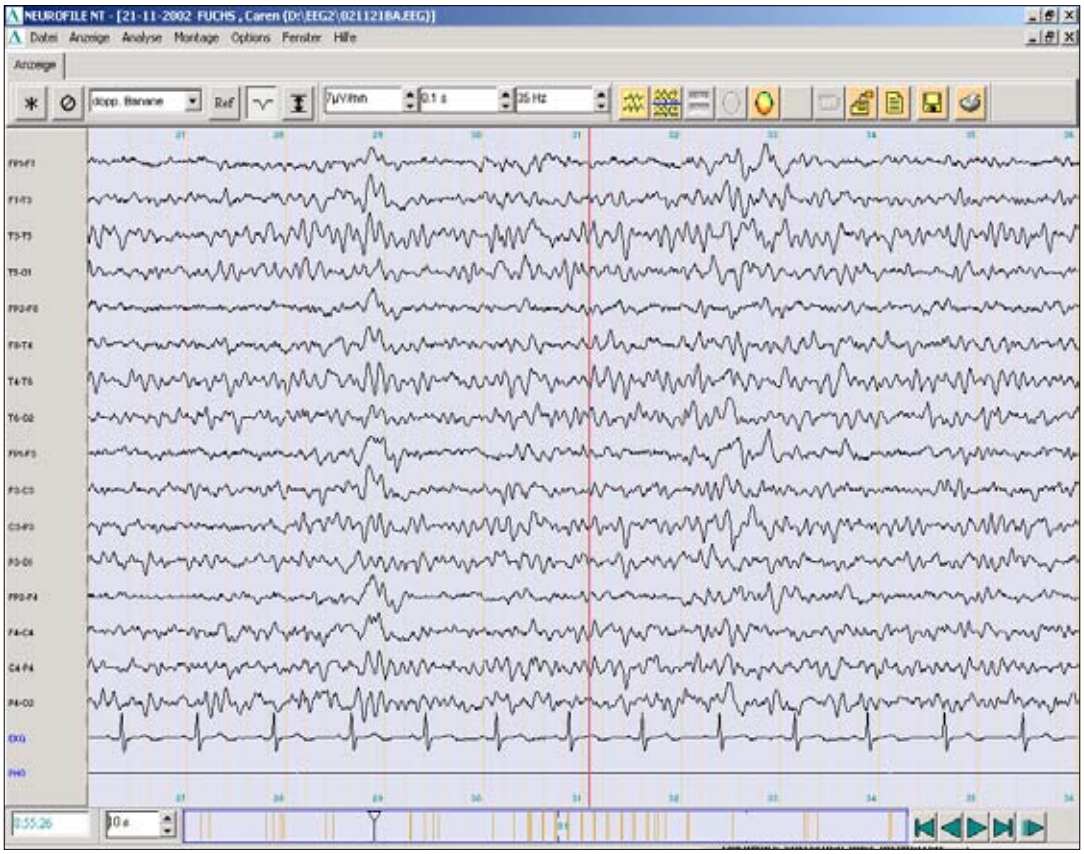
In 4/2002 she had her 2nd grand mal seizure, 8 a.m., again in school and during period. The EEG showed SW over the frontal region, SSW-complexes, especially accentuated over the frontal regions. The diagnosis of a frontal lobe epilepsy was made, and a treatment with oxcarbazepine (OXC) was started. But the myoclonic jerks in the morning were worsening. In 7/2002 she had her third grand mal seizure, and 9/2002 her 4th. OXC was raised up to 1800 mg/d. She had side effects as dysopia, dizziness, nausea, especially after the intake of OXC.

She was first seen in our clinic in 11/2002. The EEG during daytime showed a normal background activity, an intermittent slowing in both temporal regions, but also frontal and occipital, and isolated SW left parietal (P3) and left temporo-occipital (O1/P7) and 2 generalized 3/s-SSW-complexes of 3 seconds. The diagnosis of a juvenile myoclonic epilepsy, a Janz syndrome, was made.

The sleep EEG showed generalized 2,5 - 3/s-SSW- and poly-SSW-complexes, accentuated over the frontal region, left more than right, twice with myoclonic jerks of the shoulders, sometimes of the eyelids. The longtime EEG during 24 hours revealed bifrontal accentuated SSW- and poly-SSW-complexes between 1 and 5 seconds, and between noon and 5 p.m. in total 123 paroxysms, and during the first 2 hours after awakening long and frequent paroxysms, up to 8 seconds.

A treatment with valproic acid (VPA) was installed instead of OXC. Carmen became seizure free, she had no more myoclonic jerks.

Carmen was seen again in our outpatient clinic in 1/2004: still seizure free, but a weight gain of 7 kg. So a change of the medication from VPA to Lamotrigin (LTG) was initiated. In 7/2004, under VPA 2x150 mg + LTG 75-0-100 mg, and by that a loss of 4 kg of weight, she had a relapse of myoclonic jerks of the left arm with stress on account of school trouble. So VPA was raised up to 600 mg/d plus LTG 125 mg/d. But she still continued to have myoclonic jerks, so at the end she was put again on VPA monotherapy. Under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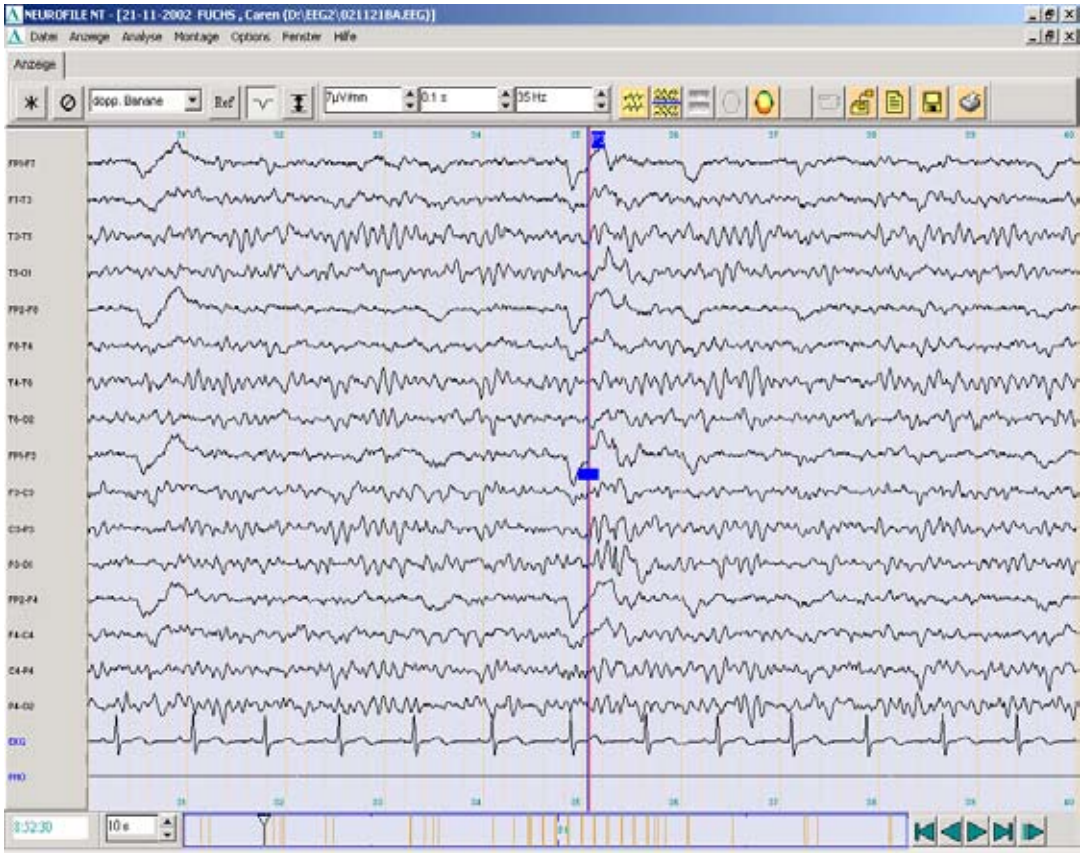
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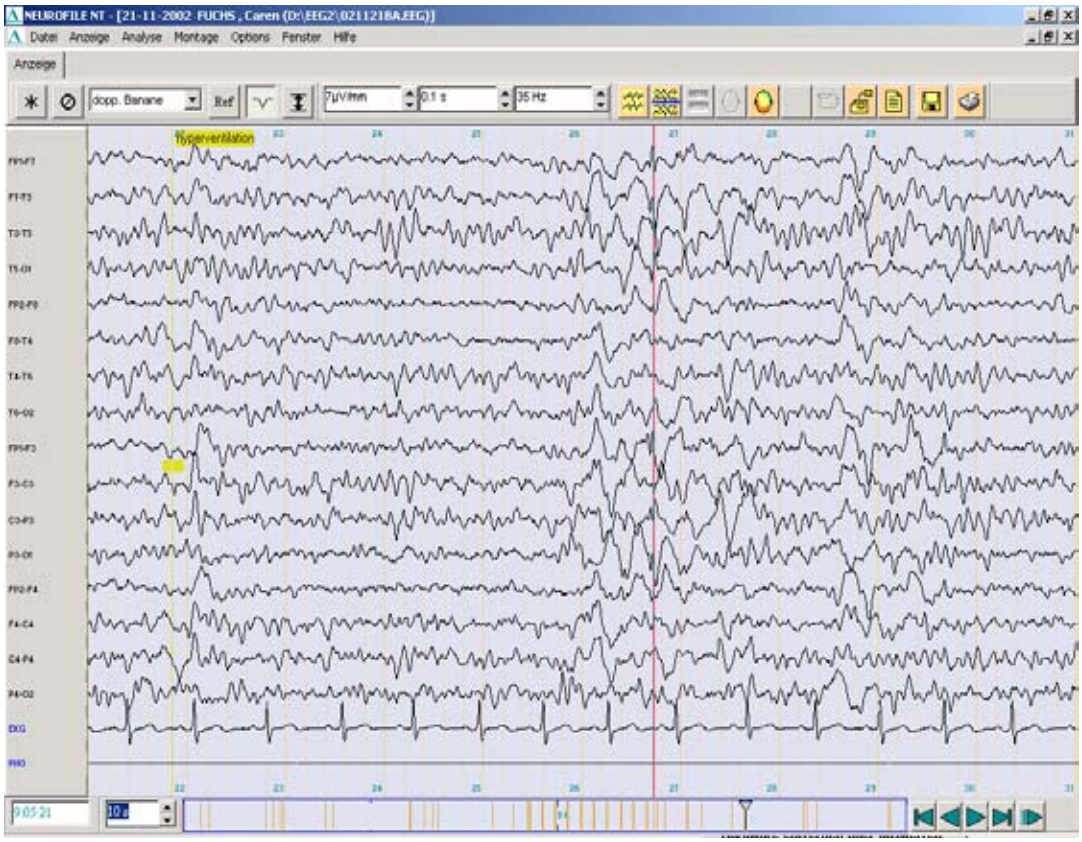
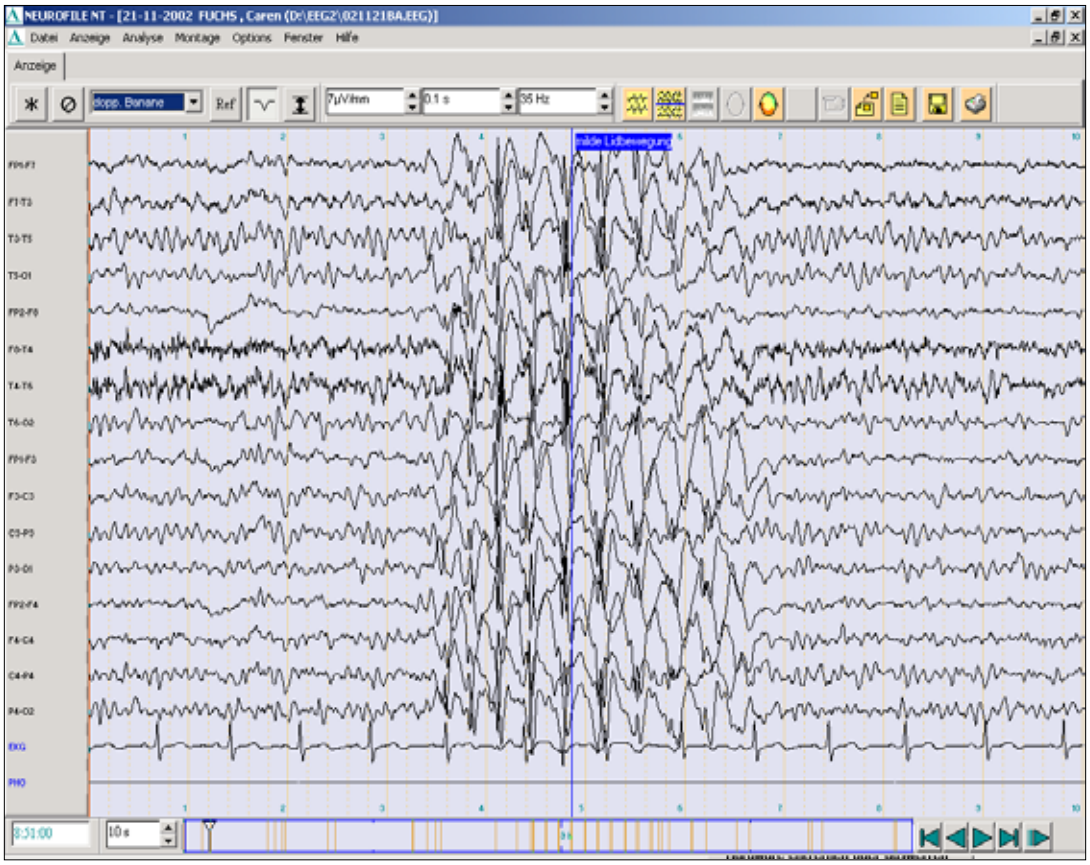
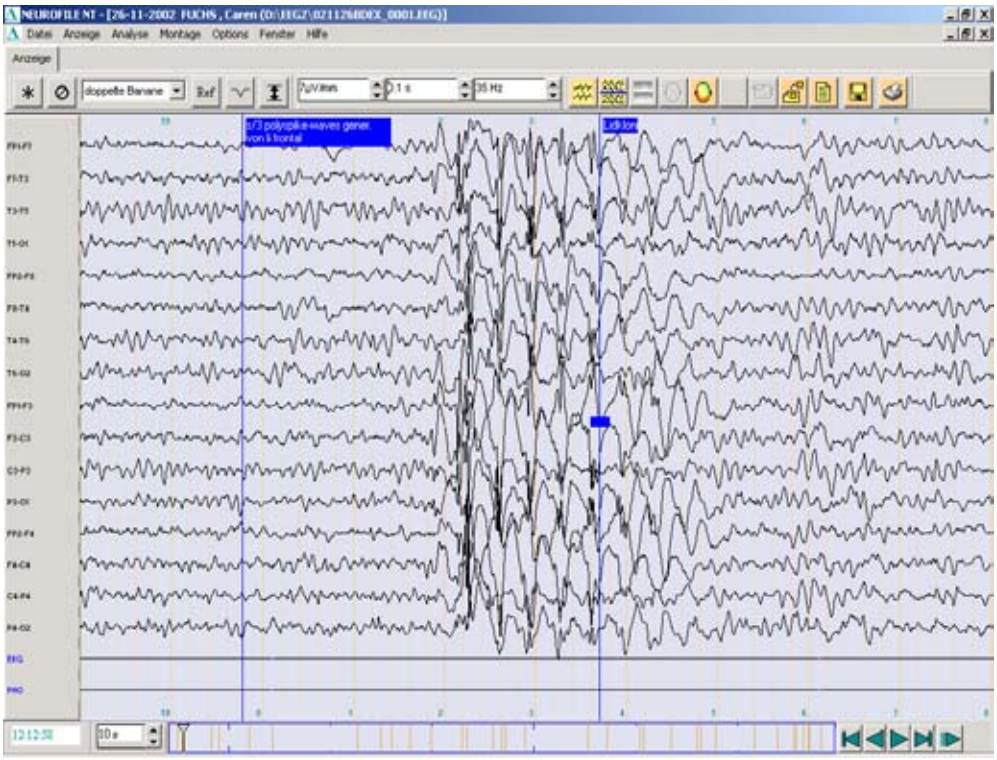
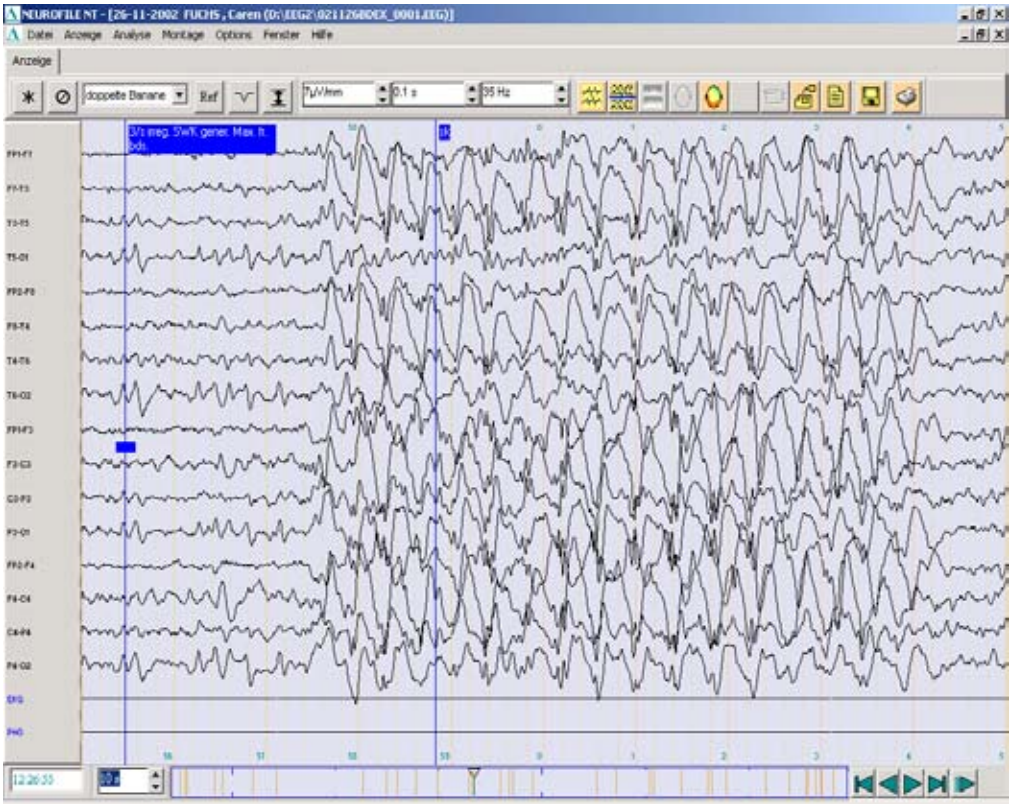




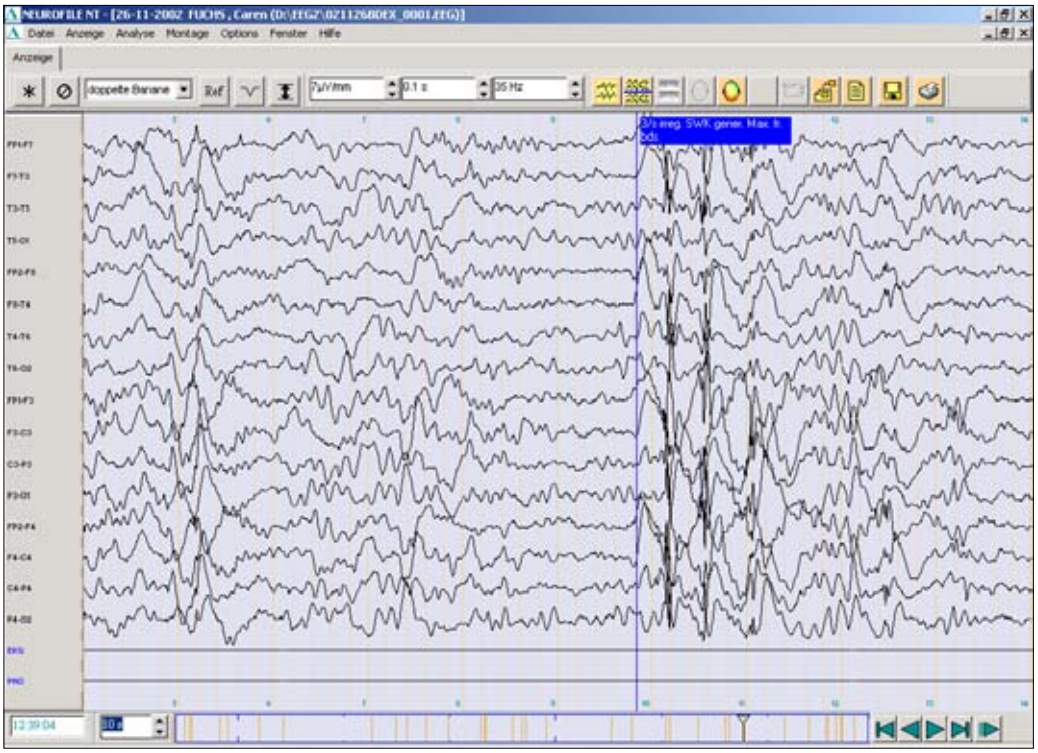
EEGs during day time



EEG during drowsiness



EEG during first sleep



EEG during first sleep

1200 mg/d VPA she had no more myoclonic jerks, but again side effects of VPA, weight gain, tiredness, lack of drive. So in 12/2004 the treatment was changed to VPA 900 mg/d in combination with Levetiracetam (LEV) 1000 mg/d. No more myoclonic jerks were mentioned, but in 5/2005 she had a weight gain of 11 kg in 7 months. Next VPA (750 mg/d) was combined with Topiramat (TPM), 200 mg/d. In 4/2006 she had a loss of weight of 7,5 kg, she was seizure free, but tired, so VPA was reduced to 600 mg/d and TPM raised up to 225 mg/d. On account of fear of recurrence of the myoclonic jerks she refused further change of the medication, such as TPM monotherapy. Carmen made her drivers licence in 2006, and she is still (last seen in 6/2008) seizure free since autumn 2004.

Conclusion:

Juvenile myoclonic epilepsy is an epileptic syndrome that is particularly easy to identify, easy to treat adequately (VPA, LTG, LEV, TPM), and has a good prognosis, nevertheless often underdiagnosed and often mistreated, as demonstrated in the case report. What you need for an exact diagnosis is a good anamnesis, an early morning daytime EEG with hyperventilation and photostimulation and a sleep EEG with wake up phase.

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