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# Late-onset temporal lobe epilepsy in a patient with juvenile myoclonic epilepsy

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**ABSTRACT** – We report a patient with longstanding, severe juvenile myoclonic epilepsy who subsequently developed features of temporal lobe epilepsy, which gradually became clinically dominant. Over the years, there was an electrographic evolution from the typical generalised epileptiform patterns, characteristic of juvenile myoclonic epilepsy, to the novel appearance of interictal temporal spikes immediately preceding bisynchronous discharges, and subsequently to temporal intermittent rhythmic delta activity and temporal lobe-onset seizures. In this rare case of coexistent primary generalised epilepsy and focal epilepsy, the epileptic networks of the two forms of epilepsy appear to overlap.

**Key words:** Juvenile Myoclonic Epilepsy, JME, TLE, temporal, coexistence

Juvenile myoclonic epilepsy (JME) is a primary, genetically heterogeneous generalised epileptic syndrome, which represents approximately 4-11% of all forms of epilepsy (Genton and Gelisse, 2001). JME usually develops at puberty. The main seizure type consists of myoclonic jerks occurring soon after awakening or on falling asleep. Generalised tonic-clonic seizures also develop in most patients and typical absence seizures in about one third. The neurological examination is normal and routine brain MRI is unremarkable. EEG features typically include diffuse, frontally predominant bilateral spikes and spike/polyspike-and-wave discharges, often irregular and fragmented (Panayiotopoulos *et al*., 1994).

The coexistence of a primary generalised epilepsy such as JME and focal epilepsy has been rarely reported (Diehl *et al*., 1998; Koutroumanidis *et al*., 1999; Usui *et al*., 2005; Jeha *et al*., 2006). One suggested reason for this rarity is the failure to recognize and correctly diagnose one of the two epilepsies (Koutroumanidis *et al*., 1999). Alternatively, it has been proposed that the presence of one epilepsy type could alter the natural history and/or phenotypic expression of the other, making the recognition of the latter difficult (Diehl *et al*., 1998; Koutroumanidis *et al*., 1999).

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We present a patient with JME who subsequently developed temporal lobe epilepsy (TLE), and discuss the potential diagnostic challenges and pathogenetic interactions between these two forms of epilepsy.

## Case study

A 49-year-old woman was referred to our epilepsy centre at the age of 30. Her first seizure occurred when she was 14. Her seizures consisted of brief arm jerks, blank stare episodes, and occasionally diffuse shaking, limited to a few minutes. Her epilepsy was poorly controlled over the years despite multiple medication trials; on average, arm jerks occurred daily and generalised convulsions one to six times a month.

The diagnosis of JME was documented by several video-EEG monitoring studies between 33 and 35 years of age. Myoclonic seizures were recorded, which mainly involved arms and were bilateral, symmetric or asymmetric with shifting preponderance. Generalized tonic-clonic seizures were also captured, which were clinically non-lateralising. These seizures were associated at onset with generalised polyspike or spike-and-wave discharges that were maximal over the frontal regions and variably asymmetric. Interictally, generalised discharges of similar morphology (*figure 1A*) and occasional bifrontal spikes punctuated an otherwise normal background.

When she was 43, her family noted new episodes of "jumbled" speech and prolonged staring. An EEG showed novel, bilateral independent temporal interictal spikes preceding bursts of generalised discharges (*figure 1B*). Brain MRI was suggestive of right hippocampal sclerosis (HS; *figure 2*). Subsequently, continuous video-EEG monitoring without antiepileptic medications at the age of 48 disclosed prominent left temporal intermittent rhythmic delta (TIRDA) and abundant right and left anterior temporal spikes. Bifrontal spikes were noted rarely; generalised discharges, which had been characteristic of her prior EEG studies, were absent. Several complex partial seizures, during which the patient looked dazed, fidgety, and displayed semi-purposeful activity, were recorded. Electrographically, these seizures were associated with an apparent right temporal onset in the setting of ongoing left temporal spikes and left TIRDA activity (*figure 3*).

The patient denied a history of febrile seizures, head trauma, or CNS infections. She reported that her mother and sister had also had seizures, the nature of which was not documented. Her son, also treated at our centre, was diagnosed with JME.

On later clinic visits, the patient continued to report episodic garbled speech and unresponsiveness, and disclosed only occasional myoclonias, compared to previous years. She currently undergoes presurgical evaluation for medically intractable TLE.

## Discussion

We report a patient with primary generalised epilepsy and concurrent partial epilepsy. It has been suggested that such coexistence is an underestimated phenomenon. Indeed, two large consecutive series conducted on this subject in tertiary epilepsy centres of patients undergoing long-term video-EEG with focal and temporal lobe resections have reported co-occurrence rates of 0.2 and 0.57%, respectively (Koutroumanidis *et al*., 1999; Jeha *et al*., 2006). The rarity of similar reports stems mainly from the under-recognition or misdiagnosis of primary generalised epilepsies (Koutroumanidis *et al*., 1999). In the case

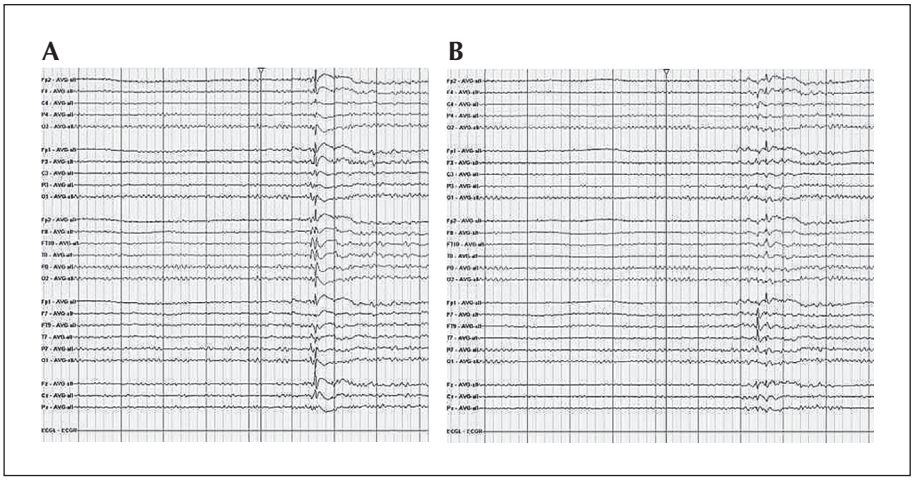


**Figure 1.** (A) Generalised epileptiform discharges (age 35). (B) Left temporal spike preceding a diffuse discharge (age 43).

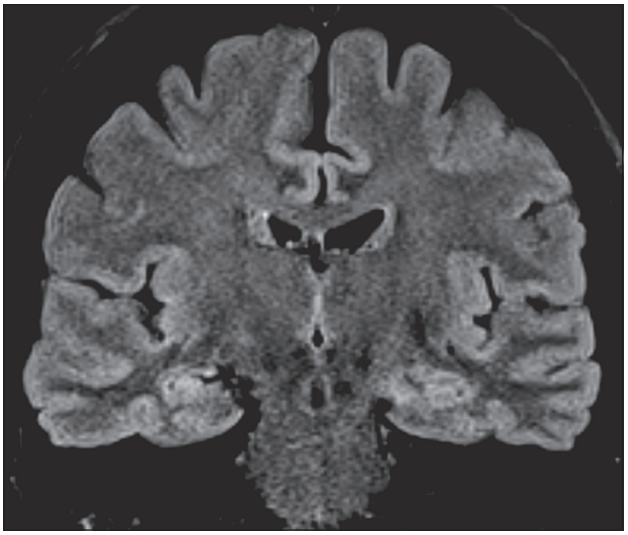

**Figure 2.** MRI brain T2 FLAIR image reveals decreased hippocampal volume and hyperintensity on the right side suggestive of right hippocampal sclerosis (age 47).

of JME, a lack of familiarity of the syndrome and failure to elicit a history of myoclonias are commonly cited reasons for under-recognition (Montalenti *et al*., 2001). Likewise, a history of generalised convulsive events without apparent focal semiology at onset is commonly elicited in patients who are eventually shown to have focal epilepsy. The misdiagnosis of JME as focal epilepsy is well known and is likely facilitated by the prominent focal or asymmetric clinical and electrographic patterns described in 16-42% and 11.1-72.7% of JME patients, respectively (Aliberti *et al*., 1994; Baise-Zung *et al*., 2006; Pedersen and Petersen, 1998; Usui *et al*., 2005). Notably, asymmetric myoclonias, as recorded in our patient, and absences might be mistaken for focal motor and temporal lobe complex partial seizures, respectively. The EEG in JME can disclose asymmetric generalised discharges and focal or unilateral spikes, sharp or slow waves, occurring either independently or preceding diffuse epileptiform patterns (Aliberti *et al*., 1994; Baise-Zung *et al*., 2006; Montalenti *et al*., 2001).

Recognising the emergence of a new form of epilepsy in a subject with chronic epilepsy requires a careful appreciation of changes in the typical ictal clinical presentation. In our patient, the appearance of spells with new "focal" semiology at the age of 43 and novel temporal interictal spikes preceding generalised discharges (*figure 1B*) led to further investigation and diagnostic update. Temporal spikes leading to bilaterally synchronous epileptiform discharges have been described in JME (Baise-Zung *et al*., 2006), usually with varying morphology and shifting from side to side; they do not necessarily imply a focal cortical origin. However, their *de novo* appearance on EEG and relative abundance should raise diagnostic red flags, as our case suggests.

There has been some debate as to whether the expression of one epilepsy type is modified by a concurrent, distinct form of epilepsy. Diehl *et al*. (1998) reported on a patient with TLE and HS who developed features of JME shortly after discontinuing valproate monotherapy and undergoing resective epilepsy surgery; the authors hypothesized that medication changes and

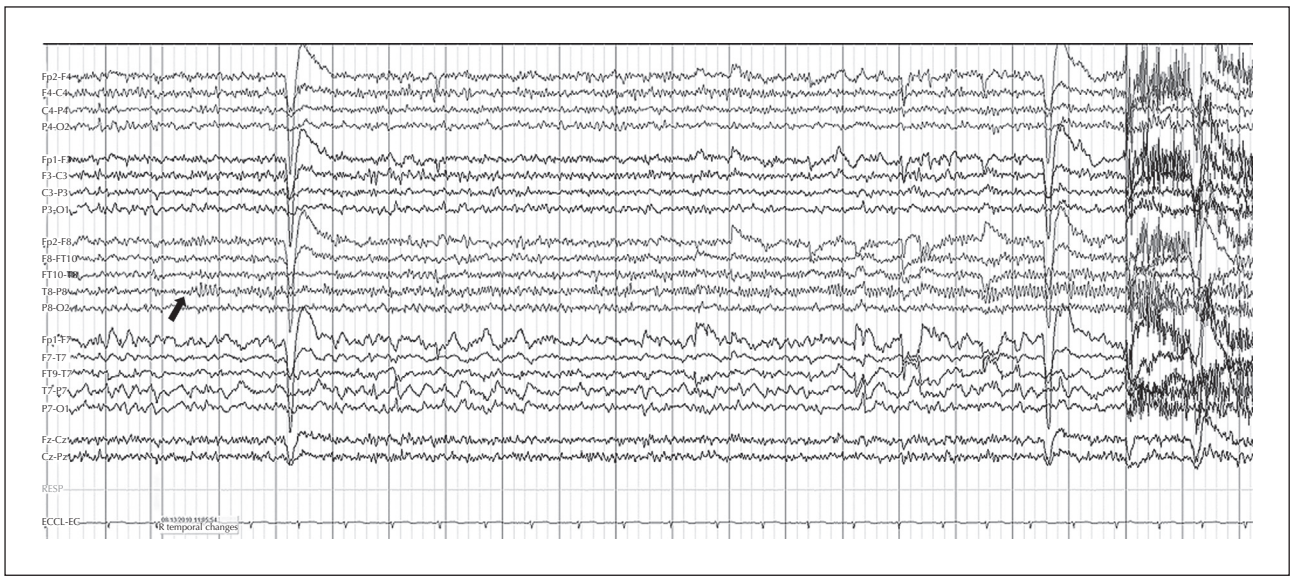


**Figure 3.** Focal seizure with apparent right temporal onset (arrow) in the presence of left temporal spikes and left temporal intermittent rhythmic delta activity (age 48).

epilepsy surgery may have had a role in the onset of JME. The series by Koutroumanidis *et al*. (1999) included a patient in whom a primary generalised epileptic syndrome (juvenile absence epilepsy; JAE) became apparent several years after TLE onset. In contrast to Diehl *et al*., the authors suggested that JAE and TLE onset occurred in the absence of significant mutual influences.

In our patient, we cannot exclude that the coexistence of JME and TLE is coincidental. While most cases of TLE express clinically in childhood or adolescence, some cases of TLE express later in adulthood (Wieser *et al*., 2004); a late TLE onset does not necessarily imply a secondary, acquired form of TLE. The increasing clinical dominance of TLE features in our patient may merely reflect a fortuitous decrease in the burden of myoclonic seizures, which has been noted in JME patients in the fourth decade of life (Baykan *et al*., 2008). Nevertheless, it is tempting to propose that the long-term frequent occurrence of generalised convulsive seizures of a particularly severe form of JME, even without a clear-cut history of status epilepticus episodes, might have led to a secondary epileptogenic process involving the temporal lobes and eventually to late-onset temporal lobe epilepsy with imaging evidence of HS. Changes suggestive of HS have been reported to occur after brief generalised seizures in adult patients (Briellmann *et al*., 2001) and animal models (Cavazos *et al*., 1994). Recent evidence suggests that status epilepticus may not be required to produce spontaneous recurrent seizures in pilocarpine-induced epilepsy in adult rats (Navarro Mora *et al*., 2009). Whether seizures beget seizures is not established definitively, however, experimental and clinical data appears to support TLE as a progressive disorder where seizure frequency and severity is augmented continuously over time after a latent period from the initial presumed precipitant events (Ben-Ari and Dudek, 2010). This concept fits the increasingly preponderant expression of TLE in our patient with time.

In addition, a growing body of evidence addresses the involvement of the temporal structures in the epileptic circuits of JME. In a PET study by Meschaks *et al*. (2005) in JME patients, hippocampal neuronal loss or dysfunction was suggested by locally decreased serotonin receptor binding. Tae *et al*. (2008) found decreased cortical thickness in temporal regions in JME patients and Ristić *et al*. (2011) reported hippocampal metabolic dysfunction in JME in a 3D multivoxel spectroscopy study. Using source analysis of dense-array EEG-recorded epileptiform discharges, Holmes *et al*. (2010) found localised involvement of basal and mesial temporal lobe structures, in addition to frontal regions, in five of ten patients. The fact that experimental hippocampal seizures can lead to slow wave activity within the orbitofrontal, cingulate, and retrosplenial cortices also emphasizes the link between the hippocampus and frontal neocortex (Englot *et al*. 2008). The disclosure of temporal spikes preceding bilaterally synchronous epileptiform discharges in our patient (*figure 1*) seems to reflect the access of temporal epileptiform patterns to the bilaterally distributed subcortical circuitry of JME. The presence of bilateral independent temporal spikes and TIRDA in later recordings may reflect the expression of a bitemporal epileptogenic process primed by the bilateral epileptic activity characteristic of JME.

Future similar reports may further our knowledge of the prevalence and potential relationships between coexistent generalised and focal epilepsies. □

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