

## The diagnostic dilemma of non-convulsive status epilepticus in sporadic Creutzfeldt-Jakob disease

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### SUMMARY

**Introduction.** The differentiation between the clinical and electroencephalographic changes in nonconvulsive status epilepticus (NCSE) and those in sporadic Creutzfeldt-Jakob disease (sCJD) is a crucial question.

**Case report.** A 77-year old woman was admitted because of fluctuating behavioural changes, adynamia and apraxia since several months for diagnostic. The diagnosis of sCJD was suggested. Subsequently, she had a generalized tonic clonic seizure (GTCS) and the EEG revealed periodic lateralized epileptiform discharges and NCSE was considered.

**Discussion.** The presented case illustrates the dilemma in the differential diagnosis of sCJD and (symptomatic) NCSE in the light of the recently published new Salzburg consensus criteria and unified EEG terminology. Concerning these criteria, the patient showed after an initial generalized seizure and substantial clinical improvement after administration of antiepileptic drugs, persisting epileptic discharges and only subtle clinical ictal phenomena during the EEG patterns with typical spatiotemporal evolution as a correlate of a symptomatic NCSE. During the further course of the disease in the presented patient the picture changed into an encephalopathic pattern.

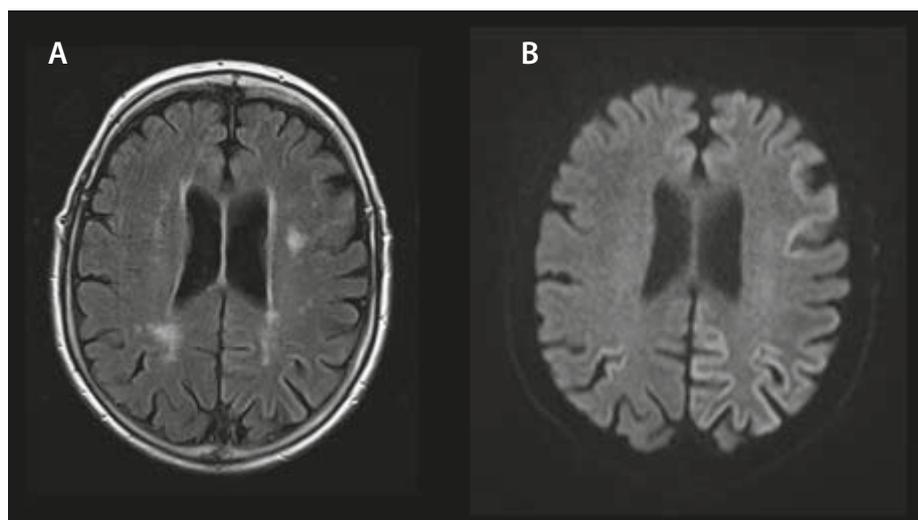
**Conclusion.** EEG criteria for the diagnosis of NCSE are complex. In our case the EEG resembled the pattern of NCSE in the postictal phase of a GTCS according to a classification of NCSE in use at this time. After initial responsiveness to antiepileptic medication the patient lost responsiveness to therapy displaying the typical encephalopathic EEG findings in sCJD. These findings may support the hypothesis of initial NCSE and transformation into prion protein induced encephalopathic EEG and demonstrated clinical usefulness of the Salzburg consensus criteria for NCSE.

**Key words:** sporadic Creutzfeldt-Jakob disease · non-convulsive status epilepticus · EEG

### INTRODUCTION

The differentiation between the clinical and electroencephalographic changes in nonconvulsive status epilepticus (NCSE) and those in sporadic Creutzfeldt-Ja-

kob disease (sCJD) is a crucial question. Changes of the electroencephalogram (EEG) are one of the diagnostic hallmarks in NCSE as well as in sCJD.



**Figure 1.** Magnetic resonance imaging (Siemens Magnetom 1.5 T): (A) FLAIR weighted axial images displaying moderate microangiopathy and (B) DWI indicating restricted diffusion throughout the left temporal-parietal-occipital cortex.

Furthermore, beside cognitive and behavioural changes, seizures of various semiologies may be one of the first symptoms in sCJD. Patients may show generalized or focal seizures as well as *epilepsia partialis continua* (Taskiran et al., 2011) in the beginning of the disease. Moreover, few cases of NCSE as the presenting symptom of sCJD have been described previously (Aiguabella et al., 2010; Beniczky et al., 2013). Additionally, NCSE may have heterogeneous presentations and differential diagnosis may be particularly difficult because clinical signs coupled with periodic EEG pattern are most often subtle or non-specific. Nevertheless, there have been attempts to define distinct EEG patterns associated with certain subtypes of NCSE (Sutter & Kaplan, 2012; Leitinger et al., 2015). In the setting of a rapidly progressive condition with no effective therapy, determining appropriate treatment for seizures may be difficult if clinical morbidity is not obvious yet the EEG demonstrates a worrisome pattern such as status epilepticus (SE). We present a sCJD patient with NCSE and discuss the case in the light of the modified Salzburg Consensus Criteria for NCSE (Leitinger et al., 2015).

#### CASE REPORT

A 77-year old woman was admitted to the Department of Psychiatry because of fluctuating behavioural changes, adynamia and apraxia since several months for diagnostic evaluation of suspected dementia. Haemoglo-

bin 6,4, haematocrit 0,32, red blood cell count 3,7, leucocytes 9,61, calcium 2,07, ASAT 41,9, Gamma-GT 89, CRP 79,5, and creatinine was 47,3 (all values in SI units). All other routine laboratory results were within the normal values. A lumbar puncture revealed normal cell count and protein levels but displayed a five-fold elevated titre of protein 14-3-3. Tau-protein values were >1200 pg/ml (normal  $\leq$ 512). A subsequent MRI showed microangiopathic white matter lesions of a moderate degree and cortical DWI enhancement on the left hemisphere (Figure 1). A diagnosis of sCJD was suggested. Subsequently, she had a generalized tonic clonic seizure (GTCS) and the EEG examination revealed left hemispheric lateralized periodic discharges (LPDs) with a frequency of 4 Hz and persisting fluctuating cognitive changes and subtle ictal phenomena and a non-convulsive status epilepticus (NCSE) was considered. She was transferred to the neurological intensive care unit (ICU) for further therapy of the NCSE. On admission the patient displayed a disturbance of consciousness and subtle myoclonic jerks of the right arm.

During the course of treatment 11 EEGs were obtained. The terminology of the American Clinical Neurophysiology Society (ACNS) for description of EEG findings in critical care was used (Hirsch et al., 2013). The first EEG before the generalized tonic clonic seizure showed a background activity in the theta range and focal epileptiform discharges in the left temporal and parietal leads. The second EEG was obtained af-

ter the seizure and showed left hemispheric LPDs with propagation to generalized periodic discharges (GPDs) and lack of reactivity. Because of these findings and the accompanying subtle ictal phenomena, a diagnosis of an NCSE in the postictal phase of a GTCS was concluded. Initially, with treatment with valproic acid (VPA) and phenytoin (PHT) the occurrence of epileptiform patterns were reduced to the left occipital and temporo-parietal leads with a frequency of 1 Hz in accordance with Salzburg criteria for NCSE (see Leitinger et al., 2015). This corresponded to the area of restricted diffusion shown by MRI. Initially, vigilance improved slightly but an altered cognitive state and subtle ictal phenomena persisted and subsequently deteriorated without EEG changes. Because the patient did not recover, thiopental narcosis was established and a burst suppression pattern was induced for 48 hours. The maximal thiopental level in serum was 3.7 µg/ml (therapeutic range 1–5 µg/ml). Afterwards the EEGs showed bilateral independent periodic discharges (BiPDs), and some days later GPDs with a frequency between one and two Hz and with static GPDs representing the change into an encephalopathic pattern in sCJD. The course of EEG changes is shown in figure 2. Additionally, the EEG displayed reactivity. Supplementary diagnostic findings (positive PrPSc-aggregation assay) confirmed the diagnosis of suspected sCJD. The patient died a few weeks after being transferred from hospital to a hospice.

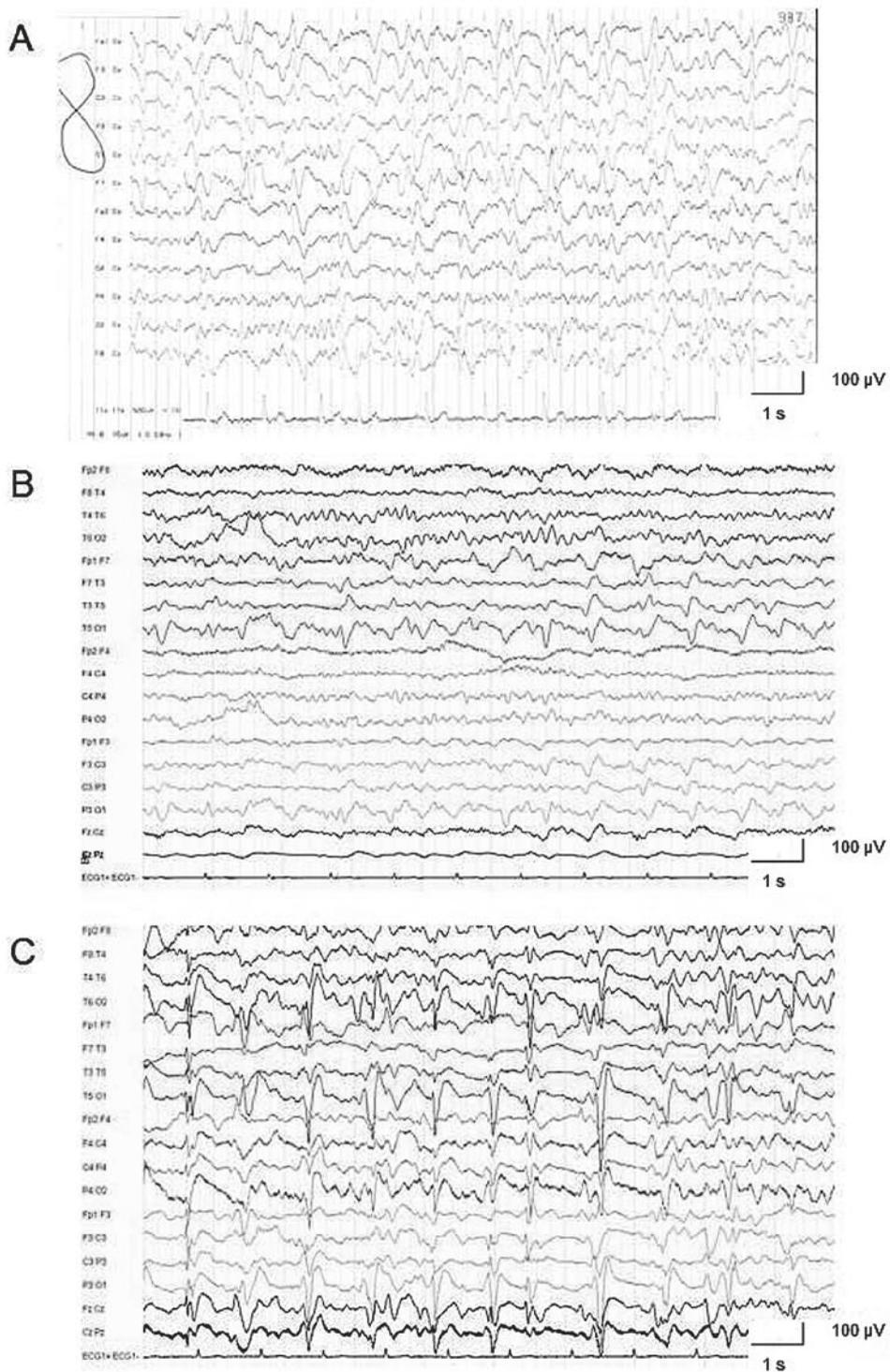
## DISCUSSION

The presented case illustrates the dilemma in the differential diagnosis of sCJD and (symptomatic) NCSE in the light of the recently published new consensus criteria and unified EEG terminology by Beniczky et al. (2013) and Leitinger et al. (2015) (Table 1).

The occurrence of NCSE in sCJD has been reported previously (Aiguabella et al., 2010; Lapergue et al., 2010). The clinical and MRI changes of the presented case may be observed in both conditions – NCSE and sCJD. Furthermore, the elevation of protein 14-3-3 can be observed in sCJD as well as in SE resulting from excessive neuronal cell death (Lapergue et al., 2010). EEG investigations are an essential approach in the diagnosis of NCSE and one of the hallmarks in sCJD. Here an essential finding is the presence of periodic sharp wave complexes (PSWC), which initially may consist of LPDs in early stages and later on GPDs with a duration of 100–600 ms and an intercomplex interval of 500–2000

ms (Wieser et al., 2006). These electrical patterns may be confusing, making it very difficult to distinguish sCJD from NCSE. Notably, the above mentioned sCJD EEG changes may mimic NCSE (Lapergue et al., 2010). There is no satisfactory model to explain the periodicity of the pattern. Traub and Pedley (1981) suggested that bihemispherically synchronized discharges such as PSWC do not necessarily imply pacing from deep midline structures but might be synchronized by way of the corpus callosum. They further speculated that fusion of the dendritic membranes of affected neurons could result in increased electrotonic coupling and pathologically synchronized bursting activity. Lateralized PSWC may resemble LPD, both are suggested to reflect early stage of sCJD. Moreover, the morphological similarities of lateralized or regional PSWC in sCJD and classical LPD associated with acute unilateral cerebral processes of various etiologies do not necessarily imply a common neurophysiological basis of the two periodic EEG patterns. Unlike sCJD-associated PSWC, LPD usually denote a transient EEG phenomenon, which typically decreases in amplitude and repetition rate during the course of the disease and usually disappears within two weeks of the acute lesion (Westmoreland et al., 1986). Furthermore, LPD but not sCJD-associated PSWC are frequently associated with epileptic seizures (Snodgrass et al., 1989). Finally, LPD are usually not influenced by manipulation and sleep, whereas PSWC in sCJD may commonly be influenced by external stimulation. PSWC may also be attenuated by sedative medication, especially benzodiazepines (Wieser et al., 2006). In the presented case, thiopental narcosis induced successfully a burst suppression EEG with maximal thiopental levels within mid therapeutic range (data not shown). Changes like the induction of persistent  $\beta$ -EEG, atypical triphasic waves or generalized and diffuse slowing were not observed (Feshchenko et al., 1997; Lancman et al., 1997).

Concerning the electroclinical criteria of Beniczky et al. (2013) and clinical consensus criteria by Leitinger et al. (2015), the patient showed, after an initial generalized seizure and slight clinical improvement after IV application of AED, persisting epileptic discharges (EDs) and only subtle clinical ictal phenomena along with the EEG patterns mentioned above with typical spatiotemporal evolution as a correlate of NCSE. With respect to type and etiology of NCSE, the patient displayed impaired consciousness and an acute onset as well as a symptomatic etiology. The EEG after the



**Figure 2.** Sequelae of EEG findings in the course of ICU treatment.

A – EEG (after generalized tonic clonic seizure) – Occurrence of LPDs, propagation to GPDs.

B – EEG during valproate and phenytoin therapy – occurrence of epileptiform patterns in the left occipital and temporo-parietal leads.

C – EEG 48 hours after narcosis with thiopental displaying GPDs without remarkable waxing and waning.

LPDs – lateralized periodic discharges; GPDs – generalized periodic discharges

**Table 1.** The modified Salzburg Consensus Criteria for Non-Convulsive Status Epilepticus, which is suggested for all patients with qualitative or quantitative disturbance of consciousness and suspicion of non-convulsive status epilepticus (NCSE). The diagnosis of NCSE is the result of combining EEG and clinical data. Clinical symptoms have to last at least 10 min.

Modified Salzburg Consensus Criteria for Non-Convulsive Status Epilepticus (mSCNC)
<b>EEG data</b>
EEG changes fulfilling the criteria $\geq 10$ s.
<b>A: Patients without known epileptic encephalopathy</b>
1. EDs $> 2.5$ Hz, or
2. Typical spatiotemporal evolution of <ul style="list-style-type: none"> <li>– EDs or</li> <li>– rhythmic activity (<math>&gt; 0.5</math> Hz)</li> </ul>
3. subtle ictal clinical phenomena with <ul style="list-style-type: none"> <li>– EDs or</li> <li>– rhythmic activity (<math>&gt; 0.5</math> Hz)</li> </ul>
4. if criteria 1–3 are not fulfilled, but one of the following patterns is present, apply appropriate AED(s) after careful consideration of clinical situation and document response <ul style="list-style-type: none"> <li>– ED <math>\leq 2.5</math> Hz with fluctuation or</li> <li>– rhythmic activity (<math>&gt; 0.5</math> Hz) with fluctuation or</li> <li>– rhythmic activity (<math>&gt; 0.5</math> Hz) without fluctuation</li> </ul>
<b>B: Patients with known epileptic encephalopathy</b>
In addition to the criteria above (A), these patients have to fulfil one of the following: <ul style="list-style-type: none"> <li>– Increase in prominence or frequency when compared to baseline with observable change in clinical state</li> <li>– Improvement of clinical and EEG features with IV AEDs</li> </ul>
<b>Clinical data</b>
<b>Add clinical data for establishing the diagnosis of NCSE</b>
– Transition from premorbid to current ill state within minutes to hours
– Patient did not improve significantly in last minutes to hours, apart from waxing and waning
– No information from brain imaging sufficiently explaining EEG pattern
– No metabolic/toxicological derangement sufficiently explaining EEG pattern

Modified from Kaplan, 2007; Bauer & Trinka, 2010; Sutter & Kaplan, 2012; Beniczky et al., 2013; Leitinger et al., 2015.

EDs – epileptiform discharges (spikes, poly spikes, sharp-waves, sharp-and-slow-wave complexes); IV AEDs – intravenous antiepileptic drugs

GTCS resembled the pattern of an NCSE in the post-ictal phase of a GTCS (Sutter & Kaplan, 2012) according to the classification of Shorvon (2007). Unfortunately the pattern is not always present in this condition (Rösche et al., 2015). The classification of Shorvon (2007) integrated semiological and aetiological aspects in one axis. In the new classification of SE (Trinka et al., 2015) these aspects were considered in different axes and the item NCSE in the postictal phase of a GTCS was abandoned. It was stated that there is no specific electroencephalographic pattern associated with a certain subtype of SE. A variety of causes of NCSE exists like e. g. autoimmune encephalitis, paraneoplastic limbic encephalitis or CNS infections (Kim et al., 2015; Espay et al., 2006; Bagic et al., 2007; Mead & Rudge, 2017) as well as CJD (Aiguabella et al., 2010; Beniczky et al., 2013). Our case has to be classified as NCSE with impaired consciousness (B.2.b.c) on axis 1 and progressive aetiology on axis 2 (here suspected sCJD). During the further course of the disease in our patient the pic-

ture changed into an encephalopathic pattern of sCJD.

In the light of the previous described aspects, a second question has to be addressed. Whether and when AED therapy is started when CJD is suspected? SE in CJD has been found to have a relatively high incidence and this may be suggested to be similar for NCSE (Appel et al., 2015). NCSE is a potentially treatable condition. Therefore we suggest that, even in an etiologically not completely clear situation, AED treatment of suspected NCSE should be begun. Sufficient AED doses should be prescribed. When clinical and electroencephalographic improvement are observed, AED treatment should be continued. Whereas the dissociation between electroencephalographic improvement and persistence of mental alteration or changes of EEG into an encephalopathic pattern should draw attention toward other diagnostic possibilities like sCJD. However the use of narcosis for treatment of NCSE should carefully be considered.

## CONCLUSION

EEG criteria for the diagnosis of NCSE are complex. They depend on whether the NCSE is focal or generalized, and rely on the rhythmicity of activity as well as its spatial and temporal organization. In our case, the EEG after the GTCS was suggestive for an NCSE. After initial responsiveness to AED medication (like valproic acid) the patient lost responsiveness to therapy displaying the typical encephalopathic EEG findings of sCJD. Additionally the EEG was affected by external stimulation. These findings may support the hypothesis of initial epileptic findings of NCSE and transformation into prion protein induced encephalopathic EEG demonstrating the usefulness of the new Salzburg consensus criteria for NCSE especially in patients with progressive aetiology of NCSE.

## CONFLICT OF INTEREST

The authors have no conflict of interest to declare.

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