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Cognitive function after status epilepticus versus after multiple generalized tonic-clonic seizures

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ABSTRACT

Objectives: Status epilepticus (SE) is considered a risk for cognitive impairment. Studies have indicated that SE cause more cognitive decline than multiple lifetime generalized tonic clonic (GTC) seizures. The aim of the study was to investigate whether patients suffering from SE or from multiple lifetime GTC seizures have cognitive dysfunction, and if the disabilities differ between these groups.

Materials and methods: Patients suffering from SE were evaluated shortly after the clinical post-ictal phase and again after one year. Their follow-up results were compared to results from patients with ≥10 GTC seizures and a group of control subjects. Tests from Cambridge Neuropsychological Test Automated Battery (CANTAB) were used. Motor Screening Test (MOT) assessed motor speed, Delayed Matching to Sample (DMS) and Paired Associates Learning (PAL) assessed memory, and Stockings of Cambridge (SOC) assessed executive function. Estimated premorbid IQ and radiologically visible brain lesions were controlled for in adjusted results. Outcome measures were *z*-scores, the number of standard deviations a score deviates from the mean of a norm population. Negative *z*-scores indicate poor performance.

Results: After the clinical post-ictal phase, performances of SE patients were poor on all domains (n = 46). Mean *z*-scores with 95% confidence intervals were below zero for tests of psychomotor speed, executive thinking times and memory. Both SE patients at follow-up (n = 39) and patients with multiple GTC seizures (n = 24) performed poorer than controls (n = 20) on tests of memory. These group differences remained significant after covariate adjustments. SE patients at follow-up scored below patients with multiple GTC seizures on tests of psychomotor speed (mean difference −0.59, $P = 0.020$), but after adjusting for covariates this difference was no longer significant.

Conclusions: Our data do not allow a firm conclusion as to whether SE is a more pronounced risk factor for cognitive dysfunction than repeated generalized tonic clonic seizures. In both patient groups, memory and learning dysfunction remained significant after adjusting for estimated premorbid IQ and structural brain lesions.

1. Introduction

Poor cognitive function has been reported in patients after status epilepticus (SE) (Aminoff and Simon, 1980; Cooper et al., 2009; Dodrill, 1986, 2004). MRI studies in humans and in animals have revealed detrimental effects of SE in brain areas important for cognition. Neocortex, cerebellum, thalamus and, in particular, hippocampus are vulnerable to damage from SE (Cartagena et al., 2014; Kersante et al., 2013; Milligan et al., 2009; Suleymanova et al., 2016).

Cognitive sequelae after SE in adults have typically been described in retrospective studies without validated evaluation tools and pre-SE intellectual assessments (Dodrill and Wilensky, 1990). In children, follow-up studies using standardized scoring systems have demonstrated neurodevelopmental impairments after SE (Martinos et al., 2013; Weiss et al., 2016). The cognitive dysfunctions were not confined to children with neurologic abnormalities prior to SE, but extended to cases of febrile SE in previously healthy children (Martinos et al., 2013; Weiss et al., 2016). Separating the cognitive consequences of SE from

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pre-existing dysfunction related to underlying brain conditions is, however, challenging. Aetiology of both SE and epilepsy is important for the cognitive prognosis (Neligan and Shorvon, 2011).

Generalized tonic-clonic status epilepticus (GTC-SE) is considered to have a high risk of cognitive sequela (Dodrill, 1986; Gao et al., 2016; Lowenstein and Alldredge, 1993). Reports of cognitive dysfunction due to focal SE are divergent (Kaplan, 2000; Power et al., 2015; Shneker and Fountain, 2003; Young and Claassen, 2010). Outcome after focal SE seems even more dependent on seizure focus, duration and the underlying vulnerability of the patient's brain than outcome after GTC-SE (Dodrill, 2004; Helmstaedter, 2007; Shneker and Fountain, 2003).

One episode of SE has been described as more harmful to cognitive function than the accumulated load of one hundred GTC seizures (Dodrill, 1986). However, epilepsy patients with SE tend to have poorer intellectual function also preceding the SE (Adachi et al., 2005; Dodrill and Wilensky, 1990; Helmstaedter, 2007). Cognitive dysfunction in domains relying on the frontal and temporal lobes is frequent in patients with epilepsy regardless of SE including impaired memory, learning, attention and execution (Beyenburg et al., 2007; Hermann et al., 2008; Witt and Helmstaedter, 2012; Witt et al., 2014). This is most common for patients with GTC seizures and a high seizure load (Dodrill, 1986, 2002; Hermann et al., 2008). Experimental studies have demonstrated neuronal loss in the temporal lobe after repeated provoked GTC seizures, similar to damage seen after SE (Cavazos et al., 1994). The time lapse between consecutive seizures seems to be a determining factor for neuronal damage (Henshall and Meldrum, 2012; Mello and Covolan, 1996; Pitkanen and Sutula, 2002).

Concern about cognitive difficulties is reported by patients as one of the most negative effects of epilepsy (Fisher et al., 2000). Early detection of cognitive sequelae is relevant with regard to possible future rehabilitation.

The aim of this study was to investigate whether patients suffering from SE or from multiple GTC seizures have cognitive dysfunction. Moreover, we wanted to study if such disabilities differed between these two patient groups. To better delineate the cognitive effects of GTC seizures versus SE, factors reflecting on the premorbid cognitive function were included in the analyses.

2. Methods

2.1. Study design

This is an observational study of adult patients exposed to either SE or to more than 10 GTC seizures but never SE. They were treated according to established routines at our neurology department which serves as the only primary unit for 510.000 inhabitants of Hordaland County, Norway. A control group of patients hospitalized for non-brain disorders was also included.

GTC-SE was defined as ≥5 min of continuous seizure activity or two or more discrete seizures between which there was incomplete recovery of consciousness (Trinka et al., 2015). Duration over 10 min was required for focal SE. EEG confirmation was not a requirement for the SE diagnosis, but was a pre-requisite if the clinical signs were not certain. SE patients were included consecutively during admissions 2012–2015, the inclusion period lasting for 30 months. The semi-computerised Cambridge Neuropsychological Test Automated Battery (CANTAB) was used for cognitive assessments (Cambridge Cognition, 2014). All SE patients were tested twice (Fig. 1): shortly after the post-ictal phase (mean 5.2 days, range 1.5–18 days after SE), and at follow-up after 1 year (mean 12.8 months, range 12–18 months after the first test).

Patients with multiple GTC seizures were consecutively identified from all epilepsy patients visiting the outpatient clinic during 12 months (2015–2016). Those not meeting the immediate exclusion criteria were investigated for a lifetime load of ≥10 GTC seizures. Patients with such a seizure load were tested once with CANTAB, always more than 14 days after their last GTC seizure.

Follow-up results for SE patients were compared to results for the group with multiple GTC seizures and the control group (Fig. 1). One researcher (K.P.) administrated all CANTAB test sessions. The study was approved by the regional committee for medical and health research ethics (REK-2011/932). Patients and controls received both oral and written information about the study before signing their consent.

2.2. Inclusion and exclusion of patients and controls

Inclusion criteria for SE patients were: age ≥16 years; residing in Hordaland County; ability to give informed consent; ability to perform the first test within 3 weeks after the SE. Exclusion criteria were: mental retardation; severe hemiparesis; significant visual defects; acute anoxic brain damage; malignant tumours causing short life expectancy; progressive neurological illness; expected brain surgery in the next year; substance abuse with subsequent expected non-adherence to re-testing. Patients were only included once. A new SE during follow- up did not cause exclusion.

One hundred twenty-five SE patients met the inclusion criteria. Seven patients died during or shortly after SE, one declined participation and 71 patients were excluded due to the listed criteria (main reasons were mental retardation, dementia or short life expectancy). Mean age of excluded patients was 58.7 years (range 17–98, SD 23) and 52 (66%) were men. Forty-six patients were included (Fig. 1).

Inclusion criteria for patients with multiple GTC seizures were more than 10 GTC seizures during lifetime, but no SE episodes as identified both from thorough review of the patient journal and from interview. Inclusion and exclusion criteria were otherwise the same as for SE patients. Thirty eligible patients were identified and all agreed to participate, but five did not show for testing and one was excluded as there was suspicion of a seizure during the testing. Twenty-four patients were included (Fig. 1). One patient performed three out of four tests, refusing completion of the session when PAL remained.

Controls were in-patients in our department with no brain disease, and hospitalized for peripheral neuropathy, low back pain, post-polio syndrome, or muscle disease. Twenty-four controls were invited and 20 accepted inclusion (Fig. 1). The control group was group-level matched to the SE group for age, education and gender.

2.3. Cognitive testing

Four CANTAB sub-tests were conducted: Motor Screening test (MOT), Delayed Matching to Sample (DMS), Stockings of Cambridge (SOC) and Paired Associates Learning (PAL) (Torgersen et al., 2010). MOT measures cognitive speed and accuracy (Luciana and Nelson, 1998). DMS measures short term memory and decision making and is sensitive to damage in the medial temporal lobe, and to some extent the frontal lobe (Lamar et al., 2004; Luciana and Nelson, 1998). SOC is a test of planning and execution, sensitive to frontal lobe dysfunction (Sweeney et al., 2000). PAL is a test of visual memory and new learning. It is sensitive to medial temporal lobe dysfunction and to some extent to frontal lobe dysfunction (Owen et al., 1995; Sweeney et al., 2000). It is considered more specific for medial temporal lobe affection than DMS (Junkkila et al., 2012; Torgersen et al., 2012).

Test performances were measured by *z*-scores, i.e. the number of standard deviations the subject's score deviates from the mean of an age- and gender-matched British reference population (Cambridge Cognition, 2014). Negative *z*-scores indicate poor performance. The tests have been validated in various patient groups, including epilepsy patients (Junkkila et al., 2012; Lamar et al., 2004; Luciana and Nelson, 1998; Owen et al., 1995; Sweeney et al., 2000; Torgersen et al., 2012), are widely used and considered reliable and valid measures of cognitive function (Barnett et al., 2016).

The Norwegian version of the national adult reading test (NART) was applied to estimate the premorbid IQ (Nelson and Willlison, 1991). NART was conducted immediately before the CANTAB test, for SE