Neurophysiological examination of the association of Alzheimer's disease and epilepsy

Doctoral theses

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Introduction

Alzheimer's disease (AD) is the leading cause of cognitive decline affecting approximately 47 million people worldwide and this number is expected to triple by 2050. Despite tremendous research effort, we are still not able to significantly decrease the progression of cognitive deterioration. In the last decades, we paid more attention to the possible modifiable comorbid conditions including epilepsy as well. Neuropathologic studies revealed tau and amyloid deposits in both conditions and the common marker of hyperexcitability, the decrease of calbindin expression in the hippocampus is also a common feature. Studies investigating the animal models of AD frequently demonstrated generalized interictal epileptiform activity and epileptic seizures, in many cases without externally visible motor activity or changes in behavior. Human prevalence studies on the frequency of epileptic seizures demonstrated that AD patients have a higher risk to develop seizures; however, their results are ambiguous due to methodologic differences. In most of the studies, EEG was not applied and they did not analyze the semiological features and risk factors of epileptic seizures. Data focusing on the interictal activity is limited and the conclusions are conflicting. Some basic research investigations suggest that concomitant epileptic activity might accelerate the progression of AD; however, human studies are almost absent. Since we have numerous available antiepileptic drugs, recognition

of epilepsy in AD and understanding the pathologic background represent a promising future strategy.

Objectives

1. To examine the usefulness of 24-hour EEG in the diagnosis of AD associated epilepsy.

2. To identify the prevalence, semiology and risk factors of epileptic seizures in rigorously selected AD patients with a prospective and retrospective set-up.

3. To identify the prevalence and the major features of interictal epileptiform activity in rigorously selected AD patients with a prospective set-up.

4. To identify the sleep macrostructure of AD patients.

5. To identify the impact of interictal epileptiform activity on the progression of AD.

6. To examine the possibility of foramen ovale (FO) implantation and video-EEG monitoring in the clinical assessment of AD-related epilepsy.

Methods

1. To measure the diagnostic utility of 24-hour EEG, we selected 5 AD patients with correspondence to the actual criteria of NIA-AA, by whom the epilepsy was proved as well according to the 2010 guideline of ILAE.

We examined the patients using 34-channel 24-hour long Holter-EEG. Recordings were analyzed visually by two independent raters. The major aim was to identify the interictal epileptiform activity (IEA). We described the detection likelihood of IEA in the different sleep stages and periods of the day. Sleep stages were defined visually based on the modified Rechtschaffen-Kales criteria. To identify the optimal monitoring length, we divided the 24-hour long recording into 30min, 1-hour, 2-hour, 4-hour and 8-hour long epochs and analyzed the presence of IEA. If the epoch contained at least one IEA, we defined as positive epoch, while the IEA was absent, the epoch was negative. EEG sensitivity was described as the number of positive EEG epochs divided by the full number of epochs. For example, if the EEG was positive only in one 8-hour epoch from the three, sensitivity was 1/3 (33%). Association between the length of epoch and the sensitivity of EEG was measured with Pearson- correlation. We also analyzed the sensitivity of different long epochs in the different periods of the day including between 0-8, 8-16 and 16-24 o'clock. Sensitivity values were compared using ANOVA analysis with Bonferroni-posthoc testing.

2. We examined 57 AD patients to analyze the prevalence and features of epileptic seizures. To increase the sensitivity of our measurement, patients with seizure provoking factors were previously excluded. Following the NIA-AA diagnostic guideline of AD, all the patients underwent detailed general, neurologic and neuropsychologic examination and we excluded 15 patients with other dementia forms. Finally, we examined

42 AD patients with 24-hour Holter-EEG. Seizure prevalence was defined based on the the collected auto- and heteroanamnestic data and the previous medical records. Semiology was described following the 2014 ILAE classification of seizures. To analyze the seizure predilection factors, we divided the patients into two groups: AD patients without seizures or epileptiform discharges and AD patients with epileptic seizures. We compared the clinical and epidemiologic data of the two groups using t-tests and Chi-square tests. Furthermore, general linear model (GLM) was applied for posthoc comparison; where the examined parameter was the dependent value, the group category was the fixed value and all the other potential affecting parameters (where the difference was significant) were added as covariates to the model.

3. Based on the method described in the 2nd point, we described the prevalence of epileptiform discharges in 42 AD patients. We also measured the spatial and temporal distribution of epileptiform activity.

4. 24-hour EEG recordings were analyzed from the the viewpoint of sleep macrostructure in case of 30 AD patients without epileptic seizures. Sleep stages were rated based on the modified Rechtschaffen-Kales criteria. We described the main sleep parameters including sleep time, sleep efficacy, sleep latency and the relative lengths of sleep stages. We statistically compared the results to an age and gender controlled normal group of 30 participants. Furthermore, we analyzed the connection on sleep parameters and the severity of AD to estimate the

possibility of sleep recordings to follow the progression of AD or predict memory decline. Neuropsychologic values were compared to sleep parameters with the application of Pearson- correlation.

5. Patients from the 2nd point were recruited into a 2-year long follow-up period and were reexamined with the same neuropsychologic test battery in every year. Since previous results suggest that epileptiform activity might accelerate the progression of AD, we selected AD patients with subclinical epileptiform activity and compared their neuropsychologic value to AD patients without epileptic seizures or epileptiform discharges. We were able to conduct the measurements in 21 AD patients. Groups were compared with repeated measure general linear model. Since some factors could augment the progression of cognitive deterioration including the onset of cognitive symptoms (faster in early onset), severity of AD (progression speeds up in the last years of the disease), gender (more progressive by women), education level (higher education is associated to faster decline); these parameters were added as covariates to the model.

6. From the 57 dementia patients described in the second point, we selected patients without seizures but existing subclinical epileptiform activity based on 24-hour EEG recordings. Furthermore, we were searching for patients with prominent daily changes in the cognitive performance based on auto- and heteroanamnestic data. To measure the objectivity the suspect of alterations, Corsi-test was applied. If the patient corresponded to the

criteria of foramen ovale monitoring, we offered the possibility of electrode implantation. Electrode position was checked by cranial CT scan in the postoperative phase and patients were video-EEG monitored in the next 3 days. Frequent neuropsychologic examination (4-times/ day) with Corsi-test was also conducted in the monitoring period.

Results

1. We identified 255 IEA in the 120-hour EEG recording (5x24 hours) of 5 AD patients. Visual inspection showed prominent diurnal variability of IEA, most of them were visible during the night. IEA occurred in 58% between 0-8 o'clock, in 3% between 8-16 o'clock, while in 39% in the period of 16-24 o'clock. The most significant part (70%) of IEA was demonstrated in the non-REM period (9% in S1, 16% in S2 and 45% in S3 sleep), while 18% occurred in wakefulness and 12% in REM sleep. Differences were significant with ANOVA analysis ($p<0.001$). Sixty percent of 30-min long epochs were negative, while 93% of 8-hour longs were positive. Significant correlation was demonstrated between the length and the sensitivity of EEG (*r=+0.972; p: 0.005*). Lowest sensitivity was measured between 8 and 16 o'clock. Sensitivity of 30-min long EEG was 18-times higher in the period of 0-8 o'clock than between 8-16 o'clock (0.0375 vs. 0.7). Measuring the 1-hour long recordings, the difference was still 16.5-times higher. Since 1-hour EEG reached already the 0.8 sensitivity between 0-8 o'clock, 8-hour was required to reach the same values in the period between 8 and 16

o'clock. ANOVA analysis revealed significant differences between the 3 recording periods in all EEG length categories: 0.5-hour- F=65.368, degree of freedom (df)=2, p<0.001; 1-hour- F=69.123, df=2, p<0.001; 2-hour - F=39.25, df=2, p<0.001; 4-hour - F=36,408, df=2, p<0.001; 8-hour , F=12, df=2- p:0.008. Bonferroni posthoc analysis revealed significant differences by 0.5-hour and 1-hour EEG in all periods, while by 2-hour, 4-hour and 8-hour EEGs, sensitivity was significantly lower only between 8-16 o'clock and the 0-8 and 16-24 periods did not differ significantly.

2. From 57 patients with initial AD diagnosis, 15 patients (26%) did not fulfill the current criteria of AD and we excluded them from further prevalence analysis. Noticeably, 80% of non-AD dementia was reversible dementia form. We diagnosed epilepsy in 10 patients from 42 (24%). In 4 cases, patients developed two or more unprovoked seizures, while in 6 cases only one. In these cases, epilepsy diagnosis was based on the positive Holter-EEG revealing interictal epileptiform discharges. In 12 patients, EEG showed epileptiform potentials without epileptic seizures. The leftover 20 patients did not show epileptic seizures and the EEG was also negative. Seventy-two percent of the seizures were temporal complex partial seizures, while we have seen grand mal seizures only in 11% of the patients. Eighty percent of epileptic patients also showed interictal pattern on the 24-hour long EEG. Seizures were not followed any external motor signs in 55%. To analyze the predilection factors of seizures in AD, we compared the epidemiologic and clinical data of AD patients with

epileptic seizures to the patient group without seizures or epileptiform discharges. General linear model revealed significant differences between the two groups in the onset of dementia, in duration of cognitive decline, in education years and in the scores of Addenbrooke Cognitive Examination. Earlier onset of cognitive deterioration, longer duration of dementia, higher severity and increased education represented risk factors for epileptic seizures in AD.

3. We have seen epileptiform discharges accompanied by epileptic seizures in 19% of 42 AD patients and without epileptic seizures in 29%. Epileptiform activity was visible exclusively on the left side in 65%, on the right side in 20%, while it was demonstrated bilaterally in 10% and centrally in 5%. Temporal electrodes were the most frequent localization with 60%, frontal electrodes represented 20% of discharges and they occurred in 15% frontotemporally.

4. AD and control group showed significant differences in the total sleep time, in the latency of sleep, in the efficacy of sleep and in the relative length of non-REM and REM sleep stages. They did not differ prominently from the viewpoint of REM latency and the number of REM phases. Total sleep time and sleep efficacy were reduced in AD, while sleep latency was elongated. The relative length of S1 has increased, while the duration of S2, S3 and REM sleep has diminished. The relative length of REM sleep and S1 sleep had a high correlation to the severity of AD, while the REM latency was dependent marginally but statistically significantly.

The duration of REM decreases, while the length of S1 and the latency of REM increase with the progression of cognitive decline.

5. We analyzed the neuropsychological results from a 3-year long follow-up period of 21 AD patients (8 with epileptiform discharges and without seizures and 13 patients with negative EEG and clinical anamnesis regarding seizures). We compared the progression rate of the two groups concluded from Addenbrooke Cognitive Examination score using repeated measure general linear model analysis, where the clinical and demographic parameters were added as covariates to the model. In the corrected model, significant differences were revealed in the progression rate (average square: 62.98, degree of freedom: 6, p-value: <0.001). Patients with epileptiform activity showed 2-times faster progression, which could be explainable with the effect of epilepsy regarding the statistic model.

6. We selected 3 AD patients to the rigorous foramen ovale (FO) protocol. Since we know that patients with non-AD dementia forms might also have a chance to present epileptic seizures, we also included 2 patients with frontotemporal dementia. Until now, we implanted FO and conducted FO video-EEG monitoring in 1 patient. Since only one American research group investigates dementia patients with FO besides our group and to our knowledge, we are the first in Europe monitoring dementia patients with FO; we demonstrate the details and conclusions of the first patient in a case presentation. The implantation and the monitoring was

eventless, surgical complication did not occur; the patient was cooperating during the entire period and did not present any complaints. EEG showed bilateral, independent spike activity in the FO electrodes, predominantly on the right side with 30/day occurrence, while it had lower frequency on the left side, with an average 4/day appearance. Spikes were visible mostly in superficial non-REM sleep. We also revealed 11-12 Hz beta series with or without spikes interposed by 5Hz theta discharges. All of these graphoelements showed right side predominance and none of them propagated to the scalp electrodes. Furthermore, we also demonstrated 1-15 sec long beta spindles with 15-16Hz frequency in wakefulness, frequently associated to cognitive tasks, blinking or eye movements.

Conclusions

1. Rigorous observance of the clinical assessment protocol of neurocognitive disorders is essential in accurate exclusion of reversible dementia forms.

2. Inclusion of EEG in the assessment of dementia might be considered.

3. 24-hour Holter-EEG is a highly sensitive, trustable and easily applicable diagnostic utility in the examination of dementia-associated epilepsy.

4. Observation of sleep EEG is essential in the accurate investigation of dementia-related epileptic activity.

5. The prevalence of epileptic seizures in AD is high affecting the quarter of patients.

6. The most frequent type of seizures in AD is the complex partial seizures with temporal lobe origin and without externally visible motor activity.

7. The main risk factors of epileptic seizures in AD are the early onset of cognitive deterioration, longer duration of dementia, higher education level and more severe disease stage.

8. Interictal epileptiform activity is frequent in AD affecting half of the patients.

9. Interictal activity is visible mostly in the frontal and temporal areas with left side predominance, with strong sleep relation.

10. Interictal epileptiform activity might accelerate the progression of cognitive decline.

11. Sleep disturbances are common in AD, sleep macrostructure shows specific redistribution might playing a role in the cognitive symptoms as well.

12. Duration of REM sleep is a good indicator of the severity of AD.

13. Epileptic seizures and epileptic activity could be hidden on the scalp electrodes in dementia.

14. Foramen ovale implantation is easily administrable in elderly dementia patients and video-EEG monitoring might reveal valuable clinical and research data.

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