Epileptic activity in patients with Alzheimer's disease and Lewy body dementia

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Background

Patients with Alzheimer's disease have an increased prevalence of epileptic seizures between 1.5 and 64% (1-6). The large discrepancy between studies is partly due to differences in methods, including whether electroencephalography (EEG) has been used (1, 3, 4). EEG records the electrical activity of the brain including whether there is evidence of seizure activity (so-called paroxysmal activity). In patients with AD, EEG is helpful since the patients may have difficulty reporting seizures, symptoms of seizures can be difficult to distinguish from the symptoms of AD and a high incidence of subclinical epileptic activity (6). Conventionally, with regards to EEG, only short EEG recordings are performed (<30 min), which may not be sensitive enough due to the short recording time. With prolonged EEG recordings (6), so-called long-term monitoring for up to 24 hours, epileptic activity has been found in up to 42.2% of patients, which is higher than for short recordings. However, this method may be inconvenient for the patient as it requires hospitalization. Therefore, in the current study we will use a newly developed type of EEG device that can be placed in the ear (ear-EEG). This technique makes it possible to record EEG while the patient is in their own home over several days without significant inconvenience for the patient. The method has several advantages. First, it will be possible to do longer recordings than before, potentially over several days, and thus gain better knowledge of occurrence and frequency of epileptic activity. Second, it will be significantly less invasive for the patients than long-term monitoring during hospitalization. This equipment has not previously been used in patients with dementia but has been used in patients with epilepsy with good detection rate of epileptic activity (7). The study that investigated patients with Alzheimer's disease has also shown that 10.5% of healthy control subjects have subclinical epileptic activity [6]. Furthermore, it is known that there is an increased risk that healthy elderly will have paroxystic activity measured by EEG. Therefore, it is also necessary to examine healthy control subjects with

ear EEG to investigate whether the incidence of subclinical epileptic activity in patients with Alzheimer's disease and Lewy body dementia is increased compared to healthy control subjects.

Furthermore, studies have found a possible link between epileptic seizures the evolution of Alzheimer's pathology (1, 8). Amyloid is believed to be involved in the processes leading to Alzheimer's disease, and transgenic mice that accumulate amyloid in the brain have epileptic activity in the hippocampus with no evidence of epileptic seizures (9). In addition, a study has shown that epileptic activity leads to decreased oxygen in the brain, leading to further deposition of amyloid. One randomized clinical trial has shown that patients with "mild cognitive impairment", which are patients who are more likely to progress to Alzheimer's disease, showed improvement in cognitive functions after 2 weeks of treatment with Levetiracetam, which is a drug used to treat epilepsy (10). Other studies have shown an increased regional blood flow (rCBF) (11, 12) in the hippocampus in patients with Alzheimer's disease, but the studies have been done on smaller groups of patients, and therefore, validation is lacking in larger cohorts of patients. In addition, the reason for the increased blood flow has not been clarified, but it could be due epileptic activity.

Patients with dementia may experience fluctuations in their cognitive functions (13), which is especially pronounced in patients with Lewy body dementia compared to patients with Alzheimer's dementia (14, 15). There are no systematic assessments of prevalence of seizures in patients with Lewy body dementia. The reported fluctuations in cognitive function could possibly be caused by epileptic seizures. We will therefore investigate whether there is epileptic activity in patients with Lewy body dementia.

Aim

The overall aim of the study is to investigate whether patients with Alzheimer's disease and patients with Lewy body dementia have a higher incidence of subclinical epilepsy as compared with healthy elderly controls and whether subclinical epilepsy is correlated with blood flow in the brain as measured with MRI.

Objective 1: Investigate whether it is possible to use ear EEG for long-term monitoring of patients with Alzheimer's disease (feasibility and compliance)

Hypothesis: Ear-EEG monitoring is possible in patients with Alzheimer's disease.

Objective 2: Investigate the incidence of paroxysmal activity in patients with Alzheimer's disease and Lewy Body dementia as measured by ear EEG as compared to healthy elderly controls

The study is considered exploratory as recordings with ear EEG and also long-term EEG recordings have never carried out in this patient group before.

Objective 3: Investigate the regional blood flow (rCBF) measured by MRI in the hippocampus in patients with Alzheimer's disease.

Hypothesis: Patients with Alzheimer's disease will have an increased rCBF in the hippocampus compared to healthy controls.

Objective 4: Investigate the correlation between increased blood flow in the hippocampus and paroxysmal activity measured by the ear EEG.

Hypothesis: Increased rCBF in the hippocampus in patients with Alzheimer's disease is associated with paroxysmal activity measured by ear EEG.

Study Design

The project consists of two sub-studies:

1) Feasibility study (Aim 1)

2) The main study (Aim 2-4)

Both sub-studies are longitudinal studies with 3 periods of 2 days of ear-EEG recordings in the patients' homes over 6 months. The healthy controls will undergo ear-EEG recording once. All participants must have had an MRI of the brain at the beginning of the study.

Feasibility study

The first part of the project is the feasibility study in which we will recruit 10 patients with Alzheimer's disease. First visit is a screening visit where patients give informed consent (patients have also been informed on a prior visit) after which in- and exclusion criteria will be assessed. Subsequently, patients will undergo MRI of the brain on a subsequent visit. At the second visit, a conventional EEG (30 mins) at the same time as ear EEG recording will be carried out. At this visit patients will also be examined by a physician, including physical and neurological examination as well as cognitive tests, questionnaires for caregivers relating to activities of daily living and

neuropsychiatric symptoms. Patients will also undergo a blood test, and the blood test will be stored in Danish Dementia Biobank.

Afterwards, both the patient and the caregiver will receive information about epilepsy and how to detect it including instruction on how to use an epilepsy diary. In addition, they will receive training in how to use the ear-EEG, which patients have to wear for 2 days, while the caregiver is asked to take note on any symptoms of epileptic seizures they may observe.

A priori criteria for whether ear-EEG recordings are suitable in patients with AD (feasibility study) are:

> 80% of the pilot study participants can wear the ear-EEG at least 24 hours in 2 days

> 50% of the participants have recorded at least 5 hours of sleep with the ear-EEG.

The main study

In the main study, we will include an additional 40 patients with Alzheimer's disease and 50 healthy control subjects as well as 20 patients with Lewy body dementia. The patients with Alzheimer's disease and Lewy body dementia will undergo the same program as for the pilot project but the total time of ear-EEG recording may be extended to up to five days.

The healthy subjects will first be examined by a physician including cognitive tests and a questionnaire on everyday activity of daily living from any relatives will be performed. On

subsequent visits, participants will undergo an MRI scan as well as a conventional EEG examination and wear the ear-EEG device for a total of 48 hours. The inclusion of healthy subjects is done in order to compare ear-EEG, conventional EEG and MRI scans in patients with AD and DLB with healthy elderly persons.

Statistical analysis plan

The study is considered exploratory since recordings with ear EEG have never been performed and only one other study has looked at long-term EEG recordings.

For the feasibility study, we plan to review the EEGs together with the feedback we receive from the participants to investigate whether they were able to wear the ear-EEG at least 24 hours in 2 days, and that over 50% were able to record at least 5 hours of sleep.

If we continue with the main study, we will investigate how frequent we observed paroxysmal activity as measured on the ear-EEG in patients with Alzheimer's disease and Lewy body dementia as compared to healthy elderly controls. Furthermore, we will compare the frequency of paroxysmal activity and CBF in the hippocampus as measured with ASL-MRI.

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