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Electroencephalogram findings in patients with posterior cortical atrophy

E.D. Goldstein [a,*], N. Ertekin-Taner [a], A. Stephens [a], M.M. Carrasquillo [b], B. Boeve [c], W.O. Tatum [a,b], A.M. Feyissa [a]

[a] Department of Neurology, Mayo Clinic Florida, Jacksonville, FL, United States
[b] Department of Neuroscience, Mayo Clinic Florida, Jacksonville, FL, United States
[c] Department of Neurology, Mayo Clinic, Rochester, MN, United States

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ABSTRACT

Aim of the study: The aim of this study is to evaluate standard scalp EEG findings in patients with posterior cortical atrophy (PCA), an atypical variant of Alzheimer's disease (AD).
Clinical rationale: PCA is a topographically selective variant of AD. Patients with typical AD have an increased likelihood of seizures, which may negatively impact overall functional performance and cognition. It is currently unknown what the typical EEG findings are for patients with PCA.
Materials and methods: A retrospective chart review was performed on patients identified either with autopsy confirmed ($n = 13$) or clinically ($n = 126$) as PCA.
Results: 139 patients were included though only 23 (16.5%) had undergone EEG recording. The EEG was normal in 6 (26%), while an abnormal EEG was present in 17 (74%). Interictal epileptic discharges (IEDs) were found in 2 of the 23 patients (9%).
Conclusions: This study of limited sample size suggests that there may be an increased predilection to find IEDs within PCA when compared to typical AD. Larger cohorts are required to determine frequency of abnormal EEGs in PCA, roles of AEDs in therapy, and in the selection of preferred AED.
Clinical implications: Patients with PCA would potentially benefit from an EEG for assessment of IEDs which may provide the clinician with a therapeutic opportunity.

1. Introduction

Alzheimer's disease (AD) is a neurodegenerative condition associated with an increased predisposition for seizures, particularly within early onset populations [1,2]. Seizures may be the presenting symptom of AD with several seizure semiologies reported [3–6]. Patients with AD have an overall 6-fold increased risk of first time unprovoked seizure when compared to healthy similarly-aged patients, and an estimated prevalence of 10–22% [7–9]. Posterior cortical atrophy (PCA) is a syndrome characterized by predominant visual deficits not

* *Corresponding author at*: 4500 San Pablo Rd, Jacksonville, FL 32224, United States.
E-mail address: Goldstein.Eric@Mayo.edu (E.D. Goldstein).
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explainable by ocular disease and with relatively preserved memory and insight early in the disease [10,11]. The most common neuropathologic etiology of PCA is AD with a disproportionately greater burden of pathology in the posterior cortical regions in PCA patients compared with typical forms of AD [10,12]. It is thought that 5% of those with AD likely have PCA [13–15], although the actual prevalence of PCA may be higher due to the potential for under-diagnosis.

2. Clinical rationale for the study

The routine use of scalp electroencephalography (EEG) within memory clinics is not standardized, though there is evidence that the presence of epileptic discharges may contribute further to cognitive decline [16]. A previous study has demonstrated that of those presenting to a memory disorders clinic without known seizure disorder, 2% are noted to have interictal epileptic discharges (IEDs) on scalp EEG, primarily of temporal lobe origin [17]. The aim of this study is to describe standard scalp EEG findings in patients with autopsy confirmed or clinically diagnosed PCA patients.

3. Materials and methods

3.1. *Study protocol and patients*

A retrospective chart review was performed on patients identified either with a neuropathologic diagnosis of posterior AD ($n = 13$) or diagnosed clinically ($n = 126$) as PCA following Institutional Review Board approval. Ethical approval was not necessary for preparation of this article. The diagnostic criteria for PCA have been previously published [10,15]. Those without EEG during evaluation and pre-existing seizure disorder were excluded from the study. Clinical data was obtained from January 1990 through December 2017, including demographic information, subjective onset of symptoms, scalp EEG descriptions as read by electroencephalographers and antiepileptic drug (AED) usage. Fig. 1 shows the study design.

3.2. *Electroencephalography*

Scalp EEGs were performed using a digital 21-channel recording with the International 10–20 system for electrode placement. Study duration varied between 30 and 80 min, including activating procedures. All recordings were reviewed using referential and bipolar montages. Each EEG was interpreted by a board-certified clinical neurophysiologist. IEDs were defined according to the International Federation of Clinical Neurophysiology [18].

4. Results

4.1. *Patients*

A total of 139 patients with PCA were identified. Of these, only 23 (16.5%) had underwent EEG recording. One patient was excluded due to pre-existing seizure disorder. Mean age of subjective symptom onset was 58 years, with scalp EEG obtained on average 2 years following onset. Eleven patients died in the years following completion of their EEG, with a mean age of death of 76 years old. A summary of patients' characteristics is provided in Table 1.

4.2. *Electroencephalography*

The EEG was normal in 6 of the 23 patients (26%), while the majority of studied patients had an abnormal EEG (17/23, 74%). Sleep EEG was achieved in 19 of 23 patients (83%). Of the 17 subjects with abnormal EEGs, 13 (74%) had varying degrees of generalized slowing, while 4 (26%) had focal slowing. Patients with focal slowing were without hemispheric preference and

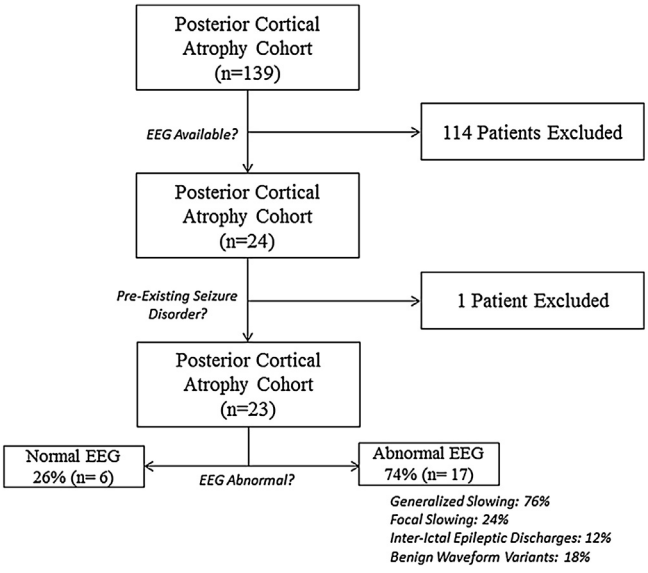

Fig. 1 – Study design.

Table 1 – Clinical characteristics of the study subjects.

	All ($n = 23$)	Abnormal EEG ($n = 17$)	Normal EEG ($n = 6$)
Male gender (%)	15 (65)	9 (52)	3 (50)
White (%)	22 (95)	17 (100)	1 (17)
Age at EEG, years	64 ± 7.8	66 ± 8.9	60 ± 4
Subjective onset age, years	59 ± 8.4	60 ± 8.9	58 ± 4
Onset to EEG, years	5 ± 3.6	6 ± 3.7	2 ± 2
Age at death, mean (%)	76, 49%	77, 53%	71, 33%
EEG to death, years	6.9	7	6.5
Slowing of background rhythm			
Generalized (%)	13 (57)	13 (74)	
Focal (%)	4 (17)	4 (26)	
Epileptic discharges	2 (9)	2 (12)	
Sleep/Drowsiness Achieved	19 (83)	15 (88)	2 (33)
Benign variants	3 (13)	3 (18)	0 (0)

primarily of temporal origin with similar age of subjective onset and onset to EEG times. Of the 6 patients with normal EEGs, only 1 was Caucasian (17%). Three patients had benign EEG variants (13%).

IEDs were found in two patients (2/23, 9%). The first patient with IEDs, a 59 year-old Caucasian woman, displayed both generalized and left temporal discharges. The second, a 61 year-old Caucasian woman, displayed independent bitemporal discharges and was subsequently admitted to the Epilepsy Monitoring Unit. Prolonged video-monitored EEG over 5 days for the second patient revealed intermittent though clustered discharges of 4–5 Hz rhythmic theta activity of 35–78 s in duration emanating from the T7 derivation with sporadic spread to the P7 and O1/Oz derivations. During these seizure discharges, the patient would display inattentiveness and have difficulty operating her phone, though remained aware and communicative. Both patients with IEDs were clinically diagnosed with PCA. Importantly, neither patient during the time of the EEG recording was taking medications that may influence the EEG, including memantine [19].

4.3. *Neuroimaging*

Magnetic resonance imaging (MRI) and positron emission tomography (PET) of the brain was performed in both patients with IEDs. The first described patient had a normal PET and subtle biparietal atrophy on MRI, whereas the second patient had biparietal hypometabolism on PET imaging and left hippocampal sclerosis on MRI. Of the total cohort of 23 patients, 4 had focal regions of encephalomalacia (1 frontal, 2 occipital, 1 temporal). One of those with focal encephalomalacia had a normal EEG.

4.4. *Antiepileptic drugs*

Of the 17 patients with an abnormal EEG, 3 were started on AEDs following an initial EEG. The first patient with IEDs was started on phenytoin 300 mg daily. The second patient with IEDs was started on lamotrigine 150 mg twice daily with levetiracetam 1000 mg twice daily resulting in improvements in the IEDs during the Epilepsy Monitoring United admission along with subjective reports of memory improvement. A third patient was prescribed lamotrigine 100 mg twice daily for reasons which were retrospectively unclear.

5. Discussion

In our cohort of 23 clinically diagnosed or autopsy-confirmed patients with PCA who underwent routine EEG monitoring, we found that 17 of the 23 (74%) had an abnormal EEG and 2 of the 23 (9%) had IEDs. The true incidence, prevalence and impact of epileptic findings on EEG for neurodegenerative conditions are unknown, although transient non-convulsive seizures or epileptic amnesia would be expected to worsen cognitive and other higher order functions [3,7]. Though our sample size is small, our study raises a possibility that patients with PCA may have a higher frequency of epileptic findings when compared to prior studies of patients with typical AD [17]. Additionally, serial EEGs in the normal cohort may be of benefit because as the underlying neurodegenerative process continues IEDs may emerge [6]. If scalp EEG is unrevealing and a strong clinical suspicion for dementia related epilepsy remains, alternative electrode placement (e.g. foramen ovale) may be of use to identify undetectable epileptic discharges due to depth from the scalp [20]. Given the correlation with abnormal EEG findings and worsened cognitive status, a more liberal use of scalp EEGs in patients with dementia may be of benefit.

The second patient with IEDs, who ultimately underwent prolonged video-monitored EEG, had clustered focal aware seizures with cognitive features. Her neuroimaging and clinical examination was suggestive of PCA though her brain MRI revealed left hippocampal sclerosis. Her seizure focus appeared to be of posterior temporal onset with a localized field of spread. It is well described that hippocampal sclerosis may coexist with other neurodegenerative conditions, namely AD, or may originate from a ''dual pathology'' as a result of uncontrolled extra-temporal lobe epileptic seizures, of which this patient may not have been aware [21,22].

AED usage in AD is sporadic and without consensus for drug choice, though there is evidence to suggest that levetiracetam and lamotrigine may provide the greatest benefit in terms of optimal tolerability, safety, and pharmacokinetic balance [23]. We observed that a variety of AEDs were used including phenytoin, levetiracetam, and lamotrigine. Although this study was not designed to examine the effect of AEDs on treatment of IEDs, in one patient with bitemporal independent IEDs and focal aware seizures with cognitive

features we observed that there was a subjective improvement in cognitive functioning. Data is available revealing a negative correlation between burden of IED and global cognitive function, which is in support of our patient's subjective cognitive improvement [24]. Though the data is not conclusive, we speculate whether early implementation of AEDs in this select subset of AD patients may provide benefit in short-term morbidity.

Our study has several limitations. Due to the restricted sample size both with IEDs and within the overall referral rate of PCA patients with EEG evaluation, inferences regarding the true prevalence of IEDs for patients with PCA cannot be made. Referral bias is also of concern as those with EEGs were typically referred with some level of concern for seizures. Additionally, the lack of prolonged video-monitored EEG may have inadvertently underestimated the prevalence of IEDs in our cohort as the majority of those studied solely had undergone a routine outpatient EEG, which is less sensitive than prolonged (48–72 h) EEG recordings.

6. Clinical implications/future directions

Our findings suggest that those patients with PCA may have a higher prevalence of IEDs which may provide a therapeutic opportunity for the treating physician. Much is not known regarding the benefit, optimal therapy, and overall clinical implications of treating patients with PCA with AEDs. Larger prospective studies are required to further evaluate the impact of IEDs on cognitive function, treatment response, and preferential AED selection in patients with PCA specifically. Further studies with quantitative EEG (qEEG) may aid in understanding IED localization, frequency, and response to treatment as well as possibly differentiating between other subsets of neurodegeneration [25,26]. These studies may well clarify the correlation of EEG findings to clinical phenotypes, the role of AEDs and implementation of a guideline-directed therapeutic algorithm in this patient population.

Contributions

All authors have materially participated in the research and/or article preparation.

Conflict of interest

None declared.

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