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Brief Communication

Balance and reaction time do not rapidly improve off antiseizure drugs☆

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ABSTRACT

Objective: People with epilepsy (PWE) exercise less than the general population and describe a lower level of fitness. Exercise improves comorbidities associated with epilepsy and may help seizure control. We aimed to record balance and reaction time in patients undergoing antiseizure drug (ASD) taper in the epilepsy monitoring unit (EMU) to determine if there is a reversible, dose-dependent effect of these medications.
Methods: We tested 21 patients and 21 controls using a Wii Balance Board (WBB) and online reaction time test. The patients were recruited during an EMU stay and were tested before and after medication taper. Drug levels were also checked. Sway from center of pressure (COP) and speed of sway were tested with eyes open on two legs, eyes closed on two legs, and eyes open on one leg. Reaction time was tested.
Results: Compared with controls, patients on ASDs had more sway from COP (with eyes open on two legs: $p = 0.0022$ in the anterior–posterior axis and $p = 0.022$ in the medial–lateral axis using linear regression) and worse reaction time ($p < 0.001$ using linear regression, adjusted for age and gender). There was no difference in reaction time or sway from COP between trials 1 and 2, before and after stopping ASDs ($p = 0.2$ using a paired t test for reaction time and $p = 0.08$ using a paired t test for speed of sway with eyes closed). There was no relationship between time since last seizure or duration of seizures and balance or reaction time.
Discussion: Balance and reaction time in patients on ASD is impaired compared with controls. There is no immediate improvement in these measures following ASD withdrawal. This difference may result from vestibular or cerebellar effects. More research is needed to determine the individual effects of particular medications on balance and reaction time.

1. Introduction

People with epilepsy (PWE) exercise less than the general population and describe a lower level of fitness than age-matched controls [1,2]. They also describe higher rates of depression, cognitive dysfunction, and cardiovascular disease [3–5]. The International League Against Epilepsy (ILAE) provided a recent guideline stating that exercise may improve seizure control and may also have other health and psychosocial benefits [6]. Exercise is known to improve depression in the general population as well as lowering risk for cardiovascular disease [7,8]. In PWE, exercise is hypothesized to counteract cognitive impairment, which is likely multifactorial related to seizures, interictal discharges, antiseizure drugs (ASDs), and comorbid mood issues [9].

One barrier to exercise may be the effects of ASDs. People with epilepsy have impaired balance function compared with controls even without subjective balance complaints [10]. Some studies have found a correlation between duration of ASD use and progressive balance deterioration [11–13]. Camara-Lemarroy et al. found balance impairment in PWE but no correlation with ASD use or seizure control [14]. There is documented slowing of mentation and processing speed while on ASDs [15]. One recent study showed that stopping ASDs improved performance on a cognitive panel that included reaction time testing [16]. This was performed seven months after stopping medication. To our knowledge, no studies have evaluated the immediate effects of stopping ASDs on balance and reaction time.

Previous studies of balance have used subjective tests, traditional posturography, and observation-guided examination techniques to assess balance in PWE. The Wii balance board™ (WBB, Nintendo 2007) is accessible and inexpensive compared with traditional posturography testing. It has been validated and used in neurology-specific populations, though it has not been used in the epilepsy monitoring unit (EMU) setting [17–19]. We used this novel device to measure sway from center of pressure (COP) in lieu of traditional posturography, which is logistically difficult in the inpatient setting.

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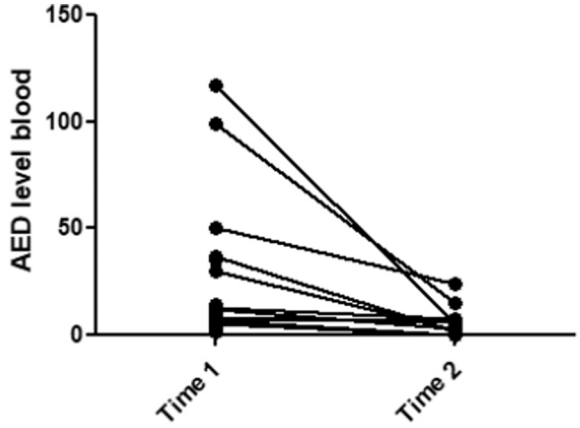

Fig. 1. Blood ASD levels at the first and second trials.

We recorded balance and reaction time in patients undergoing ASD taper in the EMU to determine if there is a reversible, dose-dependent effect of ASDs on balance and reaction time.

2. Materials and methods

We recruited patients in the EMU on ASDs and who were likely to undergo taper during admission after obtaining permission from the institutional review board. The inclusion criteria were the following: age 18–55 years and on a stable dose of ASDs defined as no medication changes in the last 30 days. We excluded patients with neuropathy, weight of more than 300 lbs, prior brain surgery, or an inability to stand for 30 s. We also recruited age-matched healthy controls taking no medications to serve as comparison using fliers placed around our hospital. Written informed consent was obtained. We recorded diagnosis, duration of seizures or spells, ASDs taken, age, gender, and time since most recent event.

Patients underwent two trials;: trial 1 while on ASDs and trial 2 was two to three days after ASDs were withheld. Blood ASD levels were checked during each trial in all patients and were significantly reduced during trial 2 in every participant (Fig. 1). A WBB measured sway from COP on two feet with eyes open, two feet with eyes closed, and one foot with eyes open. Sway from COP is the degree of deviation from neutral stance as calculated by pressure sensors on the WBB. Axis of anterior to posterior sway, medial to lateral sway, and speed of sway were measured. This was done using internet-based software connected to the WBB via Bluetooth (Neurorehabilitation & Brain Research Group). Two trials of each were performed and then averaged. Reaction times were determined using a computer-based test (Human Benchmark), and five trials were averaged for each participant. Reaction time is the amount of time it takes for the participant to click a mouse after a computer screen prompt.

Controls underwent one trial of the COP and reaction time testing as described above. Prior to testing institutional review board approval was obtained.

Table 1
Demographics.

Participants	Controls = 21	Patients = 21 2 did not complete T2	
Trials	21	42	
Male	10 (48%)	8 (38%)	p value 0.53
Female	11 (52%)	13 (62%)	
Age	32.9 ± 6.94	34.38 ± 11.2	p value 0.62
Diagnosis			
Focal epilepsy		8 (38%)	
Generalized epilepsy		1 (5%)	
Nonepileptic seizures		4 (19%)	
No diagnosis		8 (38%)	

Table 2
Antiseizure drug types and number taken by participants.

Antiseizure drug	Number of patients	Antiseizure drug number	Number of patients
Carbamazepine	3	One	11 (52%)
Lacosamide	4	Two	9 (43%)
Oxcarbazepine	3	Three	1 (5%)
Lamotrigine	6		
Gabapentin	1		
Levetiracetam	3		
Topiramate	5		
Valproate	5		
Zonisamide	2		

3. Results

Twenty-one patients and 21 controls were tested. See Table 1 for participation details and demographics. Two patients left the hospital against medical advice prior to the second trial. The control group and patient group were similar in age and gender distribution. All patients were on between one and three ASDs during trial 1. Table 2 depicts the breakdown of which medications were taken and the number of patients on each. A majority (52%) of patients were on monotherapy. The remainder were on two or three ASDs. No patients were found to have both epileptic and nonepileptic seizures.

Compared with controls, patients on ASDs had more sway from COP with eyes open on two legs during trial 1 ($p = 0.0022$ in the anterior–posterior axis, $p = 0.022$ in the medial–lateral axis using linear regression) and with eyes closed ($p = 0.0015$ in the anterior–posterior axis and 0.00033 in the medial–lateral axis). There was no difference in COP sway on one leg between controls and patients during trial 1. Speed of sway was also greater in patients during trial 1 compared with the control group (eyes open: $p = 0.0088$ using linear regression, eyes closed: $p = 1.08 \times 10^{-5}$). Reaction time was significantly worse in patients on ASDs (trial 1 data, $p = 1.75 \times 10^{-6}$ using linear regression, adjusted for age and gender). There was no difference in reaction time in patients between trials 1 and 2, before and after stopping ASDs (Fig. 2; $p = 0.20$). There was no difference in sway from COP or speed of sway between trials 1 and 2. There was no relationship between time since last seizure or duration of seizures and reaction time or balance.

No adverse events occurred during the study.

4. Discussion

Previous work suggested that mobility and balance are altered in PWE, and this may be associated with ASD use. A meta-analysis on second generation ASDs demonstrated that lamotrigine, oxcarbazepine, pregabalin, tiagabine, topiramate, and zonisamide all increased the

Fig. 2. Paired t test of trial 1 versus 2 reveals no difference in reaction time ($p = 0.20$).

risk of ataxia and imbalance by patient report, but levetiracetam and gabapentin did not [20]. With the recent recommendations from the ILAE and increasing evidence that exercise is beneficial for many epilepsy comorbidities, it is imperative to define the effects of various ASDs on exercise capabilities. The role of balance in different forms of exercise may vary.

Our study tested the immediate effects of ASD withdrawal on balance and reaction time. There was no change in sway from COP or reaction time immediately following ASD withdrawal. Balance and reaction time were worse in patients taking ASDs compared with the general population, which confirms previous findings [11–14]. No definitive conclusions could be made about individual ASDs because of the small sample size, but some ASDs are likely worse than others. A previous study by Fife et al. compared lamotrigine, gabapentin, and carbamazepine use in older adults and found that carbamazepine had a more detrimental effect on balance than lamotrigine or gabapentin [21].

It is not clear whether the difference in balance and reaction time in PWE is due to medication effect, deconditioning, the epilepsy itself, or a combination of these factors. Our study contained a mixed population of PWE and patients without nonepileptic seizure so the results suggest that the effect is related to ASDs. This effect is not rapidly reversible and may be due to subtle toxic effects to the vestibular or peripheral nervous system, which may take longer to reverse or might be irreversible. Previous work evaluated vestibular function in patients on ASDs using videonystagmography and found that a majority of patients had subjective dizziness and sense of imbalance. Approximately half had objective evidence of central and/or peripheral vestibular dysfunction [22]. Phenytoin and carbamazepine have the most profound effects due to cerebellar granule cell destruction [23]. It is also possible that there is a more long-term detrimental effect on balance networks.

5. Conclusion

We conclude that the detrimental effects of ASDs on balance and reaction time are not immediately reversible. It remains uncertain whether these functions improve with time or are permanent in nature, although duration of epilepsy had no correlation with sway from COP or reaction time. More research is needed to determine the effects of individual medications.

Declaration of Competing Interest

None.

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