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Epilepsy syndrome-associated balance dysfunction assessed by static posturography

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ABSTRACT

Purpose: To compare subclinical balance dysfunction in patients with various epilepsy syndromes with apparently healthy subjects.
Methods: Twenty-seven patients with localization-related epilepsy (LRE), 19 with primary generalized epilepsy (PGE), who had no subjective complaints of impaired balance and no abnormal neurologic findings on examination, and 22 apparently healthy subjects, underwent static posturography using the Posture Scale Analyzer (PSA) system.
Results: Sway index was higher in patients compared to healthy subjects in all tests, significant for single leg stance ($p = 0.005$). Patients with PGE had a higher sway index compared to patients with LRE in six of the tests, also significant for single leg stance ($p = 0.027$). This difference was not affected by the type of AED treatment or disease duration.
Conclusion: Posturography can improve balance function assessment in patients with epilepsy, demonstrate subclinical impairment in seemingly asymptomatic patients, and further characterize balance deficits in different epilepsy syndromes.

1. Introduction

Postural control is a complex neural function, composed of the integrated function of sensory input, motor output, and modulation by cerebellar and cognitive effects.[1] Lack of coordination and postural imbalance are common complaints in patients with epilepsy (PWE), associated with motor limitations, injuries secondary to seizures, and side effects of AEDs.[2–4] Since the neurological examination is often unremarkable and fails to detect balance dysfunction, other tests may be required to qualitatively and quantitatively assess balance dysfunction in these patients.

In PWE, subclinically impaired balance function was found to be related mainly to treatment. Polytherapy,[4] increased duration of treatment with AED, certain specific AEDs[2,3] and vagal nerve stimulation[5] were found to adversely affect postural stability. However, the cognitive modulation of postural control can also be affected by disease related factors, such as seizure type, age at disease onset, seizure frequency, duration and severity of seizures, seizure-related physiological dysfunction, structural cerebral damage caused by recurrent or prolonged seizures, and cerebral lesions acquired prior to seizure onset.[6]

Only a few studies have assessed disease-related factors that can affect balance. The results of static and dynamic balance tests were similar in patients with partial or generalized seizures.[7] In another study, patients with localization-related epilepsy (LRE) had increased body sway in several balance tests compared to patients with primary generalized epilepsy (PGE), although the difference was non significant statistically.[8]

In the present study the main objective was the assessment of a subclinical balance function in well defined populations of idiopathic PGE and LRE on AED treatment, in relation to normal controls.

2. Methods

2.1. Study population

The study was approved by the institutional review board at the Sheba Medical Center. Informed consent was obtained from all patients and healthy subjects who agreed to participate in the study.

The population studied consisted of patients with PGE and LRE, who were recruited consecutively from the epilepsy outpatient clinic in the Sheba Medical Center from June 2008 until May 2009

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during a routine follow-up visit. All patients were treated with AEDs, as either mono- or polytherapy, at stable doses for at least seven days prior to postural examination, and took their morning dose prior to the clinic visit.

Patients were not included in the study if they had any of the following:

1. Past medical history including a motor or balance disturbance due to diseases involving the central or peripheral nervous system, or due to orthopedic disorders, head or neck injuries, peripheral vestibular disease, epilepsy-related operation, vagal nerve stimulation, psychiatric diseases, malignancy, chronic illnesses requiring chronic medical treatment that might affect the nervous system, alcohol or drug addiction.
2. Motor or balance disturbance detected in the neurological evaluation prior to the posturography.
3. Imaging with lesions in the brainstem, cerebellum, insula, temporal neocortex, or in nuclei or tracts associated with motor function, proprioception, vestibular or cerebellar systems.
4. Generalized, complex-partial or simple-partial seizures with a motor component less than seven days prior to postural examination.
5. Pregnancy.
6. Inability to sign the consent form or to complete the postural examination.

The control subjects were recruited randomly and consisted mainly of hospital workers and caregivers of the patients. All control subjects were self-declared healthy persons, who were not taking AEDs or any other medications that might affect their performance.

2.2. Data collection

Demographic data were collected from the medical charts of the patients in the outpatient clinic, and included age, gender, types of seizures, the epilepsy syndrome, disease duration, results of brain imaging, medications used and their dosing, co-morbidity and additional medical treatments.

2.3. Equipment and protocol

The Posture Scale Analyzer (PSA, Gan-Ner, Israel) is a device designed for the evaluation of static postural function. The PSA consists of a simple force platform on which the subject stands and a computer. The platform is divided into four compartments: left anterior, left posterior, right anterior, and right posterior. Underneath each compartment a compressive load cells is located, so that measuring and recording the normal forces, at a rate of 2 Hz, is conducted simultaneously from the four load cells. The PSA provides information on the weight distribution, the center of pressure and the sway index (SI), defined as the standard deviation of the time and distance of the subject from the center of pressure.

The study was performed in all patients between 10 AM and 1 PM, after the epilepsy clinic visit, and consisted of seven tests for postural assessment, each lasting 30 s: (1) standing still with eyes open; (2) standing still with eyes closed; (3) standing still while performing a cognitive challenge (Stroop test[9]); (4 and 5) standing on one foot at a time, the right and then the left, with eyes open; and (6 and 7) standing still with the eyes open while holding a 2 kg weight in one hand, the right hand first and then the left. Test 1 was considered as the baseline. Test 2 was performed with eyes closed in order to assess the proprioceptive component of balance function. Standing on one foot (Tests 4 and 5) was chosen as a challenging motor balance test condition. Tests 6 and 7 assessed the effect of the deviation of the center of pressure on balance function.

Subjects were requested to stand as still and stable as possible but to remain relaxed throughout the test, with the arms hanging freely, and the feet apart at shoulder width. They were instructed to look straight ahead at a target on the opposite wall. For Test 3, the Stroop test board (30 cm $\times$ 21 cm in size) was placed 1 m in front of the subjects, and adequate vision was ascertained. The examination took place in a quiet, well-lit room.

2.4. Statistical analysis

Statistical analysis was conducted using the SPSS version 15.0, Chicago, IL. Natural logarithm transformation was performed due to the skewed distribution of the SI. Pearson Chi-Square and Fisher's exact test were used to test categorical variables. Continuous variables were analyzed by either *t*-test or analysis of variance (ANOVA). Statistical significance was set at $p < 0.05$.

3. Results

Demographic data, body mass index (BMI), type of AED treatment, number of AEDs taken and mean dose are presented in Table 1. There were no statistically significant differences between patients (PGE and LRE) and healthy subjects regarding age, gender, BMI, and dexterity, neither between the two patient

Table 1
Characteristics of the study population.

	PGE ($n = 19$)	LRE ($n = 27$)	Controls ($n = 22$)	p value
Age (years), mean ± SD	31.6 ± 10.3	38.2 ± 11.8	37.4 ± 11.6	0.127
Male/female	5/14	10/17	10/12	0.448
BMI (kg/m^2), mean ± SD	23.4 ± 4.6	22.7 ± 3.5	24.6 ± 4.1	0.27
Dexterity – right foot dominant	18	21	21	0.536
Monotherapy/polytherapy	10/9	13/14	–	0.5
Epilepsy duration (years)	17.6 ± 11.4	14 ± 13.6	–	0.383
Antiepileptic drugs				
n/dose (dose range)				
Lamotrigine	16/319 (100–700)	10/433 (200–800)	–	
Topiramate	4/106 (75–150)	6/175 (50–300)	–	
Oxcarbazepine	–	5/1025 (600–1800)	–	
Levetiracetam	2/2250 (2000–2500)	6/1958 (750–3000)	–	
Carbamazepine	–	7/914 (200–1600)	–	
Valproic acid	6/1008 (500–2100)	3/1025 (625–1250)	–	
Clobazam	–	1/30	–	
Phenobarbital	1/60	1/115	–	
Clonazepam	2/1.13 (0.25–2)	1/0.25	–	
Primidone	–	1/625	–	

n, number; BMI, body mass index; PGE, primary generalized epilepsy; LRE, localization related epilepsy. Dose is expressed in mg/day.

Table 2
Log SI (sway index) in patients with epilepsy and healthy subjects.

	PGE ($n=19$)	LRE ($n=27$)	Controls ($n=22$)
Test 1	2.2 ± 0.453	2.097 ± 0.314	2.071 ± 0.299
Test 2	2.596 ± 0.468	2.553 ± 0.361	2.432 ± 0.358
Test 3	2.274 ± 0.434	2.369 ± 0.525	2.146 ± 0.462
Test 4	$2.928 \pm 0.412^{*}$	$2.662 \pm 0.292^{*}$	2.544 ± 0.283
Test 5	$2.951 \pm 0.409^{**}$	$2.915 \pm 0.522^{**}$	$2.531 \pm 0.325^{**}$
Test 6	2.076 ± 0.47	2.072 ± 0.457	1.919 ± 0.347
Test 7	2.058 ± 0.397	2.054 ± 0.345	1.914 ± 0.434

n, number; PGE, primary generalized epilepsy; LRE, localization related epilepsy.
* $p = 0.027$ (PGE versus LRE).
** $p = 0.005$ (PGE and LRE versus controls).

groups regarding treatment with mono- or polytherapy. Due to the small numbers of the various AEDs, no statistical analysis was conducted for the individual drugs or for different dosages.

The SI results for each test in the two patient groups (PGE and LRE) and the control subjects are presented in Table 2. In general, the SI was higher in the patients compared to healthy subjects in all tests but significance was reached only for Test 5 ($p = 0.005$). Patients with PGE had a higher SI compared to patients with LRE in six of the tests but significant only for Test 4 ($p = 0.027$).

No correlation was found between disease duration and balance performance in the individual syndromes (PGE and LRE); however, when both epilepsy syndrome groups were considered together, their SI was significantly correlated with disease duration in Test 5 ($p = 0.013$, $r = 0.40$).

4. Discussion

In this study, PWE had impaired balance function compared to healthy subjects, significant for single leg stance (left). Within the epilepsy group, patients with PGE had a worse balance function compared to patients with LRE, also significant for single leg stance (right). Even though the patients tested had no subjective balance complaints, subtle subclinical balance disturbances could pose a risk for falls and injuries.

Balance function in PWE was previously reported in only four studies. Sirven et al.[3] conducted a systematic evaluation of 16 randomized controlled trials that compared adjunctive therapy with a second-generation AED versus placebo for partial epilepsy, and reported dose-related rates of ataxia or imbalance. They found that the imbalance risk is increased by the second-generation AEDs at standard dosage, except for gabapentin and levetiracetam. Fife et al.[2] studied the balance function in 30 patients on monotherapy for idiopathic partial or generalized epilepsy. Lamotrigine was found to induce less disequilibrium compared to carbamazepine in the modified Fregly ataxia battery, including the sharpened Romberg position with eyes closed, standing on one leg with eyes closed, and walking in tandem with arms folded and eyes closed. There were no differences among patients treated with carbamazepine, lamotrigine and gabapentin in the activities-specific balance confidence scale, the Berg balance scale and computerized dynamic posturography. Petty et al.[4] studied 29 twin and sibling pairs, discordant for AED exposure. Twenty-eight of the AED users had epilepsy, including focal epilepsy in 14 and generalized in 13. AED users had poorer balance function in the Lord's Coordinated Stability Test, the dynamic platform dual leg stance condition and the dual and single leg stance conditions of the static platform balance test, and the Activity Score. In addition, AED polytherapy and increased duration of AED therapy were found to be independent predictors of increased sway. Significant balance abnormalities were detected in the latter two studies and in ours as well by the unilateral stance test, which was used in order to challenge postural control due to the reduced base of support and the additional alteration of the balance state by lifting the non-stance leg forward. In all three studies, balance impairment was attributed solely to factors related to AED treatment, such as the type and number of AEDs and the duration of treatment.

In a previous study that included evaluation of disease-related factors, Gandelman-Marton et al.[8] evaluated balance performance by computerized dynamic platform posturography (CDPP) in 20 patients with epilepsy and five with a single seizure. The patients were tested during admission following a generalized tonic–clonic seizure, and none of the patients had a brain MRI. In addition to polytherapy, the total number of seizures was found to significantly affect balance function. Patients who had more than two seizures had a higher SI in all the balance tests, that included the combinations of eyes closed, eyes open, stable and angularly moving platform, and single-legged stance. The SI did not significantly differ between patients with PGE and LRE, although there was a trend towards a significantly higher SI in patients with LRE compared to those with a single seizure in the single-legged stance conditions.

In the present study, we included only PWE in the interictal state, who had been free of seizures for a minimum of seven days. Moreover, most of the patients with LRE in the present study had a brain MRI. It is possible that if a brain MRI was available in our prior study, some of the PGE patients would have been reclassified as having LRE, and this may have altered the inter-syndrome balance function differences. It should be noted that the posturography method in the present study was PSA, while the previous study[8] employed CDPP.

The mechanisms underlying the increase in postural sway seen in PWE are poorly understood. It can be assumed that in patients with a normal neurological examination efferent and afferent pathways involved in postural control are largely unaffected by either treatment or disease-related factors. Cerebellar modulation of postural control can be affected by several factors. Although uncommon, vertigo may constitute an aura localized to the posterior area of the superior temporal neocortex.[10] In addition, ataxia is a known consequence of status epilepticus and a common side-effect of treatment with AEDs or vagal nerve stimulation.[5,11,12] However, if no balance impairment or cerebellar abnormality can be detected by the neurological examination, the more likely cause of postural deficit can be related to abnormal cognitive modulation. Cognitive ability can be influenced by the etiology of seizures, such as focal brain lesion or progressive cerebral degeneration.[6] However, lower intellectual abilities were also reported in patients with idiopathic generalized epilepsy compared to the general population.[13] Impairment in verbal and visual memory, visuospatial tasks, some frontal functions, such as mental flexibility, concept formation, cognitive speed, working memory, verbal fluency, perseveration and planning, and a widespread cognitive dysfunction outside the limits of the frontal lobe were all demonstrated in patients with juvenile myoclonic epilepsy.[14] This deficit in cognitive modulation can account for the worse balance function we found in patient with PGE compared to those with LRE.

Our study population was relatively large and age-matched to the controls. All the patients were on AED treatment and in the interictal state, and none of them had anatomic structural lesions. However, this study has several limitations. Since the patients were recruited during a routine visit in the outpatient clinic, it was practically impossible to perform the posturography at a fixed interval from the last AED dose. In addition, we did not obtain AED blood levels on the day of the test, since the blood levels of the AEDs taken by most patients could not be routinely measured.

The identification of a subclinical balance dysfunction in our patients provides an additional support to the hypothesis that

patients with epilepsy do have balance dysfunction even if on direct questioning they claim to be asymptomatic. Our results support previous studies suggesting that posturography can improve the evaluation of balance function in epilepsy patients, and allows further characterization of balance function in different epilepsy syndromes. By highlighting subtle balance impairment and risk of falls in PWE, our findings may have an impact on patient safety and quality of life.

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