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Shortened cortical silent period in adductor spasmodic dysphonia: Evidence for widespread cortical excitability

Sharyl Samargia^{a,c}, Rebekah Schmidt^a, and Teresa Jacobson Kimberley^{a,b,*}

^aUniversity of Minnesota Program of Rehabilitation Science, MMC 388 420, Delaware Street SE, Minneapolis, MN 55455, United States

^bUniversity of Minnesota Program in Physical Therapy, MMC 388 420 Delaware Street SE, Minneapolis, MN 55455, United States

^cUniversity of Wisconsin River Falls Department of Communicative Disorders, 410 South Third Street River Falls, WI 54022, United States

Abstract

The purpose of this study was to compare cortical inhibition in the hand region of the primary motor cortex between subjects with focal hand dystonia (FHD), adductor spasmodic dysphonia (AdSD), and healthy controls. Data from 28 subjects were analyzed (FHD $n = 11$, 53.25 ± 8.74 y; AdSD: $n = 8$, 56.38 ± 7.5 y; and healthy controls: $n = 9$, 41.67 ± 10.85 y). All subjects received single pulse TMS to the left motor cortex to measure cortical silent period (CSP) in the right first dorsal interosseus (FDI) muscle. Duration of the CSP was measured and compared across groups. A one-way ANCOVA with age as a covariate revealed a significant group effect ($p < 0.001$). Post hoc analysis revealed significantly longer CSP duration in the healthy group vs. AdSD group ($p < 0.001$) and FHD group ($p < 0.001$). These results suggest impaired intracortical inhibition is a neurophysiologic characteristic of FHD and AdSD. In addition, the shortened CSP in AdSD provides evidence to support a widespread decrease in cortical inhibition in areas of the motor cortex that represent an asymptomatic region of the body. These findings may inform future investigations of differential diagnosis as well as alternative treatments for focal dystonias.

Keywords

Adductor spasmodic dysphonia; Focal hand dystonia; Transcranial magnetic stimulation; Cortical silent period

1. Introduction

Dystonia is a “movement disorder characterized by sustained or intermittent muscle contractions causing abnormal, often repetitive, movements, postures, or both. Dystonic movements are typically patterned, twisting, and may be tremulous. Dystonia is often initiated or worsened by voluntary action and associated with overflow muscle activation”

[1]. Dystonia is considered focal if it primarily affects a specific group of muscles such as in the hand, referred to as focal hand dystonia (FHD). The term adductor spasmodic dysphonia (AdSD) refers to focal dystonia affecting the intrinsic muscles of the larynx responsible for adducting the true vocal folds. AdSD is characterized by a strained/strangled vocal quality with vocal breaks during speech tasks. The accurate diagnosis of FHD and AdSD is particularly difficult due to similar clinical presentation as other disorders. In addition, there are no available diagnostic tests that are considered gold standard for differential diagnosis. In AdSD, differential diagnosis is particularly challenging as the perceptual voice characteristics are often misdiagnosed as a functional voice disorder, muscle tension dysphonia (MTD) [2,25,26]. Due to the differences in etiology, effective treatment options for MTD and AdSD are vastly different; people with MTD typically respond favorably to traditional behavioral voice therapy and people with AdSD can achieve temporary symptom relief through injections of botulinum toxin into the thyroarytenoid muscle (true vocal fold), denervation of the recurrent laryngeal branch of the vagus nerve and, in some cases, laryngeal framework surgery [19]. However, AdSD does not respond to behavioral voice therapy. Thus, a misdiagnosis can lead to ineffective, time consuming and expensive treatment that may not be beneficial. Similarly, FHD is commonly misdiagnosed as essential tremor, carpal tunnel syndrome, overuse syndrome or psychogenic dystonia [18].

Transcranial magnetic stimulation (TMS) is a non-invasive method to measure cortical excitability and has been used to investigate neurophysiological differences in those with focal dystonia compared to healthy populations. The cortical silent period (CSP) is one measure of cortical excitability that can be elicited using TMS. CSP is an interruption of electromyographic (EMG) activity in the targeted muscle under slight contraction [7]. The initial phase of CSP is thought to reflect spinal inhibitory mechanisms such as suppression of H-reflexes due to Renshaw inhibition [8,9], while the later phase due to suppression of voluntary motor drive by gamma-amino-butyric acid (GABA_B) receptor-mediated inhibition within the cortex [16,27,30,31]. Significantly shortened CSPs have been reported in those with task-specific focal dystonia compared to those with segmental, generalized dystonia or healthy subjects [23].

A shortened cortical silent period (CSP) measured by TMS has been reported in those with FHD supporting the idea that reduced cortical inhibition is a neurophysiological feature in this population [4,22,23]. Cakmur et al. [5] compared CSP in orbicularis oculi, orbicularis oris, sternocleidomastoid (SCM) and abductor pollicis brevis (APB) in three groups: healthy controls, blepharospasm and cervical dystonia. When compared to controls, people with either dystonia had a shorter mean CSP in both orbicularis oris and orbicularis oculi, but not in APB [6]. These findings suggest the reduction of cortical inhibition is not isolated solely to the affected musculature, but not pervasive throughout the entire representation in patients with blepharospasm or cervical dystonia. Cortical excitability has not yet been reported in AdSD. Considering shortened CSP has been reported in other forms of focal dystonia, it was chosen as the outcome variable for this study to provide an improved understanding of the neuropathophysiology of AdSD.

Thus, the purpose of this investigation was to compare CSP in first dorsal interosseus (FDI) in healthy controls, subjects with FHD and subjects with AdSD to determine if a shortened

CSP in FDI is a feature of both forms of focal dystonia which would not only provide additional evidence of widespread decreased cortical inhibition in dystonia, it may also serve as a contributing factor in differential diagnosis.

2. Methods

2.1. Subjects

All 28 subjects were right-handed and between the ages of 26–68 years of age (mean: 50.21 ± 11.18 y; FHD $n = 11$, 53.25 ± 8.74 y; AdSD: $n = 8$, 56.38 ± 7.54 y; and healthy controls: $n = 9$, 41.67 ± 10.85 y) (Table 1). All subjects with FHD were symptomatic in the right hand. Data for the FHD group were obtained from a previously conducted study using the same protocol, equipment, and location [4]. In addition to having a diagnosis of AdSD from a laryngologist and/or speech language pathologist specializing in voice, subjects in the AdSD group had voice symptoms that were task specific, received little to no reported benefit from traditional voice therapy and reported benefit from low dose botulinum toxin injections into the vocal folds. Subjects in all groups were screened for TMS safety including no history of seizures, neurologic conditions such as stroke or degenerative disease, metal implanted devices (excluding dental fillings) and pregnancy. Potential subjects were also excluded if there had been recent use of dystonia medication including botulinum toxin injection within three months. This study was approved by the University of Minnesota Institutional Review Board and written informed consent was received according to the Declaration of Helsinki prior to participation. Data collection was carried out at University of Minnesota Clinical Translational Science Institute.

2.2. Cortical silent period

All cortical excitability testing was conducted by the primary researchers to ensure consistency. Each subject was seated comfortably in a reclining chair and fit with a swim cap to allow cranial landmarks to be first approximated and later confirmed using TMS. Electromyographic (EMG) traces from target muscle was acquired at a sampling rate of 2560 Hz with a bandpass filter width of 20–2000 Hz using a Cadwell Sierra EMG amplifier (Cadwell Laboratory, Washington). Considering the evidence to support widespread reduced cortical inhibition and accessing the laryngeal musculature can be invasive and difficult, the FDI was chosen as the target muscle. Surface electrodes were placed on the right hand over the FDI muscle using a tendon-belly montage with a ground electrode placed over the dorsum of the hand. TMS was applied using a 70-mm figure of eight coil connected to a Magstim 200 Rapid magnetic stimulator (Magstim So., Whitland Dyfed, UK). Single pulse TMS was delivered over the left primary motor cortex associated with the hand region and was systematically moved in 1 cm increments until “hotspot” was found. This location was marked and used throughout the remainder of the study. Each subject’s resting motor threshold (RMT) was determined as the minimum intensity required to produce a motor evoked potential (MEP) of $\sim 50 \mu\text{V}$ in at least 3 of 5 trials while the patient was at rest [24]. The test pulse intensity used for measurement was 120% of RMT, which was approximately equal to a 1 mV response at rest. CSP was measured by having the subjects perform an isometric contraction by abducting their index finger against a ring coupled to a 5-Beam load cell (Interface Inc., Scottsdale, AZ, USA) at 25% of maximum voluntary contraction

(best of 3 maximal attempts), while the test pulse was delivered. Eight to ten trials were recorded for each subject. All EMG traces were full-wave rectified and the duration of the CSP was determined to be the duration between the first superimposed TMS-induced MEP and the return of 50% of prestimulus FDI activation [15,20] (Fig. 1). All of the trials for each subject were used for analysis.

3. Results

An analysis of variance with age and group as factors, revealed age to be a significant covariate ($df = 23$, $F = 14.21$, $p < 0.001$). Results from an ANCOVA, with age as covariate showed a significant group effect ($df = 2$, $F = 21.83$, $p < 0.001$) (Table 2). A Bonferonni post hoc analysis revealed the AdSD group to have significantly shorter CSP duration than the healthy group ($p < 0.001$) and the between the healthy and FHD group ($p < 0.001$). In addition, the mean CSP duration in the AdSD group was significantly shorter than in the FHD group ($p = 0.045$) (Fig. 2). In each dystonia group there was one subject (12% AdSD, 9% FHD) that had CSP durations within the healthy 95% confidence interval (120.40–133.63 ms).

4. Discussion

These findings demonstrate CSP in FDI to be significantly shorter in subjects with dystonic symptoms in the hand as well as those with symptoms in the intrinsic laryngeal musculature, supporting evidence of a generalized abnormality in cortical inhibition in those with focal dystonia. These results suggest CSP could be used as an indicator to assist in the differential diagnosis of FHD and AdSD.

Other studies have reported shortened CSP in cortical regions specific to the affected musculature in people with other forms of focal dystonia. Shortened CSP has been reported in other cranial dystonias such as blepharospasm, oromandibular dystonia and cervical dystonia [3,10]. In addition, prolonged CSP following low-frequency repetitive TMS (rTMS) has been reported in subjects with FHD but not in a healthy population [4,14,20,28]. These findings suggest the GABA_B-ergic mechanism is able to be altered with neuromodulation [4,28]. The source of this altered inhibitory process is beyond the scope of this project and not fully understood. Research suggests the mechanism may be due to a loss of thalamic input to motor cortices as a result of alterations in basal ganglia excitability [21] or a decrease in GABA_B in the primary motor cortex [11,17]. The impaired inhibition distant from the affected musculature in AdSD suggests this impairment is widespread beyond the cortical bulbar system into the cortical spinal system.

This is the first known investigation of CSP in subjects with AdSD therefore these findings cannot be compared within the literature. However, neuroimaging studies using functional magnetic resonance imaging have shown differences in activation patterns in those with AdSD compared with healthy individuals [12,13,29]. Subjects with AdSD have shown an increase in the extent of activation of left primary motor cortex, somatosensory cortex, and cerebellum [13,29] Broca's area, auditory cortices [13], basal ganglia and thalamus [29] during symptomatic vocal tasks. The increase in activation suggests over-excitability in

those areas that support evidence of reduced inhibition. Contrastingly, reduced activation of primary sensorimotor cortices, premotor cortex and sensory association areas have also been reported in those with AdSD [12]. A reduction in activation may be observed in subjects with impaired inhibition due to maladaptive plasticity. Specifically, functional overuse may cause the cortical map to expand, resulting in reduced intensity of activation due to larger cortical spread [12].

Currently, there are no assessment protocols that definitively and reliably diagnose AdSD; it is a diagnosis of exclusion and is often misdiagnosed as MTD [25,26]. Although features such as task specificity, frequency of phonatory breaks and production of voiced versus voiceless sounds have been identified as symptoms of AdSD, they are perceptual in nature. Perceptual assessment of voice to accurately diagnose AdSD has been under scrutiny in past years. The use of perceptual assessment in AdSD continues to encounter problems in interrater reliability. An objective diagnostic indicator, such as cortical excitability measures, particularly, CSP would be beneficial in accurate diagnosis, which would lead to more efficient treatment of AdSD.

Limitations of the current work include a relatively small sample of patients, limiting generalizability. Further, given the difficulty of diagnosing AdSD, it is possible that some patients were incorrectly included in this group; however this risk was minimized by using evidence-based screening criteria. The age difference between the control group and patient groups was different and may have contributed to the findings. This was accounted for in the ANCOVA, but future work should match groups with respect to age and gender.

5. Conclusion

The current evidence showed shortened CSP to be a pathophysiologic characteristic in AdSD in a nonsymptomatic region suggesting an imbalance of GABA-ergic mechanisms in the cortex that may be widespread. In addition, patients with AdSD may have more reduced inhibition in the hand region of the primary motor cortex than patients with FHD, even though there are no symptoms in the hand, suggesting a more severely impaired inhibitory system. Considering the challenges in accurate diagnosis of AdSD and FHD and the findings of this research, TMS may assist in the differential diagnosis of these forms of focal dystonia. To determine the full utility of this measure in differential diagnosis, future work comparing AdSD to MTD needs to be done. Given the finding of reduced inhibition in AdSD, similar investigations into interventions that can modify inhibition are warranted in AdSD.

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HIGHLIGHTS

- Cortical inhibition is significantly reduced in FHD and AdSD compared to healthy.
- Abnormalities exist in hand region of motor cortex in AdSD without hand symptoms.
- Abnormality in GABA_B-ergic mechanism may be a feature of AdSD and FHD.
- TMS response could potentially play a role in assisting in differential diagnosis.

Fig. 1.
Sample of a single cortical silent period EMG trace in first dorsal interosseus of a healthy subject.

Fig. 2.

Mean (SD) duration of cortical silent period of first dorsal interosseus in healthy, adductor spasmodic dysphonia (AdSD) and focal hand dystonia (FHD) (* $p < 0.001$; ** $p = 0.045$).

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Table 1

Subject demographics.

Healthy				Focal hand dystonia				Adductor spasmodic dysphonia			
Age	Sex	Age	Sex	Age	Sex	Symptom duration (months)		Age	Sex	Symptom duration (months)	
26	M	64	F	252				44	M	18	
28	F	42	M	168				62	F	216	
51	F	55	M	108				53	M	120	
39	F	49	F	60				50	M	408	
37	F	63	M	84				67	M	324	
40	F	41	M	36				55	F	96	
43	M	68	M	60				54	M	96	
48	F	46	M	72				66	M	228	
63	F	50	M	30							
		59	M	444							
		50	M	Unknown							

M = male; F = female.

Table 2

Descriptive statistics of cortical silent period (CSP) in healthy, adductor spasmodic dysphonia (AdSD) and focal hand dystonia (FHD) groups.

Group	Mean CSP duration (ms)	Standard deviation	95% Confidence interval	
			Lower bound	Upper bound
Healthy	125.83	32.37	120.40	133.63
AdSD	94.45	27.31	87.01	100.16
FHD	104.69	22.99	98.25	110.27