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## Secondary Blepharospasm Associated with Structural Lesions of the Brain

M. A. Khooshnoodi, S. A. Factor, and H. A. Jinnah

Department of Neurology, Emory University, Atlanta, USA

### Abstract

**Background**—Blepharospasm is a form of focal dystonia that manifests as repetitive involuntary closure of the eyes. The pathogenesis of blepharospasm and the neuroanatomic substrates involved are not fully understood. Dysfunction of the basal ganglia traditionally is presumed to be the main cause of most forms of dystonia, but a growing body of evidence suggests that a network of additional cortical and subcortical structures may be involved.

**Methods**—The medical records of 1114 patients with blepharospasm seen over past 10 years at Emory University were reviewed to identify potentially contributing brain lesions. A systematic review of the published literature was also conducted to identify potentially contributing brain lesions.

**Results**—Among patients with blepharospasm at Emory University, 18 had focal lesions on imaging studies available for review. The literature review revealed 25 articles describing 30 additional cases of blepharospasm associated with focal lesions. Among all 48 cases, lesions were found in multiple regions including the thalamus (n=12), lower brainstem (n=11), basal ganglia (n=9), cerebellum (n=9), midbrain (n=7), and cortex (n=1).

**Conclusions**—These data in combination with functional imaging studies of primary blepharospasm support a model of dystonia in which a network of different regions plays a role in pathogenesis.

### Keywords

Blepharospasm; Imaging; Basal ganglia; Cerebellum

## INTRODUCTION

Blepharospasm is a form of focal dystonia that presents with involuntary eyelid closure due to overactivity of muscles around the eyes, particularly the orbicularis oculi. It is categorized into primary and secondary forms, based on whether or not a cause can be established. The primary form of blepharospasm is more common, and a cause usually cannot be found.

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Corresponding author: H.A. Jinnah, Address: Woodruff Memorial Building Suite 6000, 101 Woodruff Circle, Atlanta GA, 30322, USA. Fax: +1 404 712 8576. [hjinnah@emory.edu](mailto:hjinnah@emory.edu).

### DISCLOSURES

The authors report nothing to disclose.

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Secondary blepharospasm can be associated with brain lesions or drugs, or it accompanies other movement disorders such as Parkinson's disease.(1)

The regions of the brain responsible for triggering blepharospasm remain uncertain. Imaging studies of primary blepharospasm have shown abnormal activity in multiple areas.(2, 3) For example, functional magnetic resonance imaging (fMRI) and positron emission tomography (PET) have pointed to abnormal activity in the somatosensory and cingulate cortices, thalamus, caudate, cerebellum, and brainstem. In these studies, however, it is difficult to discriminate which changes reflect the trigger for blepharospasm and which are downstream consequences.(4-9)

Brain regions affected in secondary blepharospasm have received less attention because focal lesions causing blepharospasm are uncommon. Most information comes from case reports or small case series. The nature of the lesions in these reports is varied and includes ischemia or stroke, tumors, demyelinating lesions, and other pathologies. The locations of these lesions also are varied. The basal ganglia are believed to play an important role in dystonia, a concept that originated from early studies showing this region to be the most commonly affected in patients with hemidystonia.(10-13) Early hypotheses suggested that dysfunction of descending basal ganglia pathways might cause hyperexcitability of brainstem interneurons responsible for the blink reflex.(14) Subsequent studies questioned this hypothesis by showing that thalamic lesions causing blepharospasm are not typically in areas receiving striato-pallidal input.(15)

Instead, they are in the receiving zone for cerebellar afferents. Other studies suggested an alternative hypothesis that cerebellar lesions might cause blepharospasm by leading to loss of inhibition of primary motor cortex.(16) Additionally, there are many reports of secondary craniocervical dystonias associated with lesions in other brain regions.(17-21) The purpose of the current study was to review neuroimaging findings in patients with presumed secondary blepharospasm associated with identifiable lesions on neuroimaging studies.

## METHODS

After obtaining approval from the institutional review board, electronic medical records of patients seen in the movement disorders and ophthalmology clinics at Emory University between January 2001 to December 2012 were queried using Current Procedural Terminology (CPT) and International Classification of Diseases Ninth Revision (ICD-9) codes for "blepharospasm" and "Meige syndrome". A total of 1114 records were identified, and 997 were left after excluding patients in whom blepharospasm emerged in the setting of other disorders such as Parkinsonism or following neuroleptic exposures. Two cases with Parkinsonism were retained because blepharospasm and Parkinsonism both emerged acutely following stroke. Imaging results, including MRI or CT, were available for 156 patients. For patients with identifiable lesions, we recorded the type of lesion, lesion location, age at symptom onset, age at presentation, age at first imaging study, sex, and associated neurological features.

In addition to reviewing records available at Emory University, we conducted a systematic review of the literature using PubMed as the search engine and "blepharospasm" or "Meige syndrome" as keywords. A total of 25 articles reporting 30 cases of presumed secondary blepharospasm were found. Each article was reviewed to extract data similar to those collected for Emory cases. Some cases with lesions in more than one region were counted more than once. Other cases with lesions that could not be localized were not counted, such as those with hypoxia/ischemia or diffuse atrophy.

## RESULTS

Of 156 patients diagnosed with blepharospasm or Meige syndrome at Emory who had clinical imaging studies available for review, 63 had MRI only, 34 had head CT only, and 59 had both MRI and head CT. There were identifiable lesions in 18 patients (Table 1). Women (n=14) were more frequent than men (n=4). The average age at symptom onset was 61.4 years (range 44-86 years). Onset of symptoms was acute in 8 patients although in many cases the relationship between onset and imaging could not be determined from the records available.

The most commonly affected region was the thalamus (n=5), especially the posterior regions (n=4). The cerebellum was the next most commonly affected region (n=4), with 2 in the hemisphere, 1 in the dentate nucleus and 1 in the inferior cerebellar peduncle. Another 3 patients had lesions in the midbrain, and 2 had lesions in the lower brainstem. The basal ganglia were affected in 3 patients, and the parietal cortex in 1. Stroke was the most common etiology (n=15), followed by vascular malformation (n=2) and a cystic lesion of unknown pathology (n=1).

From the literature, 30 cases of blepharospasm associated with brain lesions were found in 25 different articles published from 1983 - 2012 (Table 2). Women were more commonly affected (n=17) than men (n=13). The average age of at the time of presentation was 49.7 years (range 13-78 years). Stroke was the most common pathology.

Similar to results from cases identified at Emory, lesions were located in different regions. The most commonly affected region was the lower brainstem (n=6). There were 7 patients each with lesions in the thalamus or basal ganglia. The cerebellum was affected in 5 cases and the midbrain in 4.

## DISCUSSION

The current study summarizes the largest series of patients with focal brain lesions associated with possible secondary blepharospasm. It also includes a comprehensive literature review of presumed secondary blepharospasm. For all 48 subjects combined, lesions were located in various regions including the thalamus (n=12), lower brainstem (n=11), basal ganglia (n=9), cerebellum (n=9), midbrain (n=7), and cortex (n=1). These imaging studies do not point to a single dominant anatomic brain region for secondary blepharospasm.

These imaging results for presumed secondary blepharospasm point to the same regions as those from volumetric and functional imaging studies of primary blepharospasm, where focal lesions are absent. Studies involving voxel-based morphometry have reported increased volumes for the caudate and cerebellum, and decreased volumes of the thalamus and inferior parietal lobule.(22, 23) The putamen was reported to be enlarged in one study and diminished in another.(22, 23) There is only one diffusion tensor imaging study, and no abnormality was found.(24) Blink-related fMRI studies of blepharospasm have shown increased activity in the putamen, primary sensory cortex and supplementary motor area.(4, 9) PET studies have shown changes in the caudate, pons, thalamus, cerebellum, and midbrain.(7, 8, 25, 26) Taken together, these studies of primary blepharospasm point to involvement of multiple brain regions. However, imaging studies of primary blepharospasm can not discriminate the source of the problem from downstream compensatory changes.

Neuroimaging of secondary dystonia may aid in the discrimination of cause from effect. Presumably, a focal lesion that immediately precedes blepharospasm is the cause. However, studies of secondary blepharospasm also have limitations.(14, 27) First, it is difficult to

prove a causal link between the lesion and the symptoms. Even when there is a close temporal relationship between lesion and symptoms, it is not possible to rule out the occurrence of microstructural defects or functional disturbances in other brain regions that appear grossly normal. Second, it is difficult to definitively relate the observed lesion to symptoms because of possible involvement of fibers of passage and remote effects of the observed lesion. This issue is particularly relevant for lesions in the midbrain and lower brainstem. Third, it is not possible to rule out the possibility of primary blepharospasm with a coincidental lesion. A final limitation is that it is not possible to rely on a temporal association between occurrence of a lesion and emergence of symptoms for dystonia, because it has been documented repeatedly that the emergence of dystonia may be delayed by months or even years following a nervous system insult.(28-34)

Despite these limitations for both primary and secondary blepharospasm, the combined results suggest involvement of multiple brain regions rather than one dominant area. The results are more consistent with a network model for pathogenesis of dystonia.(35) In this model, several brain areas may be involved as “nodes”. Dystonia may result from dysfunction of one node in the network, from combined dysfunction of multiple nodes, or from aberrant communication among the nodes.(2) However, many uncertainties remain. For example, the typical delay between the occurrence of a lesion and appearance of blepharospasm raises the possibility that a lesion in one node may lead to maladaptive reorganization of other nodes.(2) Furthermore, it is not clear how a unilateral lesion can cause bilateral symptoms. It also is possible that a focal lesion on one side of the brain may introduce aberrant signals into the recently described subcortical connections between basal ganglia and cerebellum to yield bilateral defects.(36, 37)

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Table 1

Cases with secondary blepharospasm at Emory University

Case	Age	Sex	Onset	Side	Imaging modality	Lesion location	Lesion Side	Lesion type	Associated symptoms	Imaging after onset
1	58	F	insidious	R+L	CT	posterior thal	L	stroke	none	NA
2	57	F	insidious	R+L	CT	posterior thal	L	stroke	CD	NA
3	44	M	insidious	R+L	MRI	dentate nucleus	L	cyst	none	NA
4	79	F	insidious	R+L	MRI	CRB hemisphere	L	stroke	tremor	NA
5	62	F	insidious	R+L	MRI	parietal cortex	L	stroke	none	NA
6	41	F	acute	R+L	MRI	SN	L	AVM	CD	3 weeks
7	69	F	acute	R+L	MRI	red nucleus	L	stroke	parkinsonism	7 days
8	77	F	acute	R+L	MRI	put	R+L	stroke	parkinsonism	1 day
9	48	F	acute	R+L	MRI	put/caud	L	stroke	hand tremor	2 months
10	70	F	insidious	L	MRI	inferior CRB peduncle	L	AVM	none	5 years
11	58	F	acute	R+L	MRI	midbrain	L	stroke	none	NA
12	71	M	acute	R+L	CT	ventral pons	L	stroke	none	NA
13	64	F	insidious	R+L	MRI	CRB hemisphere	L	stroke	truncal dystonia	3 years
14	70	F	insidious	R+L	MRI	posterior thal	L	stroke	OMD	1 year
15	77	M	insidious	R+L	MRI	put/caud	L	stroke	OMD	NA
16	55	F	acute	R+L	MRI	pons	L	stroke	none	NA
17	62	M	acute	R	CT	thal	L	stroke	none	2 days
18	86	F	insidious	R+L	MRI	posterior thal	L	stroke	none	NA

Abbreviations: AVM (arteriovenous malformation), Caud (caudate), CD (cervical dystonia), CRB (cerebellum), Dent (cerebellar dentate nucleus), L (left), OMD (oro-mandibular dystonia), Put (putamen), R (right), SN (substantia nigra), Thal (thalamus).



**Table 2**

Reported cases of secondary blepharospasm

Case	Age	Sex	Imaging modality	Lesion location	Lesion Side	Lesion type	Associated symptoms
1(19)	59	F	CT	thal, midbrain	R	stroke	none
2(19)	75	F	CT	BS, thal, CRB	R	stroke	none
3(19)	52	F	CT	CRB	R	stroke	OMD
4(19)	56	F	CT	diffuse	R+L	HIE	none
5(19)	46	M	CT	diffuse atrophy	R+L	MS	none
6(19)	34	F	CT	diffuse atrophy	R+L	MS	none
7(38)	48	M	CT	olivo-ponto-cerebellar atrophy	R+L	atrophy	none
8(39)	60	M	CT	BS, CRB	L	stroke	PM
9 (40, 41)	62	M	CT	thal	L	stroke	none
10(11)	31	M	CT	put/caud	R+L	stroke	none
11(17)	51	M	CT	thal	R+L	iatrogenic	none
12(20)	43	M	MRI	thal, BS	L	mass	hand dystonia
13(21)	78	F	CT	pons	L	stroke	PM
14(42)	60	F	CT	pallidum	R+L	calcification	OMD
15(43)	66	F	MRI	midbrain	R	cyst	hand tremor
16(44)	59	F	MRI	thal, midbrain	L	metabolic	left INO
17(45)	60	M	CT	basal ganglia	R+L	calcification	none
18(46)	13	F	MRI	put/caud	R+L	stroke	rigidity
19(47)	43	M	CT	parietal cortex	L	tumor	jaw closing
20(48)	46	F	MRI	dorsomedial lower pons	L	stroke	dystonia
21(49)	60	F	MRI	pons	L	stroke	none
22(50)	52	M	MRI	paramedian thal	R+L	stroke	none
23(51)	25/F	F	MRI	frontal cortex	L	stroke	none
24(12)	60/F	F	CT	put	R+L	stroke	OMD
25 (52)	25/F	F	MRI	lateral ventricle	L	ganglioma	none
26(13)	69/F	F	MRI	put/caud	R	stroke	none
27(53)	73/M	M	MRI	pallidum	R+L	stroke	OMD

Case	Age	Sex	Imaging modality	Lesion location	Lesion Side	Lesion type	Associated symptoms
28(54)	35/F	F	MRI	CRB	R+L	stroke	CD
29(55)	23/M	M	MRI	lateral ventricle	R	ependymoma	CD
30(56)	30/F	F	MRI	pons	L	capillary telangiectasia	none

Demographics, clinical and imaging data of 30 patients with secondary blepharospasm reported in the literature. Abbreviations: BS (brainstem), Caud (caudate), CD (cervical dystonia), CRB (cerebellum), HIE (hypoxic-ischemic encephalopathy), INO (internuclear ophthalmoplegia), MS (multiple sclerosis), OMD (oro-mandibular dystonia), PM (palatal myoclonus), Put (putamen), Thal (thalamus).