Risk Factors for Blepharospasm

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BACKGROUND

Blepharospasm is a focal dystonia characterized by repetitive, sustained contractions of the orbicularis oculi and frontalis muscles. The prevalence of blepharospasm is estimated at 5 per 100,000. Epidemiologic reviews have revealed a family history ranging from 7 to 27.8% of cases, and an autosomal dominant, polygenic pattern of inheritance has been postulated. Factors contributing to the difficulty of studying the genetics of blepharospasm include the relatively rare occurrence of blepharospasm, geographical barriers for examination of symptomatic family members, and phenotypic heterogeneity.

Clinical features of blepharospasm include involuntary eye closing aggravated by bright lights, wind, pollution, smoke, emotional stress, fatigue. This eye closing may interfere with reading, driving, watching television, and other visual activities, and is rarely associated with retro-orbital pain. Blepharospasm may be associated with other dystonic disorders, such as oromandibular or cervical dystonia, and usually occurs in the 5th to 7th decades of life. There is no clinical difference between the eye findings of primary and secondary blepharospasm with the possible exception that primary blepharospasm is sometimes relieved with a sensory trick (touching face, humming, singing, talking, pinching skin), and this has not been documented in secondary cases.

Historically, blepharospasm and other dystonic disorders may be associated with tremor, bruxism, writer's cramp, restless legs; or a family history of tremor or dystonia. Aggravating factors include wind, bright lights, pollution, and stress. Some patients report relief with a sensory trick or rest. Medications associated with dystonia are major tranquillizers, some anti-hypertensive medications, and anti-nausea drugs.

A recent survey of primary dystonia in Europe found that blepharospasm was present in 28.9% of 957 dystonia patients, second only to cervical dystonia. In this population women were 2.3 times more likely to have this symptom, and on average were 4.7 years older. These investigators noted that all patients had onset of symptoms between 40-60 years of age, and more than 50% reported spread to include another area of the body. In this study risk factors for blepharospasm included a history of head or facial trauma or family history of dystonia or tremor disorder.

In a related study, it was noted that spread to another location is more likely seen in women, and is associated with head or facial trauma or edentulousness. Patients not exhibiting spread to another location were more likely to report a history of ocular disease or family history of dystonia or tremor. In the 55 patients with multiple locations for dystonia, 43% had spread to lower face, 27% to the cervical muscles, 7% to the laryngeal muscle, and 5% to the limbs. Spread was seen in 18.9% the first year, 36.4% the second, and 34.6% of 159 patients by the 5th year.

Several genes have been associated with dystonia. In addition, a higher prevalence of Obsessive Compulsive symptoms are seen in Blepharospasm subjects when compared to a similar population of Hemi-Facial Spasm subjects. [Table 1]. Finally, the differential diagnosis for involuntary eye closing is extensive, but will not be reviewed in detail in this manuscript. [Table 2]

Table 1. Clinical and Molecular Information on the Primary Dystonias

Disease Name/ Gene Symbol	Chromosomal Location	Mode of Inheritance	Phenotype
DYT1	9q34	Autosomal dominant	Childhood and adolescent; limb onset
DYT2	Unknown	Autosomal recessive	In Spanish Gypsies; not confirmed
DYT3	Xq13	X-linked recessive	Parkinsonism-dystonia (Lubag, Philippines)
DYT4	Unknown	Autosomal dominant	Whispering dysphonia in Australian family
DYT5/ Dopa-responsive dystonia	14q22	Autosomal dominant	Dopa-responsive dystonia
DYT6	8p21-p22	Autosomal dominant	Mennonite/Amish dystonia with mixed face/**eyes**/neck or limb onset; childhood or adult onset
DYT7	18p	Autosomal dominant	German families; adult neck, **face** or limb onset
DYT8	2q33-q35	Autosomal dominant	Paroxysmal dystonia; paroxysmal dystonic choreoathetosis; may be the same as DYT10
DYT9	1p	Autosomal dominant	Paroxysmal choreoathetosis with episodic ataxia and spasticity
DYT10	Unknown		Paroxysmal kinesigenic choreoathetosis; may be same as DYT8
DYT11	Unknown	Autosomal dominant	Myoclonic dystonia; hereditary alcohol-responsive myoclonus
DYT12	19q13	Autosomal dominant	Early-onset Parkinsonism
LDYT	Mitochondrial DNA		Leber's hereditary optic neuropathy

Modified from de Leon and Bressman

Table 2: Conditions Associated with Involuntary Eye Closing

Physiologic – LED-induced	•Myoclonus
Metabolic – Aceruloplasminemia, Wilson's Disease	•Reticular – branchial or ocular
Drug-Induced	•Cortical – CJD, JME
•Tardive	Hemifacial Spasm – bilateral in up to 3% of cases
•Acute Dystonic Reaction	Tetany
•Dopaminergic agents	Facial nerve synkinesis
•Lithium	Myokymia
Environmental toxins	Intramedullary Brainstem Lesion
•Tear gas	
•Pollution	Seizures
Chemical burns producing local eye injury	Eyelid Weakness
Peripheral nerve injury	•Oculomotor nerve palsy
Post-traumatic with LOC	•Myasthenia Gravis, Eaton-Lambert Syndrome
Dental extraction	•Diphtheria, Botulism
TMJ	•Guillain-Barre Syndrome
Central Lesions involving rostral brainstem	•Myotonic Dystrophy
Vascular – thalamus, midbrain, pons	Ophthalmologic Disorders
Demyelinating Disorders (multiple sclerosis)	•Dry eyes
Brain Tumor	•Blepharitis, iritis, uveitis
Infectious diseases	•Corneal erosion
Malformations	•Foreign body
Hydrocephalus	•Photophobia
Parkinsonian Disorders	•Glaucoma
•Parkinson's disease	
•Post encephalitic parkinsonism	Excessive Blinking
•Progressive Supranuclear Palsy	•Emotional Stress
•Shy-Drager	•Conversation
•Hallervorden-Spatz syndrome	•Levodopa, Apomorphine, Bromocriptine, Atropine
Movement Disorders	Decreased Blinking
•Tics	•Physostigmine, Alcohol
•Choreiform Disorders	•Eyelid Apraxia
•Huntington's Disease	Physiologic
•Neuroacanthocytosis	•Voluntary
•Sydenham's Chorea	•Sleep
•Essential Chorea (edentulous)	•Reflex
	Psychogenic

PURPOSE

In an attempt to clarify and gather genetic information in the blepharospasm population, the BEBRF funded the first nationwide evaluation of the familial occurrence and clinical risk factors of benign essential blepharospasm (BEBRF grant to Padma Mahant, MD). The long-term goals were to develop a database of clinical information on familial blepharospasm, and integrate this data with gene hunters interested in blepharospasm. The identification of candidate genes for Benign Essential Blepharospasm may allow for better clinical description of the condition, and allow for new therapies in treating this condition.

METHODS

In 2001 over 4000 questionnaires were mailed to BEBRF participants, and to patients with a diagnosis of blepharospasm followed at the Muhammad Ali Parkinson Research Center in Phoenix, Arizona.

Questionnaires contained questions about demographic data; biographical data including age, education, birth region, occupation; medical history including diagnosis, age at onset, age at diagnosis, symptom description, associated conditions, birth history, prior diagnoses, medication history, tobacco and caffeine intake, nutrition, exposures to chemicals, and treatment history; and family history including grandparent's country of origin, religious background, and history of family members with movement disorders.

RESULTS

The data provided in this progress report is preliminary, and based on only a portion of the over 800 surveys completed.

Demographic/ Biographical Results

The age at onset of blepharospasm symptoms ranged from 6 to 84 years, with an average of 53.4 years (table 3). The average age at diagnosis was 56.9 years, with an average of 3.3 years from symptom onset to diagnosis (table 4, fig 1). Seventy three percent of the patients were women (fig. 2). Ninety-two percent of patients were Caucasian (fig.3). Seventy-two percent achieved at least a high school degree (fig. 4). The majority of patients were born in the south or midwest, with 26.3% reporting a southern state and 29.7% reporting a midwestern state as their state of birth (fig. 5). The occupation most represented in this sample of surveys was clerical work, with 42.6% of patients (fig.6). The number of years spent in each occupation ranged from 10-20 years, with the exception of military work (table 4).

Table 3. Age at First Symptoms vs. Age at Diagnosis (n=209)

	Mean	Confidence Interval	Range	50th Percentile
Age at first symptoms	53.4	[51.8,55]	6-84	53 (5% <35)
Age at Diagnosis	56.9	[55.5, 58.1]	27-84	57 (5% <45)
Time from symptoms to Dx	3.3	[2.4,4.1]	0-40	1 year

Fig. 1

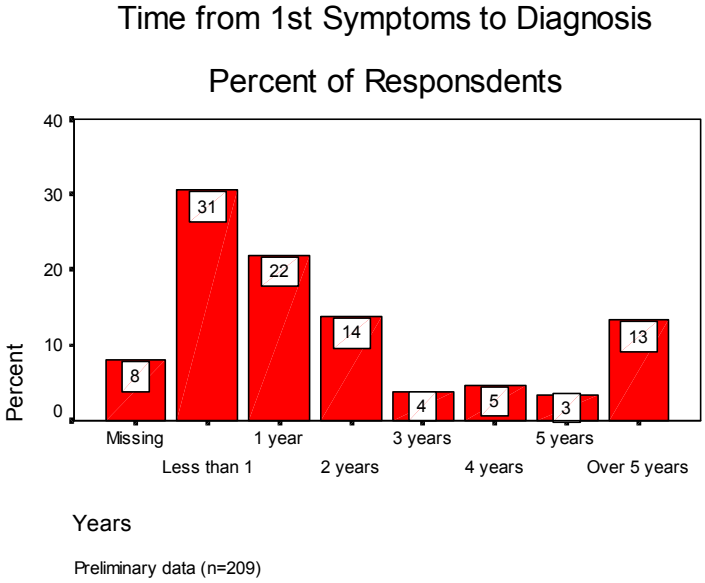
Time from 1st Symptoms to Diagnosis
Percent of Responsdents
Percent
40
30
20
10
0
8
31
22
14
4
5
3
13
Missing
Less than 1
1 year
2 years
3 years
4 years
5 years
Over 5 years
Years
Preliminary data (n=209)

Fig. 2

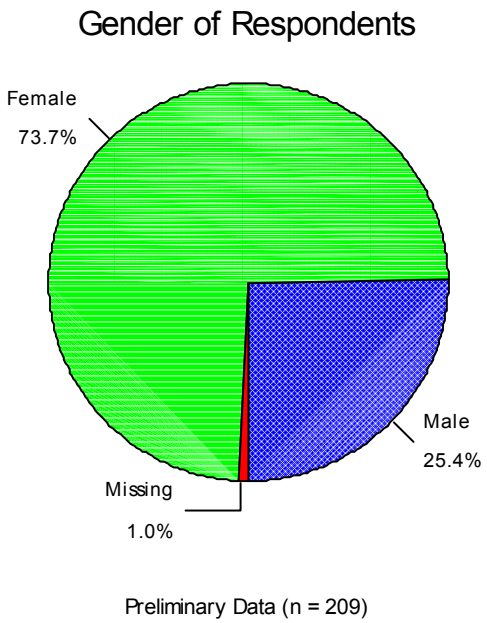
Gender of Respondents
Female
73.7%
Male
25.4%
Missing
1.0%
Preliminary Data (n = 209)

Fig. 3

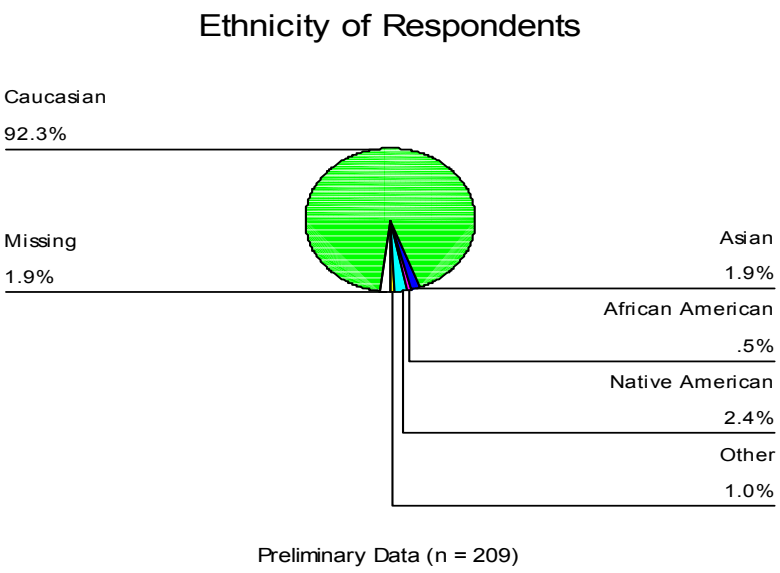
Ethnicity of Respondents
Caucasian
92.3%
Missing
1.9%
Asian
1.9%
African American
.5%
Native American
2.4%
Other
1.0%
Preliminary Data (n = 209)

Fig. 4

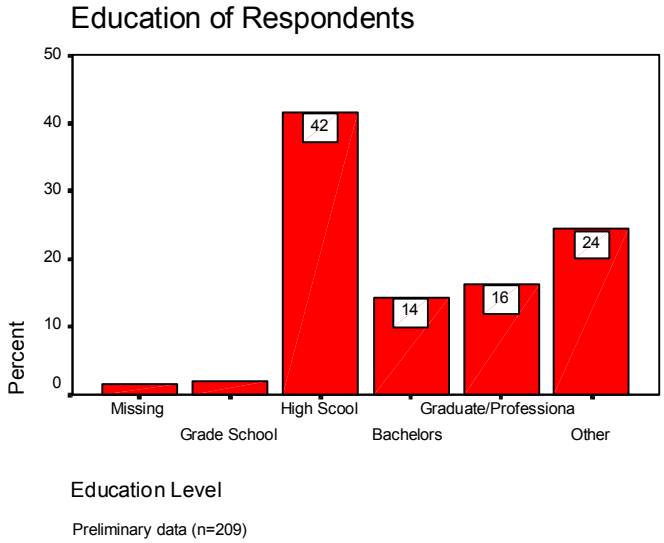
Education of Respondents
Percent
50
40
30
20
10
0
42
14
16
24
Missing
Grade School
High Scool
Bachelors
Graduate/Professiona
Other
Education Level
Preliminary data (n=209)

Fig. 5

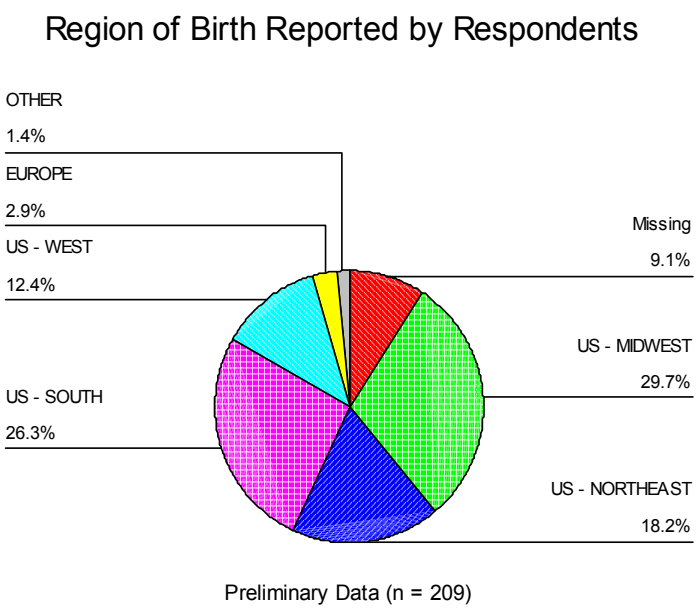

Fig. 6

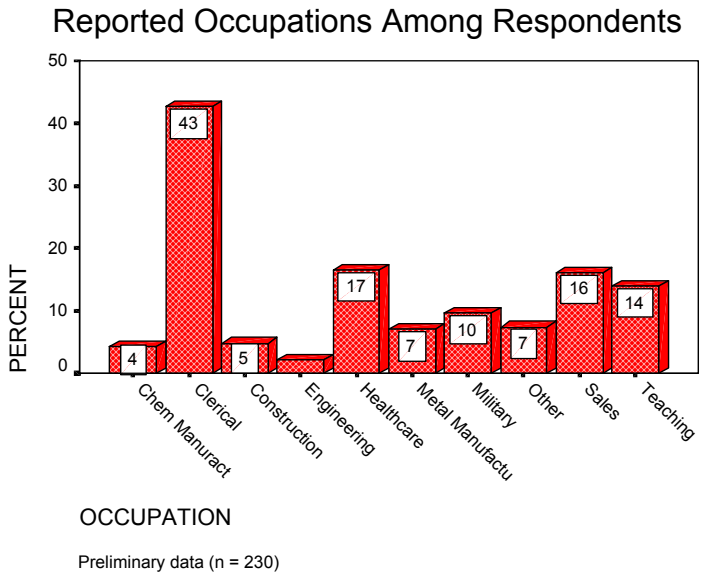

Table 4: Average years in selected occupations. (n = 230)

Description	Average Years	Confidence Interval
Clerical	19.55	[16.24, 22.86]
Healthcare	19.13	[13.55, 24.71]
Sales	18.23	[13.55, 22.90]
Metals manufacturing	10.40	[3.27, 17.53]
Chemical manufacturing	16.00	[4.93, 27.07]
Construction	20.00	[8.74, 31.26]
Engineering	19.25	**only four records
Military	4.45	[3.17, 5.73]
Teaching	15.39	[10.01, 20.76]
Other	19.77	[10.89, 25.65]

Medical History Results

The majority of patients, 62.2%, reported increased blinking as the initial symptom of blepharospasm, this was followed in frequency by involuntary eyelid closure, twitching of eyelids, and finally powerful or sustained closure of eyelids (table 5). Other symptoms were reported in 25% of cases, and included photophobia, dry eyes, and squinting. Twenty two percent of patients reported tremor, with the majority of patients reporting head tremor as location of tremor (table 7). Thirty-one percent of patients reported an eye condition prior to the onset of their blepharospasm; the majority described conjunctivitis (fig 7). Eleven percent of patients reported a difficult or premature birth (table 6). Other diagnoses which preceded symptom onset included head trauma (14.1%), depression (6.5%), and anxiety (2.3%) (table 7).

Table 4. Initial Symptoms Reported

	N	%
Twitching	65	31.1
Blinking	130	62.2
Involuntary Closure	111	53.1
Powerful, Sustained Closure	30	28.7
Other	52	24.8

Table 5: Tremor reported by respondents (n = 185)

Descriptions	Percent reporting
Any tremor	22.2%
Head	11.9%
Jaw	9.7%
Upper Extremities	6.5%
Trunk	0.5%
Lower Extremities	2.2%

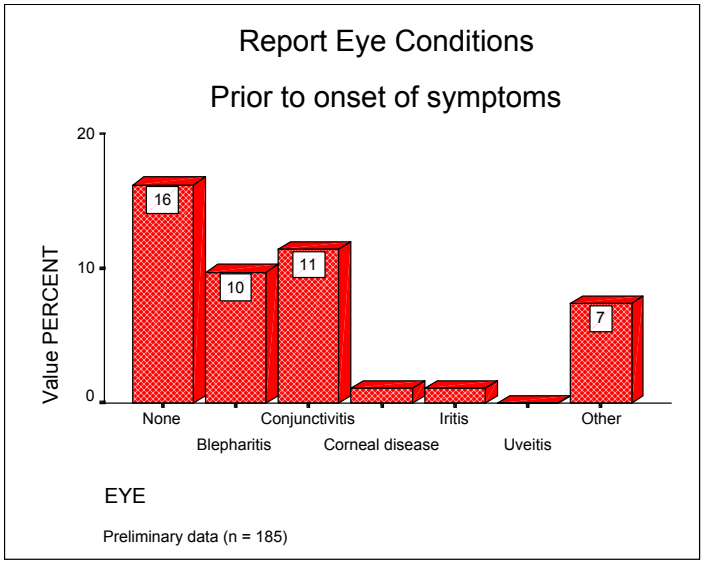

Fig 7

Table 6: Birth History (n = 185)

Descriptions	Percent Reporting
Patient does not have information	22.7%
Premature birth	1.1%
Pregnancy complications	6.9%
Labor and Delivery complications	2.2%
Resuscitated / Respiratory assistance	0.5%

Table 7: Other Diagnoses by Doctor (as reported by respondents) (n=185)

Descriptions	Reporting	# Prior to symptom onset‡
Head Trauma/Concussion	14.1% (28)	14/19
Face Trauma	None	n.a.
Brain Tumor or Brain Mass	0.5% (1)	Unknown
Parkinson's Disease	None	n.a.
Progressive supranuclear palsy	None	n.a.
Multiple system atrophy	None	n.a.
Shy-Drager Syndrome	None	n.a.
Tics or Tourette Syndrome	None	n.a.
Syndenham's chorea (St. Vitus Dance)	None	n.a.
Stroke	1.0% (2)	0/1
Myotonia	None	n.a.
Myasthenia Gravis	None	n.a.
Depression	6.5% (12)	4/10
Bipolar disorder	None	n.a.
Anxiety disorder	2.2% (4)	1/3
Schizophrenia	None	n.a.

‡only includes those who provided age of diagnosis

Family History Results (Table 8)

A positive family history of a movement disorder was reported in 10.5% of patients in this sample. The majority of symptoms in these patients' family members were blepharospasm; other associated diagnoses included tremor and other focal dystonia.

Of those who reported a positive family history, 37.5% were eligible for genetic research, based on the number of affected relatives and relationship of those affected. All patients with positive family history who qualified agreed to be contacted by a geneticist for possible participation in genetics research. Overall, 3.9% of the total sample in this report qualified for genetics research.

Table 8: PATIENTS WITH POSITIVE FAMILY HISTORY (n=153)

PATIENT # AND SEX	AGE AT ONSET	FAMILY MEMBER	ABNORMAL FAMILY HX.
1. F	-	PAT. GM	-
2. F	-	DAUGHTER	-
3. F*	-	NEPHEW	-
4. F*	-	SISTER	-
5. F	40	MOTHER	BLEPH
6. F	43	PAT. AUNT	BLEPH
7. M	13	MOTHER	BLEPH
8. F	46	MOTHER	BLEPH
9. F	50	FATHER MOTHER SON	BLEPH TREMOR TREMOR
10. F*	11	FATHER 2 GRD.SONS	BLEPH BLEPH
11. M	65	FATHER SISTER	BLEPH BLEPH
12. F *	55	BROTHER BROTHER SISTER SISTER SON DAUGHTER	BLEPH PD BLEPH H.F. SPASM WRITER'S CRAMP BLEPH
13. M	16	DAUGHTER	BLEPH
14. F *	65	PAT GM COUSIN	BLEPH BLEPH
15. M *	55	PAT GF SISTER	BLEPH BLEPH
16. F	15	BROTHER	BLEPH

* indicates those patients referred for potential participation in genetic research

DISCUSSION

The etiology of blepharospasm is multifactorial. In some patients, blepharospasm may result from genetics alone, whereas other patients might be genetically susceptible to blepharospasm, but a specific risk factor may be necessary to trigger the onset of symptoms. This is the first and largest nationwide study of blepharospasm patients aimed at the description and recruitment of families with blepharospasm for genetic research.

Blepharospasm is an adult-onset focal dystonia, with onset usually in the sixth decade. Our study revealed mean age of onset of 53.4, consistent with previously reported series. The majority of patients, 73.7%, in our study are women, again consistent with other studies. The majority (53%)

of patients in this analysis reported time from symptom onset to diagnosis as within 1 year (fig1); this relatively quick diagnostic time is likely due in large part to the efforts of the BEBRF, in educating patients as well as healthcare professionals.

Many patients reported tremor, 22.2% in our series, somewhat less than the frequencies reported in other studies, ranging from 33 to 51%, this association supports the potential role of the basal ganglia in the pathophysiology of blepharospasm. Head trauma frequently preceded the diagnosis of blepharospasm, a finding similarly present in Anderson's study of 1653 patients, similarly recruited from the BEBRF. Anxiety and depression were somewhat underreported in this series, at only 8.7%, compared to other series, which ranged from 18-34%. Although we will await the final analysis to determine whether this is a true difference, it is possible that patients underreported these diagnoses as the surveys were not anonymous; although confidentiality was maintained, contact information was requested in order to maintain a database of patients interested in future studies.

The familial occurrence of blepharospasm has been described in several reports; the results of these studies are summarized in the following table. It is clear from comparing these studies that a higher incidence of dystonia is found among relatives of patients when examined, and when the pool of index patients consists of other types of adult onset focal dystonias, such as torticollis and writer's cramp. Our finding of a 10.5% family history of dystonia among respondents in this preliminary analysis is consistent with studies that involved questioning of patients rather than examination of relatives. Although examination of relatives would increase the probability of discovering more familial cases of blepharospasm, it is only feasible with a small number of index patients, and the size of this study precluded such an extensive evaluation. However, consideration might be given to such an undertaking in the future, provided there is enough interest among patients and their relatives.

STUDY AUTHOR	#INDEX PATIENTS	#RELATIVES EXAMINED	FAM HX DYSTONIA (% OF INDEX PTS)	FAM HX MOVEMENT D/O (% OF INDEX PATIENTS)	OTHER FINDINGS
Jankovic / Orman	250 bleph, meige	-	-	6%	
Jankovic/ Ford	100 bleph,	-	7%	25%	
Jankovic/ Nutt	238 bleph	-	14%	36.5%	control group: 2% movement d/o
Grandas et al	264	-	9.5%	19.7%	
Stojanovic et al	43 bleph, tort, w.c.	168	27.8%		
Defazio et al	29 bleph, meige	189	27.6%		Pt sibling dystonia: 4.2% vs. control group: 0%
Waddy et al	40 bleph, tort, w.c	153	21.4%		

The patients in this analysis who reported a positive family history were found to have a younger average age of onset of symptoms, at 39.5 years compared to the average age of 53.4 for all blepharospasm patients in this analysis. The final report of our study, which will include an evaluation of all 800+ surveys, will include a comparison of several factors among patients with

and without family history, to determine if further differences exist among patients with positive family history of blepharospasm or dystonia.

As stated previously, 6 patients or 3.9% of the total sample analyzed in the family history section qualified for genetic research. An additional 20-80 families may be identified for genetic analysis in the remaining data set.

CONCLUSION

Although data from a questionnaire study of familial occurrence and risk factors must be interpreted cautiously, the information provided will contribute to a further understanding of this disorder, and through collaboration with geneticists, this study may contribute to the identification of gene(s) and eventually a cure for blepharospasm.

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Presented at:
20th Annual International Conference and Scientific Symposium of the Benign Essential Blepharospasm Research Foundation
Houston, TX
August 23-25, 2002

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