

WHAT WE CAN LEARN ABOUT HEREDITARY DYSTONIA FROM HIGH SPEED DIGITAL IMAGING (HSDI) OF THE GLOTTIS?

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A prospective clinical cohort study of mannose binding lectin and other immunological parameters with diagnostic use of phonatory function studies
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ABSTRACT

This study examined efficacy of the innate immune defence via the mannose binding lectin (MBL) in a cohort of 55 dystonic patients prospectively referred to the clinic with laryngeal mucosal complaints, who were placed on local steroids (budesonid inhaler, 400 µg 2 times daily) and antihistamines (fexofenadin 180 mg mostly 3 times daily) with adjuvant lifestyle corrections.

Treatment efficacy of the larynx was assessed based on mucosal findings of the vocal folds examined with High speed mucosa studies comprising simultaneous high speed digital imagines (HSDI), kymography, electroglottography (EGG) and voice acoustics combined with a visual score of arytenoids oedema, as these measures are indicative of the magnitude of laryngitis.

Lactose and gluten intolerance and immunological analyses of the innate system were made systematically. Results showed that the genetic aspects of immunology did not reveal a role for the innate immune system, represented by the mannose binding lectin (MBL).

An unexpected positive effect of the larynx treatment on dystonia symptoms was found evidenced by reduction of dystonic complaints and more normative results of High speed mucosa , and a reduction of oedema of the inter arytenoids region. Symptoms relieve and better quality of life was observed on follow up for the dystonia complaints.

INTRODUCTION

Dystonia represents a neurological syndrome dominated by involuntary muscle contractions.

Theories of the development of dystonia include genetic- and immunological aspects and also acute provocations by e.g. infection disorders.

Syndromes of dystonia are clinically and genetically heterogenic disorders, the recent aspects include that the disorder can be reversible.

The treatment of dystonia is done by painful injections of neurotoxins with only one product in an evidence-based study comparing two different products

Since 1976 treatment of laryngeal spasmodic dystonia is controlled by unilateral section of the recurrent nerve denervation either surgically or chemically. Through this approach understanding of laryngeal dystonia has been gained, and systematic diagnosis and treatment of spastic dysphonia was presented by Dedo and Izdebski 1984, yet, randomized controlled trials of treatment of spasmodic dystonia have not been made.

MATERIAL AND METHODS

4

The 55 patients experienced dystonia for an average of 13 years.

Age: 55 years, The symptom duration time was Average between half a year and 42 years.

	Females N=41	Males N=14	Total (all patients) N=55
Age (yrs)			
Mean	57.0	50.7	55.4
SD	12.9	16.1	13.9
Range	29-79	9-69	9-79
Symptom duration (yrs)			
Mean	11.7	15.9	12.7
SD	11.2	14.4	12.1
Range	0.5-50	3-41	0.5-50
Mannose binding lectin			
MBL<500µg/L	19 (46%)	7 (50%)	26 (47%)
MBL>500µg/L	17 (42%)	4 (29%)	21 (38%)
Missing	5 (12%)	3 (21%)	8 (15%)

Table 1: Patient description

MATERIAL AND METHODS

The localisation of the dystonia symptoms with laryngeal mucosal symptoms.

Only 2 patients had genetic lactose intolerance and 1 had gluten intolerance out of the 55 dystonia patients. Out of nine patients examined for various dystonia genes 2 (22%) had DYT 1 genes. Botox had been given to all patients in the Danish hospital system. From the systematic blood test, twenty-six (47%) patients had a reduced function of the innate immune system (MBL<500µg/L).

Symptoms	1 st consultation		2 nd consultation after 2 – 3 weeks	
	n	%	Average improvement	Range
Laryngeal	55			
Focal symptoms	36	(65%)	40%	0,1 -75
segmental	18	(33%)	20%	0-50
multifocal	21	(38%)	31%	0-50
general	26	(47%)	60%	0-98

Table 2: Number of patients in each subdivision of dystonia symptoms

MATERIAL AND METHODS

Laryngitis complaints included: sore throat, dysphonia and mucosal complications. The intention was to evaluate an eventual immunological factor with the use of High speed measures of voice function.

Medication of local steroids and antihistamines as well as lifestyle corrections was given, based on mucosal findings.

Front, centre and rear part of the vocal cords during intonation, and the acoustical measures based on the high speed films were performed. Qualitative evaluation of the regularity of vocal folds mobility and motility were assessed using kymography, electroglottography and acoustical measures obtained simultaneously.

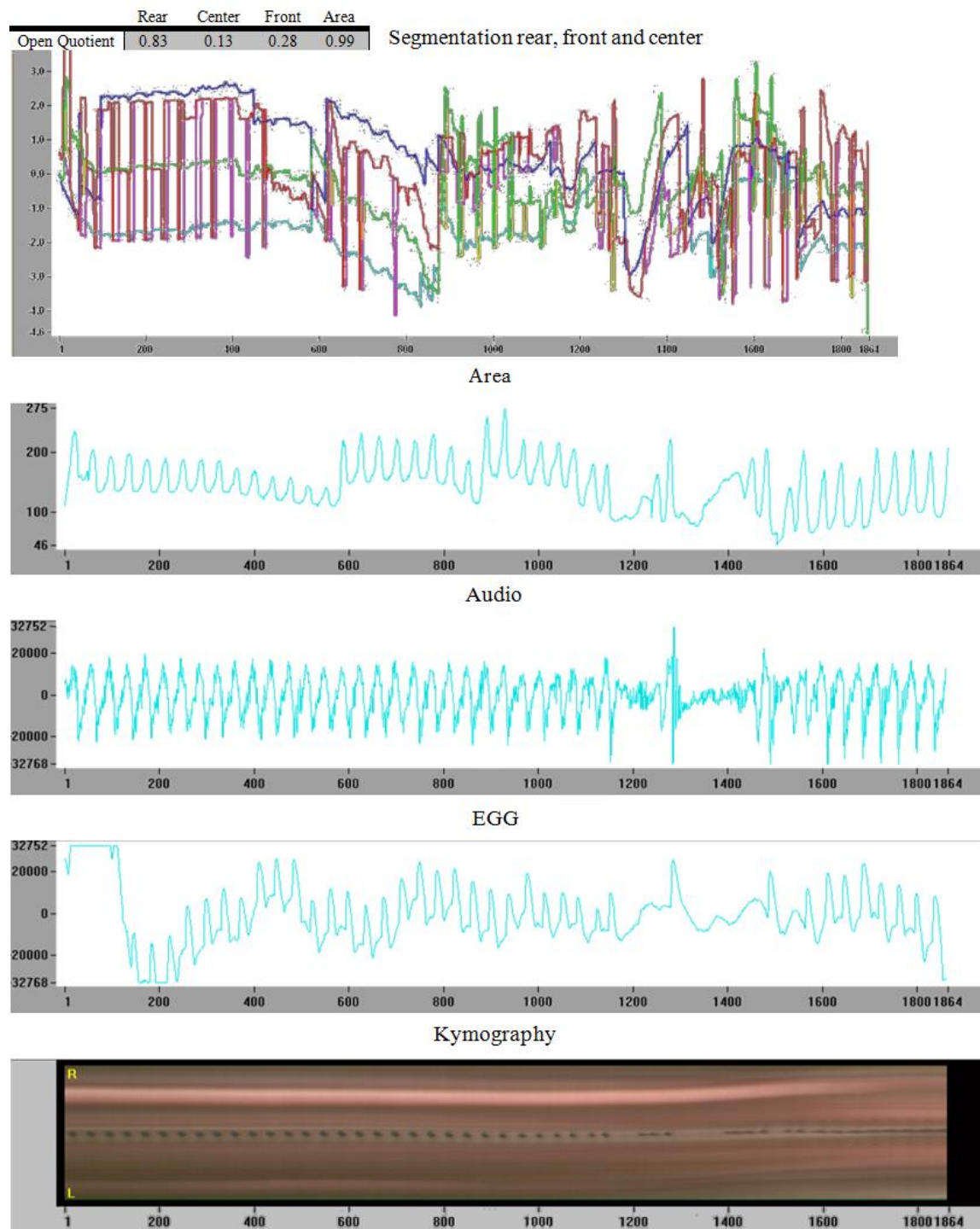
Multivariate statistical voice analyses were made combined with the high speed images, frequency and intensity measures of a sustained tone 'ah' as well as reading of a standard phonetically balanced text.

Segmentation curves for high speed film calculations of open quotients in the front, center and rear parts of the vocal cords.

Visual irregularities illustrated due to a dystonia spasm – on movement curves of the vocal cords in front, center and rear, as well as area-, acoustical-, electroglottographical-, and kymographical curves.



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RESULTS

Our first dystonia patient where high speed images were used to document changes, had total elimination of universal dystonia symptoms. In addition high speed films showed regularity of laryngeal actions. The elimination of dystonia in the larynx and in other parts of the body in some of these patients suggested a relationship between immunological deficiencies of the upper airways and the nature of dystonia, with relapses when the medication was terminated.

Fexofenadin works as an anti inflammatory agent also influencing the brain. local steroids (budesonid) work as an anti inflammatory way. A focus was placed on the innate immune system, mannose binding lectin (MBL) since this is a very active agent in the early defence of the mucosa.

RESULTS

The oedema of the arytenoids regions was statistically significantly reduced ($p=0.0003$), but no difference between normal versus abnormal MBL values.

	1 st consultation			2 nd consultation			Change (2 nd -1 st consultation)			
	N	Mean	Std	N	Mean	Std	N	Mean	Std	p-value
All dystonia patients	55	2.71	0.60	49	2.35	0.63	49	-0.35	0.72	0.0003*
MBL<500 µg/L	26	2.69	0.62	22	2.32	0.57	22	-0.36	0.73	
MBL>500 µg/L	21	2.67	0.58	20	2.30	0.73	20	-0.40	0.75	
MBL<500µg/L vs MBL>500 µg/L										0.90§

Table 4: High speed films. Inter-arytenoid region oedema - statistical analysis

§: Test in the linear statistical model where mannose-binding lectin (MBL) is included as a fixed effect and baseline is included as a covariate, before and 2-3 weeks after treatment of the larynx.

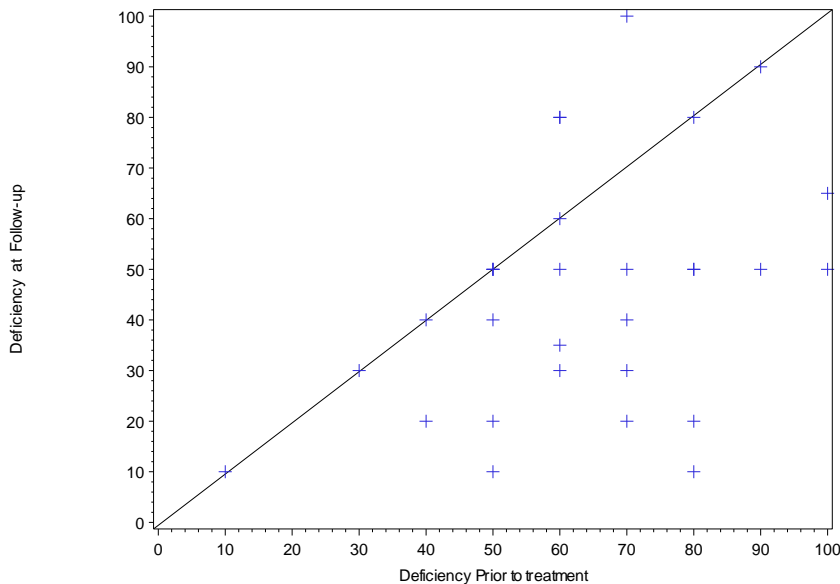
*: Statistically significant on a 0.1% significance level

RESULTS

10

- The assessment of the severity of disease at the follow up showed an improvement specific of disorders of 18.3 ($p=0.0001$) and an improvement for the quality of life of 7.3 ($p=0.073$) as seen in figure 2 and 3.

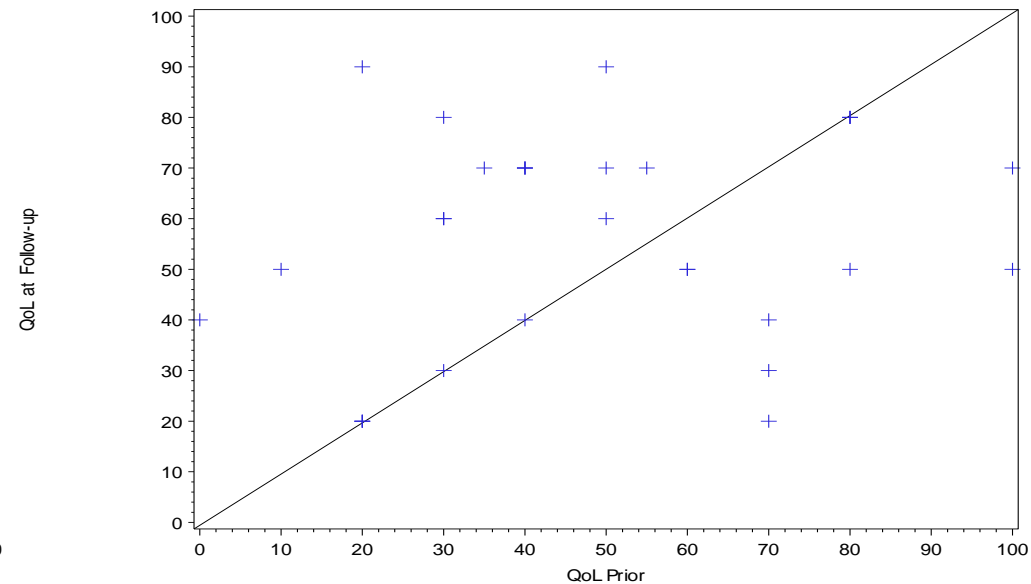
Scatter plot - Deficiency self assessment



VSSolutions - Generated 30MAR11/scatter_deficiency.cgm

Mean change from prior assessment to follow up assessment of -18.3 ($p=0.0001$).
95% CI: [-27; -10].
0=no sickness, 100=very sick.

Scatter plot - Quality of Life



VSSolutions - Generated 30MAR11/scatter_qol.cgm

Mean change from prior assessment to follow up assessment of 7.3 ($p=0.072$). 95% CI: [-0.7; 15].
0=worst possible quality, 100=best possible quality of life.

Table 3: High speed films and MDVP results statistical analysis

§: Test in the linear statistical model where MBL is included as a fixed effect and baseline is included as a covariate, a difference is seen from before till after 2-3 weeks of treatments in all patients.

*: Statistically significant on a 5% significance level

	1 st consultation			2 nd consultation after 2 – 3 weeks			Change(2 nd -1 st consultation)			
	N	Mean	Std	N	Mean	Std	N	Mean	Std	p-value
Open quotient front										
All dystonia patients	53	0.51	0.29	44	0.60	0.28	44	0.11	0.36	0.014*
MBL<500 µg/L	25	0.53	0.30	20	0.60	0.27	20	0.08	0.32	
MBL>500 µg/L	21	0.54	0.27	17	0.57	0.34	17	0.05	0.40	
MBL<500µg/L vs MBL>500 µg/L										0.80§
Open quotient middle										
All dystonia patients	53	0.51	0.26	44	0.60	0.26	44	0.09	0.34	0.023*
MBL<500 µg/L	25	0.50	0.24	20	0.60	0.24	20	0.09	0.34	
MBL>500 µg/L	21	0.56	0.27	17	0.61	0.31	17	0.06	0.34	
MBL<500µg/L vs MBL>500 µg/L										0.99§
Open quotient rear										
All dystonia patients	53	0.59	0.26	44	0.59	0.30	44	-0.02	0.37	0.65
MBL<500 µg/L	25	0.58	0.22	20	0.63	0.28	20	0.02	0.32	
MBL>500 µg/L	21	0.66	0.28	17	0.59	0.32	17	-0.10	0.40	
MBL<500µg/L vs MBL>500 µg/L										0.58§
MDVP – reading										
Reading variation Frequency%	32	17.65	17.31	15	11.14	6.18	12	-2.45	10.54	0.17
Reading Intensity%	32	15.73	6.02	15	18.54	7.34	12	3.67	7.36	0.13
Reading Qx%	32	46.19	7.42	15	46.97	6.24	12	-0.55	5.79	0.73
MDVP – sustained tone										
Tone Jitter%	31	6.97	14.49	15	4.07	5.30	11	0.70	5.46	0.68
Tone Shimmer%	31	13.20	13.57	15	9.70	9.24	11	-0.77	7.46	0.75
Tone Qx%	31	47.85	11.04	15	49.93	10.61	11	3.24	5.86	0.11

RESULTS

In table 3, the acoustical measures before and after routine treatments of the patient complaint of symptoms of the larynx are presented. The electroglottographical measures showed no significance of change related to the upper airway mucosa, corresponding to the kymography measures in the high speed digital imaging (HSDI).

The subdivisions of diagnoses of the dystonia cases were seen in table 2. Mostly the shorter duration of symptoms, the better effect of treatment of the upper airways was seen.

DISCUSSION

Randomised controlled studies are necessary in the future for various aspect of treatment of dystonia.

The presented prospective observational cohort study shows

that the immune system in the dystonic population treated for symptoms of laryngitis complaints was optimised locally in the larynx, but also that some dystonia symptoms were reduced.

In our study the mannose-binding lectin (MBL) as a part of the immune system did not seem to be involved. High Speed Digital Imaging (HSDI) were useful to show better laryngeal function after laryngeal treatment.

One possible explanation of effect is 1. that the mucosa in the upper airways in the dystonia syndrome is related to neurological sensors in the mucosa, even if the dystonia is universal. Another speculation may be 2. that the voice and the upper airway mucosa has a much more integrated function, not yet understood, for regulating the symptoms of dystonia. Repairing the histamine related function in itself can have yet undefined results. One other possible explanation is 3. that the dopamine D1 receptor is involved in voicing in animal experiments and ablation of D1 dopamine receptor has effect on voicing also in humans.

DISCUSSION

- The high speed images (HSDI) are interesting for the documentation of neurological deviations of the larynx because the true on line movement of the vocal cords and the laryngeal vestibule are captured.
- In summary, the results of this study indicates that the group of dystonia patients with low MBL ($MBL < 500 \mu\text{g/L}$) responds to the treatment with local steroid inhaler of budesonid and antihistamine fexofenadin as well as the patients with normal levels of MBL. Other immune system related factors should systematically be analyzed in the future.

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15

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