Dystonia – aspects of genetics and immunology

A prospective cohort and case-control study with follow up

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Abstract

- **Introduction:**
- We have earlier presented our prospective cohort study where dystonia in some cases was reduced or disappeared with immunological treatment of laryngeal complaints. It is possible that genetic related dystonia is different from the immunological responding dystonia.

- **Material:**
- 55 consecutive patients were included in our study during an 8 month period. Focus was on genetics of the dystonic patients who responded to immunological treatment of the larynx.

- **Method:**
- The dystonic patients were referred to the clinic to be treated for their laryngeal mucosal disorders, mostly with medication of steroids and antihistamines as well as lifestyle correction, not for dystonia.
- The medical diagnostics were made of laryngitis and small benign neoplasms related to pathology in the immune system in the same way as suggested for evidence based studies in the European Guidelines on rhinology (EPOS Primary Care Guidelines: European Position Paper on the Primary Care Diagnosis and Management of Rhinosinusitus and Nasal Polyps, 2007). Routine immunological genetic analyses were made when possible.

- **Results / conclusion:**
- The genetic aspects of immunology did not show any role of the innate immune system (MBL) for the unexpected positive effect on dystonia - of the routine treatment of laryngitis and small benign neoplasms on the vocal cords The reason may be that the genetic measures only included a few genes. There is no explanation why the treatment of the throat disorders influenced the dystonia symptoms. High speed films documented a reduction of edema of the inter arytenoid region in these patients.

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Objectives

- The objectives were to evaluate immunological innate genetic treatment of dystonia patients that consecutively were sent to the ear-nose-throat clinic because of mucosal complaints of the upper airways. The reason was that not only the laryngeal complaints but also the dystonic complaints were reduced.

- The routinely used immunological treatment of the larynx disorder (antihistamines and local steroids) was evaluated – in many cases affecting the dystonia symptoms to partly disappear, but showing up again when not taken.
- Focus was on the serum mannose-binding lectin (MBL) levels and the associated MBL gene – comparing patients with low levels to patients with normal higher levels.
- (Only 9 patients had been examined for DYT genes at the neurological departments in Denmark, 2 were positive for DYT 1. 2 out of the 55 patients consecutively examined in our clinic had lactose intolerance genes, and only 1 patient was found out of 55 with gluten intolerance)

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Flowchart 1: Overview of study method

Trial start

2-3 months

6 months

Dystonic patients

The dystonic patients were referred to the clinic with the intention of diagnosing and treating their laryngeal mucosal disorders. By observing a treatment effect on their dystonic symptoms, a prospective cohort study was planned.

Reasons of exclusion were pregnancies, young age, malignancies and lack of cooperation.

Tests performed at the first examination: High speed (HS) films, video-stroboscopy, voice analysis including jitter%, shimmer%, electroglottography (EGG) closed phase Qx% on a sustained tone (/ah/), frequency variation%, loudness variation%, electroglottography (EGG) closed phase Qx% on reading of a standard text. Assessment of inter-arytenoid oedema on HS films.

Patients were given fexofenadine, 180 mg 1-3 per day (antihistamines) and budesonid (local steroid/ anti inflammatory treatment with minimal absorption, lactose free), inhaled to land on vocal cords.

Bloodtests checking for standard inhalation and food allergies and genes of mannose binding lectin levels (MBL), lactose and gluten were taken**.** Genetic tests (DYT gene) were performed on some patients based on availability.

Each patient filled out two questionnaires on their specific symptoms and illness history.

Clinical re-examination and follow-up: High speed films, video-stroboscopy, voice analysis including jitter%, shimmer%, electroglottography (EGG) closed phase Qx% on a sustained tone (/ah/), frequency variation%, loudness variation%, electroglottography (EGG) closed phase Qx% on reading of a standard text. Assessment of inter-arytenoid oedema on HS films. Visual score of treatment effect compared to 1st examination was determined by the clinical staff and patients

Patients were sent a follow up questionnaire on the subjective symptom effect of the referred treatment on their dystonia. The general aspects that were interesting were, how the patients rated their quality of life prior to the first examination and after treatment, and how the severity of the disease was rated prior to first examination and after treatment.

This was done in order to see whether those dystonic patients who were suffering from genetic innate immune system deficiencies (low mannose binding lectin – MBL - levels) responded better/poorer to the medical treatment given, with respect to treatment of their dystonic symptoms. Questions asked in the quenstionnaire:

Have you been examined for the DYT gene 1-5-11? If yes, please send the report.

- Highlight primary dystonia symptoms (prior to first examination).
- Highlight your current dystonia symptoms.
- Are you still taking the antihistamines and local steroids?
- Other medication?
- On a scale from 1-100%, how would you rate your quality of life prior to the first examination (100% being excellent quality of life)
- On a scale from 1-100%, how would you rate your quality of life currently (100% being excellent quality of life)
- On a scale from 1-100%, how would you rate the severity of the disease prior to the first examination (100% being extremely severe)
- On a scale from 1-100%, how would you rate the severity of the disease currently (100% being extremely severe)

The subjective complaints were compared in relation to the patients' immune system.

The voice analysis results of dystonic patients were compared with a control group (N=42)

Patient description:

	Males	Females	Total (all patients) N=55
Age (yrs)			
Mean	50,71	57,02	55,41
SD	16,11	12,88	13,90
Range	9-69	30-79	9-79
Symptom duration (yrs)			
Mean	15,86	11,68	12,75
SD	14,38	11,17	12,06
Range	3-41	0,5-50	0,5-50

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Number of patients in each subdivision of dystonia symptoms

Symptoms	**1st consultation** *No. of patients*
Facial dystonia symptoms	36
Laryngeal symptoms	54
Torticollis	18
Truncal dystonia symptoms	21
Dystonia symptoms in limbs	26

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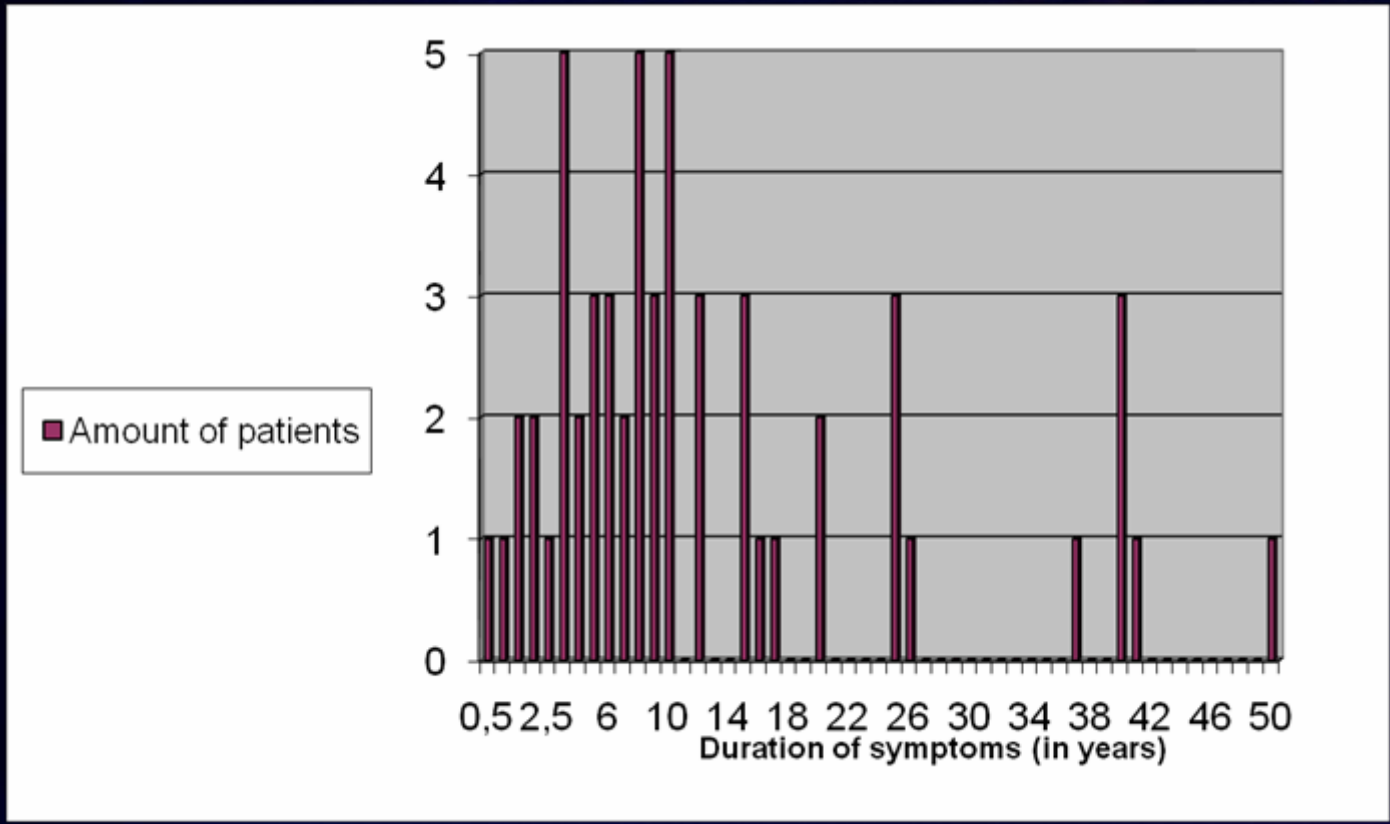
Duration of dystonia symptoms (years) versus number of patients



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High speed films and MDVP of dystonic patients and a normal control group

	Dystonia patients (N= 55)		Control group (N = 42)
	1st consultation	2nd consultation	Control group examination
	Mean (SD)	*Mean (SD)*	*Mean (SD)*
High speed results			
Open quotient front	0,52 (0,29)	0,61 (0,30)	0,48 (0,36)
Open quotient middle	0,51 (0,26)	0,60 (0,28)	0,54 (0,26)
Open quotient rear	0,59 (0,25)	0,59 (0,27)	0,59 (0,31)
MDVP (SPEAD) – sustained tone			
Jitter%	6,97 (14,49)	4,07 (5,30)	0,62 (1,09)*
Shimmer%	13,20 (13,57)	9,7 (9,24)	6,95 (4,22)*
QX%	47,84 (11,04)	49,92 (10,61)	47,01 (6,34)
MDVP (SPEAD) – reading			
Frequency variation%	17,64 (17,31)	11,13 (6,18)	6,04 (3,11)*
Intensity variation%	15,72 (6,02)	18,54 (7,34)	15,15 (2,85)
QX%	46,19 (7,42)	46,97 (6,24)	50,15 (4,45)

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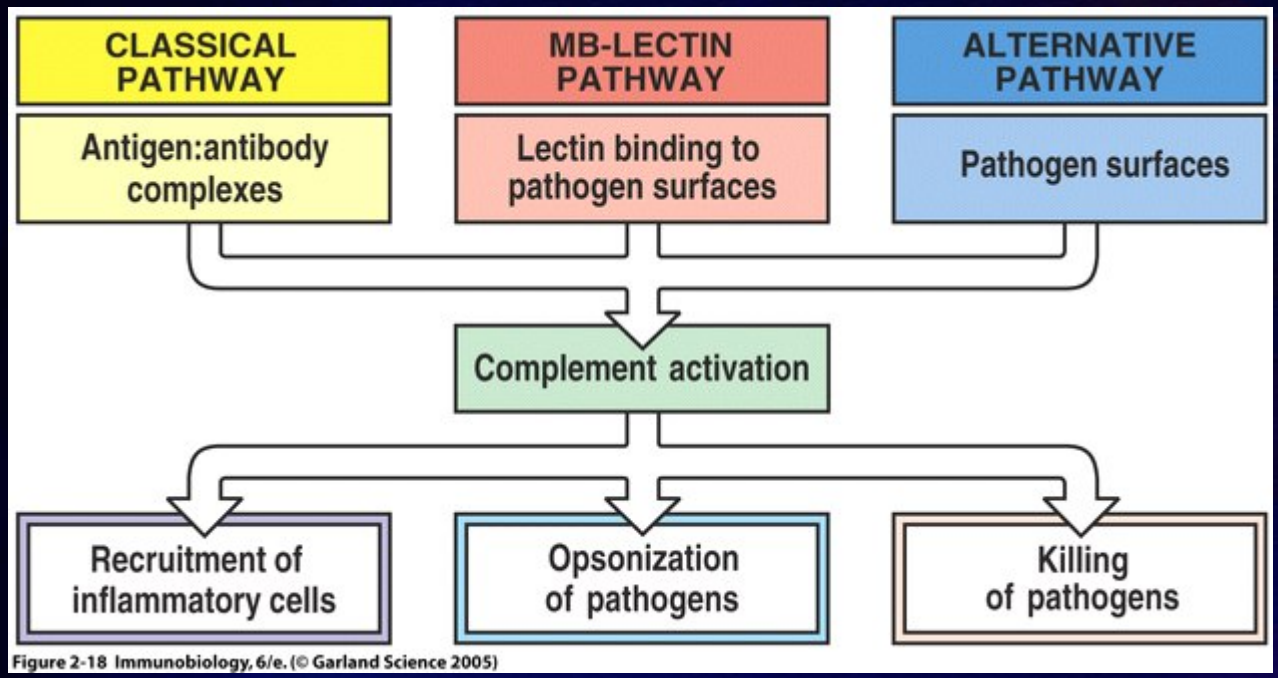
Mannose binding lectin (MBL)

The MBL gene provokes the
MBL pathway of complement activation when infection is found:



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Mannose binding lectin (MBL)

Polymorphisms in the MBL gene reduces total serum MBL concentration, and are associated with the risk of infection:

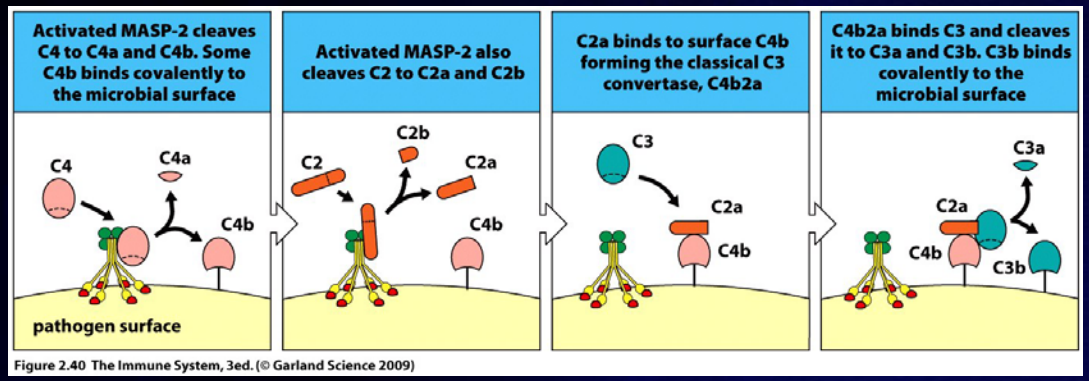

Figure 2.40 The Immune System, 3ed. (© Garland Science 2009)

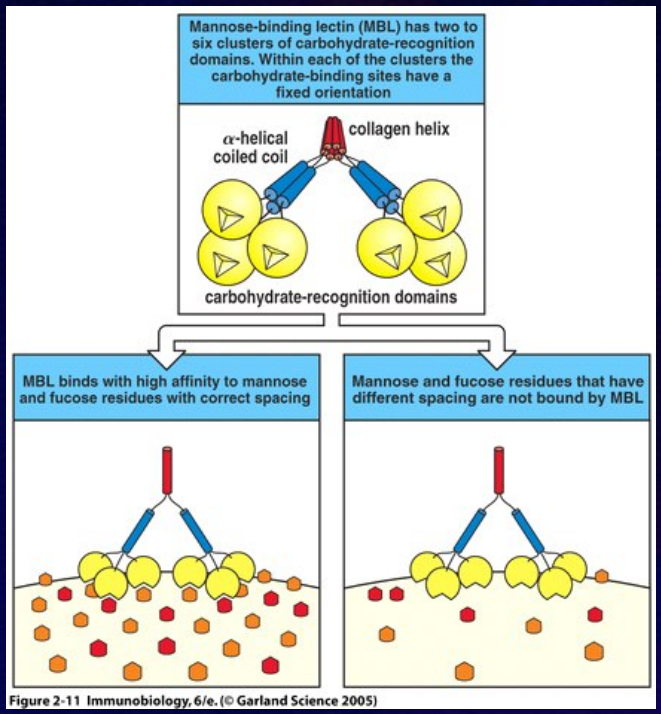

Figure 2-11 Immunobiology, 6/e. (© Garland Science 2005)

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Interarytenoid region oedema comparisons on high speed films, patients with MBL<500 and MBL >500

Oedema of the arytenoids	Dystonia patients with MBL <500 N = 26 Mean (SD)	Dystonia patients with MBL >500 N = 21 Mean (SD)
1st consultation	2,68 (0,57)	2,7 (0,57)
2nd consultation	2,32 (0,57)	2,3 (0,73)

With the UNIVARIATE procedure (studentized residual), no difference was found in the category MBL <500 and >500.
A significant reduction of edema was found equally in the two groups after routine treatment, fexofenadin and budesonid,

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High speed films with voice analyses and MDVP comparisons

	Dystonia patients with MBL <500		Dystonia patients with MBL >500	
	1st consultation	2nd consultation	1st consultation	2nd consultation
	Mean (SD)	*Mean (SD)*	*Mean (SD)*	*Mean (SD)*
High speed results				
Open quotient front	0,52 (0,3)	0,60 (0,27)	0,54 (0,27)	0,57 (0,34)
Open quotient middle	0,50 (0,24)	0,60 (0,24)	0,56 (0,27)	0,61 (0,31)
Open quotient rear	0,58 (0,22)	0,63 (0,28)	0,66 (0,28)	0,59 (0,32)
MDVP (SPEAD) – sustained tone				
Jitter%	7,62 (17,98)	5,07 (6,03)	6,57 (9,91)	1,31 (6,01)
Shimmer%	14,44 (17,93)	10,7 (11,79)	12,19 (5,41)	9,18 (6,44)
QX%	47,09 (10,52)	53,32 (11,38)	50,00 (11,81)	45,47 (7,86)
MDVP (SPEAD)– reading				
Frequency variation%	14,75 (11,62)	12,03 (6,77)	23,01 (26,96)	7,78 (2,84)
Intensity variation%	15,14 (5,53)	19,49 (9,11)	16,06 (7,92)	18,25 (5,52)
QX%	47,64 (6,00)	48,08 (7,08)	42,03 (8,02)	45,19 (5,84)

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Subjective rating of quality of life and severity of disease (visual score 1-100) before treatment

	Dystonia patients with MBL <500 N = 26	Dystonia patients with MBL >500 N = 21
Severity of disease at first examination (visual score 1-100 - 100 being most severe)		
Mean	63,85	63,84
SD	25,01	18,50
Quality of life at first examination (1-100 - 100 being excellent quality of life)		
Mean	54,23	49,23
SD	28,12	26,29

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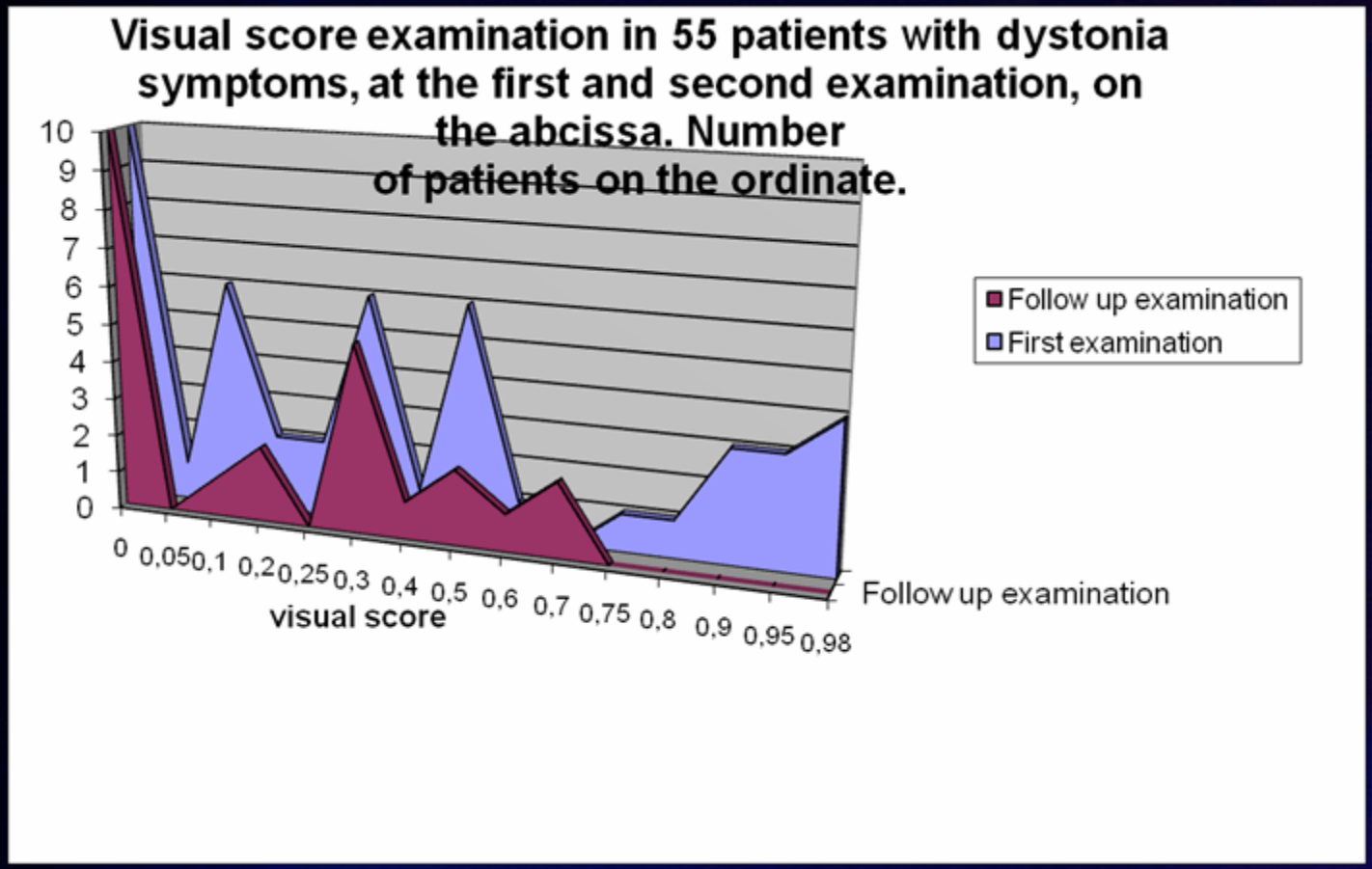
Presentation of the problem of treatment effect with fexofenadine and budenosid locally in the throat



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Average effect is 18.3 improvement (p=0.0001)

Mean change from prior assessment to follow up assessment of -18.3 (p=0.0001). 95% CI: [-27; -10].

0=worst possible quality, 100=best possible quality of life.

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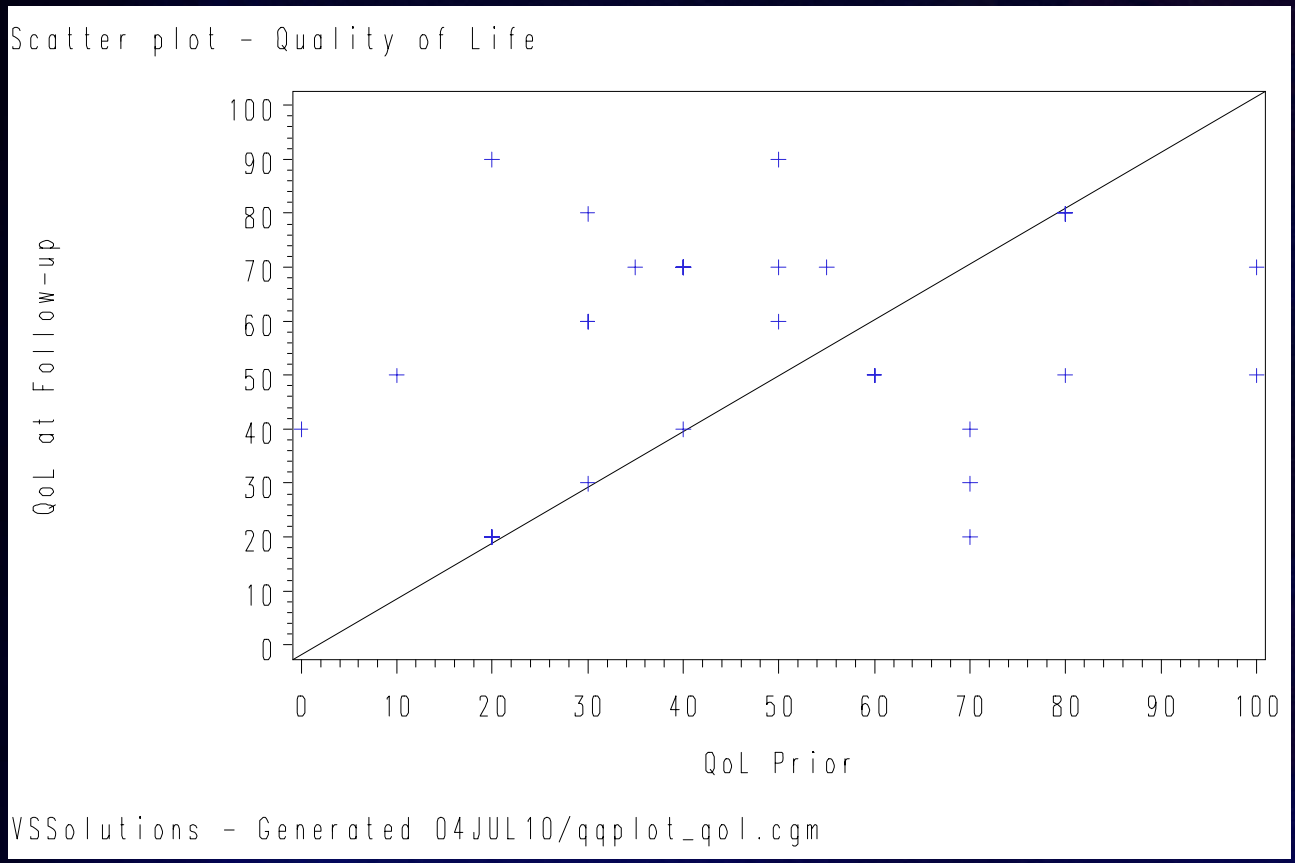
Average effect is 7.3 improvement (p=0.073)



Mean change from prior assessment to follow up assessment of 7.3 (p=0.073). 95% CI: [-0.7; 15].

0=worst possible quality, 100=best possible quality of life.

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Conclusion

- Immunological aspects of dystonia are discussed in a prospective cohort (case-control) study, with a possible related mucosal dysfunction in the upper airways.

- In our measures on upper airway disorders, the genes for lactose intolerance, gluten intolerance and mannose binding lectin (MBL) are routinely studied.

- Due to the fact that almost half of the dystonic patients had low levels of MBL, we focused on a possible connection to treatment effect, which was not found.

- Since the treatment with fexofenadine and budesonid had an effect on the visual scores of severity of the dystonia of 7,3 %, and overall quality of life of 18,3%, it might in the future be possible to find and understand other aspects of immunological treatment effects on dystonia.

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