Advances in Cellular and Molecular Otolaryngology

COACTION

GUEST EDITORIAL

Future aspects of cellular and molecular research in clinical voice treatment

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Until now, we have had no understanding of normal voice function at a cellular or molecular level. Social/psychological aspects on one side and some surgical/physiological aspects on the other side have been elucidated.

We had an opportunity to conduct a Cochrane review of a survey of vocal nodules. Nodules are destroying the voice function of many singers (1). This survey has been updated from 2001 to 2012 and until now there is no evidence of surgery or speech therapy. With our knowledge of high-speed films, we conducted another Cochrane review of laryngopharyngeal reflux (LPR), which showed no evidence of treatment (2). With video stroboscopy based on an average of 25 pictures per second, there were many descriptions in the literature of various kinds of larynx disorders, which were not found on high-speed films with 4,000 pictures per second. LPR as a symptomatic entity was therefore questioned, and a new setup was suggested for the description of the larynx findings in LPR based on graduation of oedema in the arytenoid regions in the larynx (3) (Fig. 1). A randomised controlled trial of LPR showed that the diet correction without acid provocations in the larynx based on lifestyle change was essential, the supplementary use of proton pump inhibitor not being better (4). We noticed that the use of fexofenadine tablets and budesonide inhaler had an effect on the swollen mucosa in the upper airways – due to a direct effect in the upper airways (5) (Fig. 2).

Questions

A young female patient came into the clinic with hoarseness and universal dystonia referred by her physiotherapist. She had been on pension for one-and-a-half years and was sitting in a wheelchair. We used high-speed films to document the vocal spasms due to her dystonia and gave her local budesonide inhaler as well as fexofenadine tablets in maximal doses, as earlier experienced with LPR treatment (6) (Fig. 3). Two weeks later, she came walking in without hoarseness and dystonia symptoms. She later had recurrent symptoms provoked by acute tonsillitis. After this experience, we made a prospective cohort study which showed on average a reduction of dystonia symptoms by 20% using fexofenadine tablets and local budesonide inhalers in the throats of the patients. Of course, we thought that a genetic effect somehow was involved in the treatment. The cohort study (6) (Table 1; Fig. 4) involved two comparable groups of patients with normal/low mannose-binding lectin (MBL). There was no statistical difference. In this study, our research focus was on fexofenadine tablets in high doses (dosage: 2–3 times daily) and local budesonide inhalers in the larynx in maximal doses. We found a statistically significant reduction of oedema in the arytenoid region, also on spasmodic symptoms. Genetic studies in the population in the cohort study did not give significant relations.

Gastroesophageal reflux disorder (GERD) is known to be inherited. In the cohort study (6), no pattern was found of this genetic aspect. Still, the genomic questions are whether primary/secondary dystonia have special relations to fexofenadine tablets or budesonide inhaler locally in the larynx (7–9). The genome analysis in patients is time consuming, and some exons that express dystonia could be focused upon for locating genes related to fexofenadine tablets and budesonide inhalers in the larynx. Probably, parents and siblings must also be focused upon for understanding genetic relationships (10).

Studies at molecular and cellular level related to clinical results in voice treatment are needed. There is a known relationship in the literature between dystonia and mucosal function in the larynx. In animals, it was shown that

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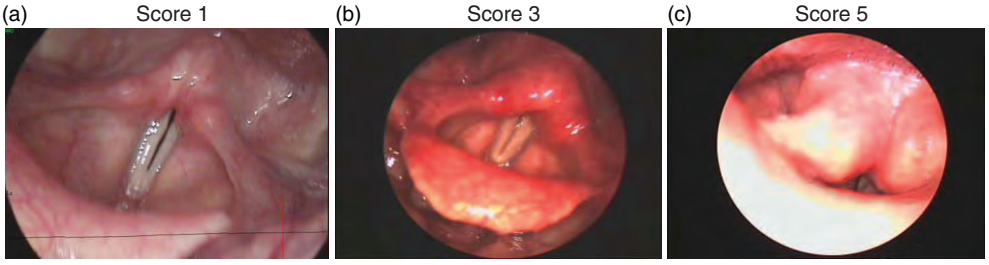


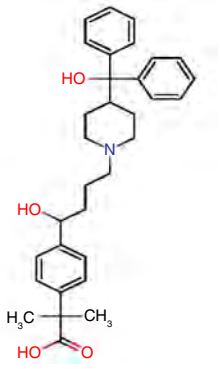
Fig. 1. High-speed films scores with 4,000 pictures per second of the larynx including the arythnoid regions. Score 1 is a normal arytnoid region. Score 3 is presenting a moderate oedema. Score 5, almost total closure of the larynx due to arytenoid oedema (3).

the excision of the larynx mucosa provokes dystonia (11). Most studies of budesonide inhalers are made in the lower airways, thereby not allowing us to extrapolate to the upper airway, where the effect theoretically is to be related to a laryngeal effect. The fexofenadine tablet treatment is related to the immune system, blocking reactions to attacks from outside, (12, 13). It is a well-known fact that fexofenadine tablets are effective on the inhabitancy of oedema in the mucosa (14, 15). An understanding on a genetic level is of major interest in a new genomic research setup in Oxford (16). The principal effect of fexofenadine tablets in the referred cohort study seemed to be that some mucosal voice-related functions came under control.

Analysis

Until now, high-speed films of the vocal folds and the arytenoid region mucosa have not given us any explanation for the medical effect, reducing LPR or dystonia. The vocal fold anatomy was always normal. We can see on high-speed films that in LPR there is a lack of closure of the back of the vocal folds with oedema of the arytenoid region being involved, and in dystonia patients,

The chemical structure of fexofenadine

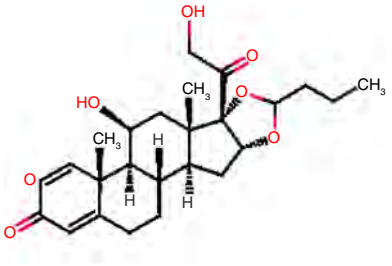


It was developed as a successor of and alternative to terfenadine.

Fexofenadine is a second-generation, long lasting H1-receptor antagonist (antihistamine) which has a selective and peripheral H1-antagonist action. Fexofenadine blocks one type of receptor for histamine (the H1 receptor) and thus prevents activation of cells by histamine. Fexofenadine lacks the cardiotoxic potential of terfenadine, since it does not block the potassium channel involved in repolarization of cardiac cells.

http://www.drugbank.ca/drugs/DB00950

The chemical structure of budesonide



Budesonide has a high glucocorticoid effect and a weak mineralocorticoid effect. It binds to the glucocorticoid receptor with a higher binding affinity than cortisol and prednisolone. Furthermore, a decrease in airway reactivity to histamine and other entities has been observed with the inhaled formulation. Generally, the inhaled formulation has a rapid onset action and improvement can occur within 24 hours of initiation of treatment.

http://www.drugbank.ca/drugs/DB01222

Fig. 2. The chemical structure of a) fexofenadine and b) budesonide.

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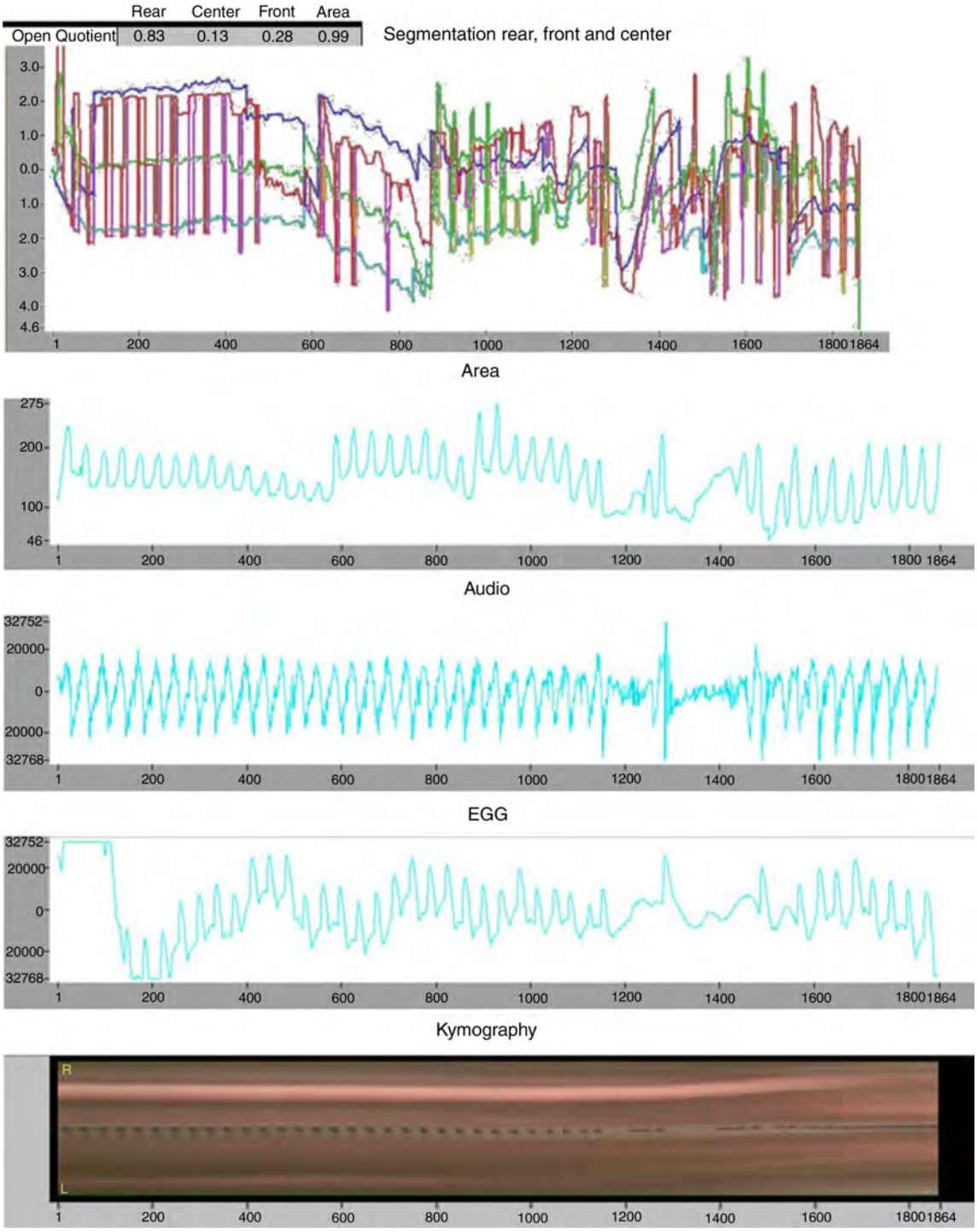

Fig. 3. Segmentation curves of high-speed film with 4,000 pictures per second with calculations of open quotients in the front, centre, and rear parts of the vocal folds. Visual irregularities are illustrated due to a dystonia spasm – from segmentation curves of the vocal folds in front, centre, and rear parts. Area between the vocal folds during intonation, acoustical, electroglottographical, and kymographical curves are also presented (6).

irregularities of rhythm in single movements of the vocal folds. We can also see on high-speed films that the pathology disappears or is reduced with fexofenadine tablets and budesonide inhalers in the larynx (4, 6). Advanced computer reproduction of the single movement of the vocal folds might give more information to be used in the future (17) (Fig. 5).

We are focusing on optical coherence tomography (OCT) of the swallowing process in the oesophagus and larynx as well as on the vocal fold function (18–20).

Table 1. High-speed films, comparing dystonia patients with and without low mannose-binding lectin, inter-arytenoid region oedema, visual score 2nd–1st consultation

	1st consultation			2nd consultation			Change (2nd–1st consultation)			
	N	Mean	Std	N	Mean	Std	N	Mean	Std	p
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 < 500 µg/L vs. MBL > 500 µg/L										0.90§

§Test in the linear statistical model where MBL is included as a fixed effect and baseline is included as a covariate.
***Statistically significant on a 0.1% significance level.
Note: There was no difference. All dystonia patients were better at the 2nd consultation.

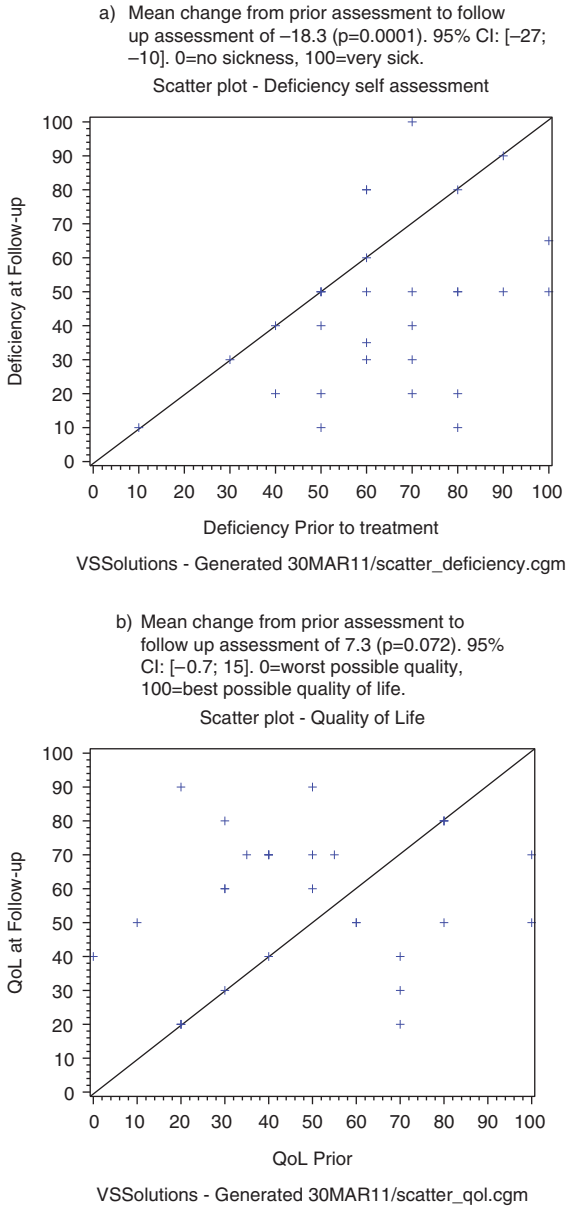

Fig. 4. a) Shows that the whole spasmodic patient population was better at the follow-up on treatment with fexofenadine and local budesonide inhaler in the larynx for the symptom deficiency. b) Mean change on quality of life (6).

It can be shown on OCT how the layers of the vocal folds develop, possibly corresponding to hormonal and paediatric development (21, 22). The arytenoid area in the larynx should be focused upon with OCT in pathology.

The thyroid function is related to voice and the swallowing function, both hormonally and pathoanatomically. We know too little about voice and thyroid hormones in an updated way as well as the outer anatomic supporting muscular structure of the larynx, related to thyroid immune degeneration and cysts (23). Also, here OCT analyses might be of value.

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a

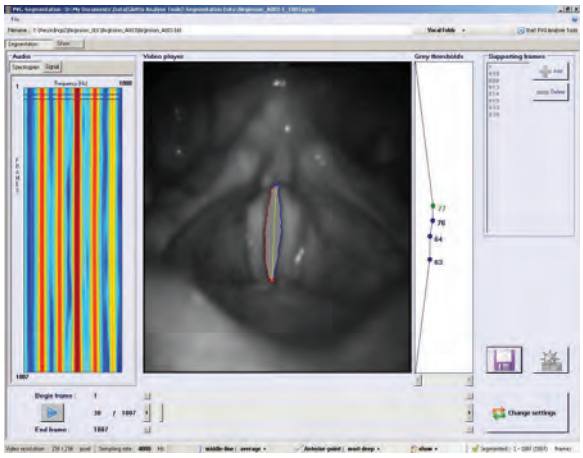

Figure a shows the imported recording and the segmentation in Glottis Analysis Tools (M Döllinger). The possibilities are many to ensure an accurate segmentation: varying black/white balance and segmentation area during the length of the film are just some of them.

b Glottal Analysis Tools along moving high speed films. An increased control with contrast ensures accurate segmentation, and the area is calculated in each vocal fold cycle. This also ensures accurate jitter, shimmer and opening quotients. (Pubertal singing soloist, boy)

b

Shimm(%)	5,048				
HNR(dB)	11,048				
Jitt (%)	0,542				
		Mean	Std	Min	Max
ClosingQuotient(CQ)		0,4149	0,0602	0,2727	0,5455
AsymmetireQuotient		0,4872	0,0721	0,3333	0,5833
Stiffness	Left	0,4919	0,1902	0,254	0,9897
Stiffness	Right	0,4769	0,1664	0,2625	0,8411

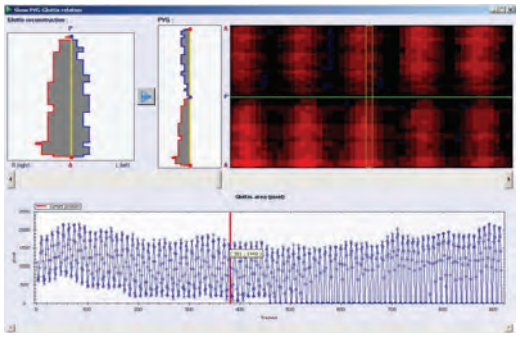

Fig. 5. The Glottis Analysis Tool for advanced quantitative software analysis of high-speed films.

Discussion and conclusion

The aim of this overview was to elucidate voice problems related to molecular and cellular research based on evidence findings. Since no evidence was found in the referred Cochrane reviews on vocal nodules and hoarseness and on LPR and hoarseness, the focus was on clinical experience in a prospective cohort study on dystonia where the mode of treatment was fexofenadine tablets and local budesonide inhaler in the larynx, and in a randomised controlled trial of lifestyle change related to acid provocation of food and habits in LPR. The advanced high-speed films is one new tool, another being OCT, which is to be used in randomised controlled trials. With molecular and cellular knowledge on fexofenadine tablets and budesonide inhaler, and to some extent on diet, clinical trials of voice in the future could include the molecular and cellular understanding in a much better way. Better understanding of genetic pathways should also be focused upon.

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Conflict of interest and funding

There are no conflicts of interest.

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