The influence of botulinum toxin on auditory disturbances in hemifacial spasm

Wpływ toksyny botulinowej na zaburzenia słuchu w połowiczym kurczu twarzy

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Abstract

Background and purpose: Hemifacial spasm (HFS) is frequently accompanied by other symptoms, such as visual and auditory disturbances or pain. The aim of the study was to assess the occurrence of auditory symptoms accompanying HFS using subjective and objective methods, their relation with other HFS symptoms, and their resolution after botulinum toxin (BTX-A) treatment.

Material and methods: The occurrence of hypoacusis, ear clicks and tinnitus was assessed by questionnaire in 126 HFS patients from an electronic database which included medical data such as severity of HFS rated by clinical scale and magnetic resonance imaging focused on the presence of vascular nerve VII and VIII conflict. Forty consecutive patients treated with BTX-A and 24 controls matched by sex and age underwent laryngological examination including audiometry, tympanometry and acoustic middle ear reflex before injection and two weeks later.

Results: About 45.2% of patients complained of auditory disturbances (31.7% hypoacusis, 30.2% ear clicks and 7.1% tinnitus) on the side of HFS. Auditory disturbances correlated with severity of HFS symptoms but not with age, disease duration, or neurovascular conflict with nerves VII and VIII. We did not find abnormalities in audiometric and tympanometric assessment in patients in comparison with con-

Streszczenie

Wstęp i cel pracy: Połowicznemu kurczowi twarzy (hemifacial spasm – HFS) często towarzyszą inne objawy, takie jak zaburzenia widzenia, słuchu czy ból. Celem pracy była ocena występowania zaburzeń słuchu i analiza ich związku z innymi objawami choroby, a także ich zmiana pod wpływem toksyny botulinowej (BTX-A).

Materiał i metody: Obecność i nasilenie niedosłuchu oraz kliku i szumu usznego oceniono na podstawie wywiadu u 126 chorych na HFS zarejestrowanych w elektronicznej bazie danych, która zawiera m.in. ocenę nasilenia HFS w odpowiednich skalach oraz ocenę konfliktu naczyniowego z nerwem VII i VIII w badaniu za pomocą rezonansu magnetycznego. Czterdzieściu kolejnych pacjentów leczonych BTX-A oraz 24 osoby tworzące grupę kontrolną poddano szczegółowej ocenie laryngologicznej z badaniem audiometrycznym i tympanometrycznym przed wstrzyknięciem BTX-A i po 2 tygodniach od jej podania.

 Wyniki: Spośród chorych na HFS 45,2% skarżyło się na zaburzenia słuchu [31,7% na niedosłuch, 30,2% na trzask („klik”) uszny i 7,1% na szum uszny] po stronie HFS. Zaburzenia słuchu częściej występowały u chorych z nasilonymi objawami HFS, ale nie miały związku z wiekiem chorych, czasem trwania choroby czy występowaniem konfliktu naczyniowego z nerwem VII i VIII. Nie stwierdzono różnic w ba-
Hemifacial spasm (HFS) is a movement disorder characterized by unilateral clonic or tonic contractions of muscles supplied by the facial nerve. HFS begins most commonly in the fifth decade and is twice as common in women (14.5 vs. 7.4/100 000) [1]. Involuntary movements usually affect the orbicularis oculi muscle at first, and then spread gradually to other muscles innervated by the facial nerve. It is thought that the muscle contractions in HFS are secondary to the compression of the facial nerve with the vessel within the facial nerve exit zone from the brainstem and result from abnormal impulsion within the facial nerve due to the occurrence of artificial synapses between adjacent axons or due to the reorganization of the facial nucleus [2-4].

Besides the typical muscle twitching of half of the face, many patients with HFS suffer from additional symptoms and signs, including abnormal tearing, salivation or auditory disturbances [3-5]. The most frequently reported (13-32% of patients) [3-7] auditory symptoms include hypoacusis and tinnitus, sometimes in the form of specific intermittent crackles, called ear clicks. Unilateral tinnitus may result from the activity of the tensor tympani muscle and/or motor units of the stapedius nerve, as its fibres travels through the facial nerve. The contractions of the stapedius muscle may evoke oscillations of the auditory ossicles within the middle ear. Close proximity of the facial and vestibulocochlear nerve might facilitate the occurrence of neurovascular conflict with the latter one, and this could be another cause of auditory disturbances. Damage of the vestibulocochlear nerve usually causes an increase of the hearing threshold, accompanied by an increased threshold of the stapedius reflex and alterations in brainstem auditory evoked potentials.

The aim of the study was to assess the occurrence of subjective and objective auditory disturbances accompanying HFS, their relation with other HFS symptoms, and their resolution after botulinum toxin (BTX-A) treatment.

Material and methods

The study comprised 126 patients with HFS (66.6% were women; mean age: 62.2 ± 10.8 years; mean duration of HFS: 9.4 ± 10.6 years) who were treated in the Movement Disorders Outpatient Clinic at the Department of Neurology (University Hospital of Kraków) between 2004 and 2010. The diagnosis of HFS was established in each case by the movement disorder specialist (M.R.), according to the clinically observed unilateral clonic or tonic contractions of muscles innervated by the facial nerve.

Demographic and clinical data were recorded in the dedicated electronic database. The registered variables included, among others, age at onset of the disease, duration of the disease and its course, affected side, associated symptoms, including auditory ones (tinnitus, and, separately, ear clicks, because those were very often and clearly reported by the studied patients), hypoacusis, factors that exacerbate or relieve muscle contractions, comorbidities, family history, and treatment.

The severity of HFS was assessed according to the seven-point Clinical Global Impression Scale (CGI) [8] and with the five-point scale proposed by Tan et al.
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Each patient had magnetic resonance imaging (MRI) of the head performed with detailed assessment of the cerebellopontine angles in 3D FIESTA sequences to establish the presence of neurovascular conflict (compression of the seventh or eighth cranial nerve or compression of the brainstem).

Written consent was obtained from each patient before the beginning of the study.

A more detailed assessment of auditory disturbances was performed in 40 (out of the 57) consecutive patients with HFS who were treated with BTX-A in the last quarter of the year 2009. Those patients required repeated BTX-A injections because of the severe HFS symptoms; the time from the previous injection was at least 12 weeks. Those patients were additionally tested just before and two weeks after the injection of BTX-A (Botox®) in the total dose of 25 units in 5 standardized locations within the face (three points near the external angle of the eye, one point at the level of the zygomatic arch, and one point within the mentalis muscle).

Hearing tests were performed by otolaryngologists (K.Z., K.H.-S.). Tests included a detailed history of previous and current disorders of hearing and balance, with special attention paid to the occurrence and the type of hypoacusis and tinnitus, as well as the assessment of the tinnitus loudness. During the tinnitus loudness test (measured in dB), the patient is presented with the noise of various frequencies generated by an audiometer to compare it with the subjective tinnitus reported by the patient. Then, the patient reports the masking of his/her tinnitus by the externally generated noise (up to the level of 15 dB above the hearing threshold). In case of difficulties in finding the appropriate masking noise, white noise combining all frequencies of the given audiometer can also be used.

Further otolaryngological assessment included otoscopy, and audiometry, both tonal and impedance (tympanometry and stapedius reflex). Brainstem auditory evoked potentials (BAEP) (Viking Quest, Nicolet) were performed before BTX-A injection in patients with auditory disturbances. Two weeks after the injection of BTX-A, changes in the severity of the tinnitus were assessed according to the patients’ reports as complete resolution, decrease, or no change in the severity of tinnitus.

The study also involved a control group of 24 subjects (mean age 58.3 ± 9.1 years) who were age- and sex-matched with the patients. Control subjects were patients of the Outpatient Clinic within the Department of Otolaryngology, Jagiellonian University College of Medicine in Kraków, who were treated because of upper respiratory tract infections and were scheduled for tonsillectomy due to chronic tonsillitis. Control subjects had no subjective or objective otological symptoms, and no clinical features of otitis media or Eustachian salpingitis.

Controls were subjected to interview, assessment of the level of tinnitus, otoscopic and audiometric testing, with tympanometry and assessment of the stapedius reflex, similarly to the patients with HFS.

Pure-tone audiometry included measurements of air and bone conduction to establish the hearing threshold. Testing included appropriate tones within the hearing range at the frequency of 125, 500, 1000, 2000, 4000, and 8000 Hz. Tests were performed in a sound-proof chamber, starting with the side of the worse hearing, with synchronous masking of the other ear with noise. The same conditions were applied when the tympanometry was performed using Zodiak 901 apparatus (Masden). The objective testing of eardrum compliance uses measurements of the pressure within the tympanic cavity, analysis of the shape of the curves, as well as bilateral assessment of the stapedius reflex. The following three types of tympanogram were discerned: type A – normal; type B – abnormal, suggesting the presence of fluid within the tympanic cavity; and type C – abnormal, suggesting negative pressure within the tympanic cavity, usually associated with Eustachian tube dysfunction (type C1, pressure between 0 and – 200 daPa, and type C2, pressure below – 200 daPa).

The stapedius reflex (acoustic reflex) is the contraction of the stapedius muscle in response to stimulation with a loud acoustic stimulus. The technique of stapedius reflex testing includes insertion of an acoustic probe into one ear and placement of an audiometric earphone on the other ear (Fig. 1). The acoustic stimulus generated by the probe evokes the occurrence of the reflex in the other ear (contralateral reflex). The probe also contains an additional earphone that enables registration of the ipsilateral reflex. The probe was performed using Zodiak 901 apparatus (Masden). The intensity of the tone at the frequencies of 500, 1000, 2000, and 4000 Hz was gradually increased from 65 to 100 dB, to determine the threshold for the stapedius reflex. The presence of the reflex was noted if the reflex was present at least at one frequency.

Statistical analysis

Variables were characterized with the mean ± standard deviation (SD) depending on their distribution, which was tested with the Kolmogorov-Smirnov test.
The statistical significance of differences between numerical variables was analysed with the $\chi^2$ test with Yates correction where appropriate. Student’s $t$-test was used to assess the differences between normally distributed variables, and Mann-Whitney $U$-test was used to assess differences between other variables. All calculations were performed using a commercially available statistical package (STATISTICA for Windows v. 6.0, StatSoft Inc.). A $p$-value < 0.05 was considered statistically significant.

**Results**

Fifty-seven out of the 126 patients with HFS (45.2%) registered in the electronic database reported auditory symptoms. Forty patients (31.7%) complained of hypoacusis, 38 subjects (30.2%) reported ear clicks, and 9 patients (7.1%) complained of tinnitus ipsilaterally to the HFS. Auditory symptoms were significantly more prevalent in patients with severe signs of HFS, either on the CGI scale ($\geq 4$) ($\chi^2 = 4.80$, $p = 0.028$) or on the 5-point Tan scale (4 or 5 points) ($\chi^2 = 6.15$, $p = 0.01$), but were not related to patients’ age, duration of the disease, or presence of neurovascular conflict with the seventh or eighth cranial nerve (Table 1).

More detailed hearing testing was performed in 40 consecutive patients with HFS. This subgroup did not differ from the whole group of 126 patients regarding sex (women: 65% vs. 64%), age (58.3 ± 9.1 vs. 62.2 ± 10.8 years), duration of HFS (9.2 ± 6.9 vs. 9.4 ± 10.6 years), age at onset of HFS (50.7 ± 10.4 vs. 53.6 ± 11.2 years) or presence of neurovascular con-
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Twenty out of 40 subjects reported auditory symptoms. Patients with auditory symptoms did not differ from those without auditory symptoms regarding age (59.0 ± 9.0 vs. 57.5 ± 9.3 years), duration of HFS (10.6 ± 6.9 vs. 7.8 ± 6.8 years), age at onset of HFS (49.6 ± 10.9 vs. 51.7 ± 10.2 years), severity of HFS symptoms on the CGI scale (5.0 ± 0.9 vs. 5.1 ± 1.2) or on the Tan scale (3.0 ± 0.9 vs. 3.1 ± 1.2) or the presence of neurovascular conflict with the seventh (80% vs. 60%) or eighth cranial nerve (45% vs. 30%).

Mild hypoacusis, mainly receptive, was found in audiometry in 90% of patients with HFS (mean 30 dB; range 10-70 dB) and in 87.5% of control subjects (mean 30 dB; range 10-70 dB), which is within the normal range for the given age. No difference in the prevalence of hypoacusis was found between patients with and without auditory symptoms.

Audiometric assessment of tinnitus revealed its presence in 14 patients (70%) who reported auditory symptoms and in none of the control subjects.

Normal tympanogram (type A) was recorded in more than 95% of controls and in more than 80% of patients with HFS, both with and without auditory symptoms. Abnormal tympanogram of C type, suggesting dysfunction of the Eustachian tube, was recorded in six patients, and abnormal tympanogram of B type was noted in one patient.

Loss of the stapedius reflex ipsilaterally to the side of HFS symptoms with the stimulation ipsilaterally and contralaterally to the affected side was found in 50% of patients who complained of auditory symptoms. Stimulation ipsilaterally to the healthy side did not evoke the stapedius reflex in 10% of patients only.

Among patients without auditory symptoms, loss of the stapedius reflex occurred as often as in the control group, i.e. in 5% of patients during ipsilateral stimula-
tion and in 25% of patients on the side of HFS and in 65% of patients on the other side during contralateral stimulation.

Loss of the contralateral stapedius reflex was found in 40% of controls, and loss of the ipsilateral stapedius reflex was noted in 6% of controls.

The difference between patients and controls regarding presence of the ipsilateral stapedius reflex was significant ($\chi^2 = 4.69, p = 0.03$). No correlation was found between loss of the stapedius reflex on the side of HFS during stimulation of the affected side and the severity of HFS or presence of neurovascular conflict involving the seventh or eighth nerve.

Brainstem auditory evoked potentials (BAEP) were tested in 20 patients who complained of auditory disturbances on the side of HFS. In 5 patients, the recordings contained artefacts that excluded an analysis, and in 6 other cases the recordings were abnormal. On the healthy side, artefacts were noted in 3 patients and an abnormal recording was found in 6 other patients, similarly to the results obtained on the side of HFS. The recorded abnormalities, including prolonged latencies, lack of specific waves, or longer distances between waves, were associated with different waves or distances and were noted in single patients. An analysis of findings did not reveal any common or typical pattern of abnormalities. No association was found between the abnormal results of brainstem auditory evoked potentials and neurovascular conflict involving the eighth nerve or loss of the stapedius reflex.

Two weeks after the last injection of BTX-A, auditory disturbances were reported by 7 patients out of 20 patients who complained of them earlier and by none of the patients who did not complain of them before ($\chi^2$ with Yates correction $= 16.41, p = 0.0001$). The reduced number of complaints included both hypoacusis and ear clicks or tinnitus. The results of all audiometric and tympanometric studies performed after BTX-A injection did not differ from those performed before BTX-A injection (Table 2).

**Discussion**

The group of patients described here is the largest one among all analysed cohorts in the available literature. Our study showed that complaints of auditory disturbance including hypoacusis and ear clicks or tinnitus ipsilaterally to the side of HFS occur in approximately half of the patients with HFS. Patients with those complaints, however, have no important abnormalities in objective audiometric testing, except for more common loss of the ipsilateral acoustic (stapedius) reflex.

Studies on acoustic disturbances in patients with HFS are scarce, and reported rates of patients complaining of hypoacusis are smaller (15% [6] and 13% [5]) than in our study (32%). Important differences are noted also regarding the side of the hypoacusis. We have registered the complaints of hypoacusis which were either ipsilateral to the HFS or more severe on the side of the HFS, while the above-mentioned studies reported hypoacusis independently of the HFS side.

Ear clicks in our patients were as common as hypoacusis (30%). In otolaryngological practice, the ear click is a subtype of tinnitus rather than a distinct auditory symptom. In our study, ear clicks were differentiated from complaints related to tinnitus because of their typical clinical picture (short-lasting sound located in the ear, occurring periodically and synchronous with the facial muscle contractions). The one study published so far on this topic comes from New York and reports the presence of ear click in 4% of patients [5].

Audiometric testing, both in patients and controls, revealed sensorineural hearing loss in 90% of subjects; it ranged between 20 and 30 dB, which suggested lack of an association with the comorbidity. Those findings are in agreement with the data published by Lee et al. [12], showing the mean hypoacusis of 19 dB (range 7-44 dB) in 90% of patients with HFS. Moller and Moller obtained somewhat different results and suggested that the audiometry was abnormal in 33 out of the 143 (23%) patients with HFS. Those were selected, isolated receptive deficits in the range of low or medium frequencies in 11% of patients and abnormal reception in the range of low frequencies in 12%. That type of abnormal audiogram is very rare (about 1% of normal subjects) [14,15]. Those authors suggested that the abnormalities in acoustic assessment were due to the selective damage of the cochlear part of the eighth cranial nerve by the probable vascular compression of both the seventh and eighth cranial nerve by the same vessel. We did not find such a specific hearing deficit in any of our 40 patients; there are no other reports on that finding in the available literature.

Subjective complaints on tinnitus were confirmed with laboratory testing in all patients. Tinnitus was more prevalent in patients with HFS than in controls. Studies published to date assess neither the prevalence of tinnitus nor its pitch and loudness.

The stapedius reflex threshold in patients with HFS, but not in relation to auditory disturbances, was assessed.
in two studies by Moller and Moller [13,16], who tested consecutively 39 and 137 subjects and reported findings similar to ours. They reported loss of the ipsilateral stapedius reflex in 39-41% of patients and loss of the contralateral stapedius reflex in 42% of patients. Loss of the ipsilateral reflex on the side of HFS and loss of the contralateral reflex evoked on the healthy side and recorded on the side of HFS might suggest, according to Moller and Moller, that the disturbances are located within the facial nerve itself or in its motor nucleus [16]. No studies have been published so far regarding presence of the stapedius reflex in patients with HFS and with auditory symptoms in comparison with controls. In our group of patients with HFS, the loss of the ipsilateral stapedius reflex on the side of HFS was significantly more common than in controls (45% vs. 6%). Such a difference was not found in the case of loss of the ipsilateral stapedius reflex contralaterally to the side of HFS when compared with controls (10% vs. 6%). This might be explained by excessive impulsion from the facial nucleus that led not only to contractions of the mimic muscles but also caused synchronous contraction of the stapedius muscle, which interfered with the normal stapedius reflex and led to loss of the reflex. Audiatory symptoms in HFS were more common in patients with absent stapedius reflex and with more severe motor HFS symptoms, according to the CGI and Tan scales. This finding supports the notion that auditory disturbances in HFS are not related to concomitant damage to the eighth nerve, but arise from abnormally increased impulsion in the facial nerve, producing additional contractions of the stapedius muscle, and tensor tympani muscle (which was not tested directly).

Contralateral stapedius reflexes were absent in 50-60% of patients and in almost 40% of controls. The reflex arc in the contralateral reflex, in contrast to the ipsilateral one, includes nerve fibres in the brain stem. This part of the pathway might be impaired in subjects older than 50 (such patients constituted the majority of both patients and controls) due to degenerative or vascular lesions, even small ones, and may lead to elevation of the reflex threshold above routinely used values.

We did not find any difference in abnormal BAEPs ipsilaterally to the side of acoustic disturbances in patients who reported such complaints. The few studies published so far have provided similar findings. Moller and Moller [16] did not find any difference in prevalence of abnormal BAEPs in HFS patients with an abnormal audiogram when compared with HFS patients without an abnormal audiogram. The same authors studied 39 patients with HFS [17] and found significantly more common prolonged latency of III and V wave on the side of HFS when compared with the healthy side. Significance was not achieved in patients with right-sided HFS because of the small sample (15 subjects). Increased latency of III and V wave was explained by probable compression of the brain stem with the vessel that also simultaneously compressed the eighth nerve.

Studies on the pathomechanism of an ear click accompanying idiopathic palatal tremor showed that its origin was importantly related to the Eustachian tube. Opening of the nasopharyngeal terminus of the Eustachian tube is made possible by the action of the tensor tympani muscle and the tensor veli palatini muscle, which receive motor innervation from the trigeminal nerve. The levator veli palatini muscle, innervated by the vagus nerve or greater petrosal nerve, a branch of the facial nerve, acts synergistically with the two just-mentioned muscles. Contraction of the levator veli palatini causes distention of both walls of the cartilaginous part of the tube, leading to increase in the diameter of the tube and augmentation of the action of the tensor veli palatini muscle. It narrows the nasopharyngeal orifice of the tube, causing bulging of the mucosa in the lower circumference of the tube. Sudden closure of the tube may generate an ear click. Abnormally increased impulsion descending from the facial nucleus, observed in HFS, causes contractions not only in the lower half of the face, but also generates an ear click through the contraction of the levator veli palatini and sudden opening and then sudden closure of the Eustachian tube.

Subjective hypoacusis reported by the patients probably also results from the dysfunction of the tube. Pressure fluctuations within the Eustachian tube, synchronous with the contractions of facial muscles and caused by the contractions of the levator veli palatini, as well as prolonged closure of the tube, might be the reason for the hypoacusis reported by the patients.

The association found between presence of auditory disturbances and severity of HFS motor symptoms assessed with various scales additionally supports that pathomechanism.

The hypothesis of Eustachian tube dysfunction as a cause of auditory disturbances is further supported by the decrease of subjective auditory disturbances at two weeks after the injection of BTX-A, which was not reflected by an improvement in hearing parameters evaluated in audiometry, objective testing of tinnitus, tym-
panometry or presence of the stapedius reflex. Improvement after BTX-A was related to subjective hypoacusis only. Diffusion of the BTX injected in the standard points within the face to the levator and tensor veli palatini (both responsible for opening of the Eustachian tube) led to the decrease of their abnormally high activity generated by the pathological impulsion in the facial nerve. Lack of changes in presence of the stapedius reflex after BTX-A injection shows that BTX-A does not affect the stapedius muscle directly through antidromic transportation of BTX-A by the nerve fibres to the central nervous system.

Conclusions
1. Auditory disturbances, including hypoacusis, ear clicks and tinnitus ipsilaterally to the side of HFS, are found in about half of the patients.
2. The above-mentioned disturbances are not accompanied by any important abnormalities in subjective audiometric testing, objective tympanometry or auditory evoked potentials. The one exception was more common loss of ipsilateral acoustic reflex in patients with HFS.
3. BTX-A injected into the facial muscles decreases subjective auditory symptoms, both hypoacusis and ear clicks or tinnitus, in about 50% of patients with HFS. It does not affect, however, any objective parameter of hearing testing.
4. The results of this study suggest that the reported auditory disturbances are not related to the damage of the eighth nerve but are probably associated with contractions of the stapedius muscle and with Eustachian tube dysfunction due to the abnormally increased activity of the seventh nerve, which improve after BTX-A injection.

References