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Hypoglossal nerve stimulation [HGNS] for Obstructive Sleep Apnea [OSA] treatment – a review

Stymulacja nerwu podjęzykowego [SNP] w leczeniu obturacyjnego bezdechu sennego [OBPS] – przegląd piśmiennictwa

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ABSTRACT: Obstructive sleep apnea (OSA) is characterized by recurrent periods of upper airway obstruction (hypopneas and apneas) during sleep. It leads to repeated oxyhemoglobin desaturations, nocturnal hypercapnia and arousals. Common symptoms include loud snoring with breathing interruptions. Excessive daytime sleepiness and cognitive impairment occurs. Obstructive sleep apnea is a major cause of morbidity and mortality in Western society. Its association with an increased risk of development and progression of neurocognitive, metabolic, cardiovascular and oncologic diseases and complications is well described. Significant factor in OSA pathogenesis is reduced muscle tone in the tongue and upper airway. In the recent years, devices providing neurostimulation of the hypoglossal nerve (HGNS) were developed as an alternative for noncompliant CPAP (continuus positive airway pressure) patients. Clinical trials suggest that electrical stimulation of the hypoglossal nerve is effective. This is considered to be one of the targets of neurostimulation in the treatment of obstructive sleep apnea (OSA).

KEYWORDS: upper airway stimulation, obstructive sleep apnea, neurostimulation, hypoglossal nerve

STRESZCZENIE: Obturacyjny bezdech senny (OBPS) jest chorobą charakteryzującą się nawracającymi epizodami zwężenia (spłycenie oddechu) lub zamknięcia (bezdech) dróg oddechowych. Zaburzeniom towarzyszy spadek saturacji krwi, hiperkapnia oraz powtarzające się wybudzenia. Schorzenie to dotyka częściej mężczyzn niż kobiety. Za powikłania OBPS uważa się nadciśnienie tętnicze, udar mózgu, chorobę wieńcową, cukrzycę typu 2 oraz zwiększone ryzyko wypadków komunikacyjnych. Diagnostyka oraz skuteczne leczenie powinny być wdrożone jak najwcześniej. Leczenie opiera się na chirurgicznej korekcie przeszkód anatomicznych, jeżeli stwierdza się je w badaniu klinicznym oraz stosowaniu aparatu CPAP (continuus positive airway pressure), który generując dodatnie ciśnienie, zapobiega zapadaniu się ścian dróg oddechowych. Stymulatory nerwu podjęzykowego są nową metodą leczenia i uważane są za dobrą alternatywę dla pacjentów ze średnim lub ciężkim OSAS, u których leczenie CPAP nie przyniosło oczekiwanych rezultatów lub było źle tolerowane. Leczenie obturacyjnego bezdechu sennego za pomocą SNP staje się rutynową metodą leczenia w trudnych przypadkach.

SŁOWA KLUCZOWE: obturacyjny bezdech senny, neurostymulacja, nerw podjęzykowy

INTRODUCTION

Obstructive sleep apnea (OSA) is characterized by episodes of airway obstruction recurring during sleep. Apnea is defined as an episode of total (>90%) restriction of airway patency lasting at least 10 seconds with an intercurrent decrease in blood saturation of 4%. In turn, hypoapnea denotes a decrease (of a minimum of 30%) in airway lumen and a decrease in saturation of a

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value less than 4%. The severity is determined as an AHI index (Apnea/Hypoapnea Index) which describes the number of apneas and episodes of shortness of breath during an hour of sleep. According to the American Academy of Sleep Medicine (AASM), OSA is divided into three degrees of disease severity: mild (AHI 5-15/h), moderate (AHI 15-30/h) and severe (AHI above 30/h). Occurrence of OSA is facilitated by the presence of anomalies in the anatomy of upper airways. The predisposing risk factors in the extent of anatomical changes in upper airways are deformations and polyps of nose, tonsil hypertrophy, excessive enlargement of tongue (macroglossia), abnormalities in the build of mandible, excessive soft palate and uvula flaccidity and impairment of nose patency. During the course of disease it comes to decrease in blood saturation, hypercapnia and repeating awakenings. The disorder concerns more frequently men than women. Among the French population 4% of men and 2% of women suffer from OSA. With age, the frequency of respiratory disorders during sleep significantly increases, occurring in 10% of people above 65 years of age. Among the patients with OSA 50% of cases are patients with obesity. The complications of OSA are: arterial hypertension, ischemic heart disease, and diabetes type 2. Sleepiness during daytime, predisposition to traffic accidents and mood disorders are also observed. [5,25,1]

The diagnostics of OSA is based on polysomnographic examination, during which, among others, AHI (apnea hypopnea index) and ODI (oxygen saturation and desaturation index) indexes are being assessed. In the clinical evaluation additionally subjective scales of sleepiness during daytime are used e.g. Epworth Sleepiness Scale (ESS), Functional Outcomes of Sleep Questionnaire (FOSQ), and Calgary Sleep Apnea Quality of Life Index (SAQLI). The methods of treatment may be divided into: conservative treatment (protruding mandible mouth devices, aiming for maintaining tongue extension and supporting soft palate, uvulopalatopharyngoplasty, hyoid bone osteotomy, ortognathic surgeries). [23]

In case when conservative treatment and/or surgical correction of anatomical abnormalities do not give results, treatment with CPAP machine is a standard of proceedings. The generated pressure is maintained at a constant level or undergoes autoregulation so that it effectively prevents airway walls from collapsing. In France, the percentage of patients undergoing this therapy is 600 000 people. [5,1] Due to inconveniences of therapy, only 40-60% of patients uses CPAP according to the doctor's recommendations. In case when the results of treatment are not satisfactory, alternative treatment solutions should be sought, among which are neurostimulation of hypoglossal nerve or directly of tongue muscles. [22,3]

First experiments were carried out in animals. In 1989 Miki et al. showed that stimulation of genioglossal muscle conducted in

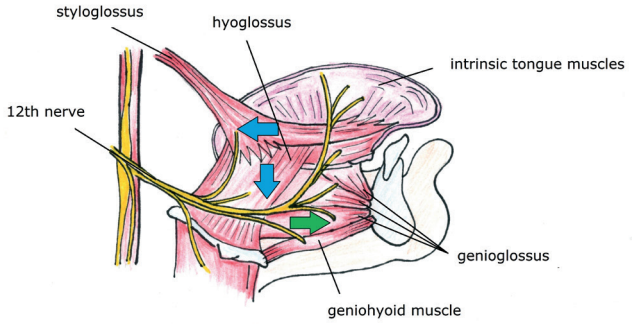

Fig. 1. Figure of muscles of the tongue innervated by the 12th nerve.

anesthesia in dogs led to a decrease in air resistance in airways and a decrease in collapsing of their walls. Similar results were obtained in year 1993 by Schwarz, who conducted a bilateral stimulation of hypoglossal nerve in cats which was completed with success. [20,26] In 1978 Remmers et al. as first examined the correlation between loss of genioglossal muscle tone and collapsing of airways in patients with OSA. This observation was confirmed by Mezzanotte et al., who showed that at the time of loss of tone of the genioglossal muscle it comes to loss of wall stiffness and collapsing of walls. [19,21]

This discovery allowed for developing of a method of treatment based on the electrical stimulation of hypoglossal nerve which has been used with success since 1994. So far extraoral (percutaneous), intraoral, and intramuscular electrodes have been used. [3] First systems were based on the stimulation of the muscles of throat. Their use was limited because during the time of their action it came to awakening of the patient from sleep. Next modifications enabled improvement of this method and increase of its effectiveness and comfort of the patient. Adding the breathing sensors allowed for a synchronization of the stimulator's action with breath and equipping the electrode with a special silicone cuff prevented constant stimulation of the nerve. [16]

The aim of neurostimulation is to improve the tone of the tongue without its excessive protrusion which will prevent airways from collapsing. [9] The function of HGNS (hypoglossal nerve stimulation) is based on stimulation of tongue muscles by the electrodes placed within the branch of the 12th nerve which allows for its selective action. Depending on the system, electrodes are localized bilaterally or on one side – usually on the right. Stimulation of tongue muscles with bilateral localization of electrodes leads to its protrusion along a straight track while their unilateral localization results in tongue deviation. [11]

Electrical stimulation of genioglossal muscle is considered as a promising trend in the treatment of sleep apneas. It is thought

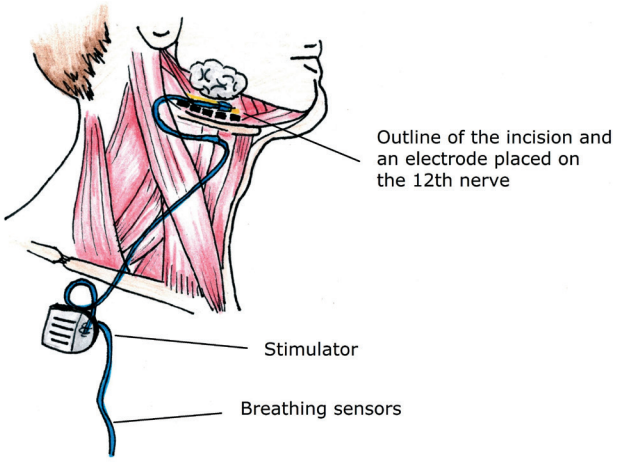

Fig. 2. System of the 12th nerve stimulation including an implanted neurostimulator and electrodes with a cuff and breathing sensors.

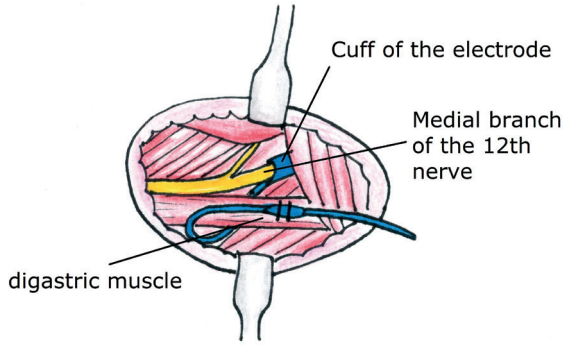

Fig. 3. System of the 12th nerve stimulation including an implanted neurostimulator and electrodes with a cuff and breathing sensors.

to be an effective alternative to CPAP in patients with moderate/severe OSA. [6] This is confirmed by the studies carried out by Eastwood et al. with the use of genial electrodes, in which a significant improvement of airway patency was found. It allowed for achieving a decrease in the frequency of apnea/hypoapnea by 55-65% during the 6 month observation period. [6] Time on the basis of which the HGNS results were evaluated was minimally 6 months from the implantation of stimulator. It was found that the longer period of observation, the higher stability of treatment results. [17]

Stimulation of hypoglossal nerve as a method of treatment has also limitations of use. It is not recommended in patients with airway constriction localized on many levels, of a multifactorial origin, and also in patients with concentric collapsing of the throat wall. [6]

PHYSIOLOGY

Hypoglossal nerve is the 12th cranial nerve and motorically innervates external and internal tongue muscles except the palatoglossal muscle. On the level of hyoid bone, the nerve divides into two branches: medial and lateral. The medial branch supplies in motor fibers the genioglossus as well as longitudinal, transverse and vertical muscles of tongue. The lateral branch innervates styloglossus, hyoglossus and inferior longitudinal muscle of tongue. Tongue muscles can be divided into those located in the anterior part (intrinsic muscles of tongue which are responsible for its shape) and in the posterior part (extrinsic muscles responsible for its position). The posterior group of muscles is responsible for maintaining its position. Long-lasting maintaining of tongue muscle tone does not allow its collapsing and closing of the lumen of airways. [4,10]

Among the extrinsic muscles of the tongue, genioglossus is responsible for protrusion of tongue and styloglossus and hyoglossus are responsible for its retraction. Selective stimulation of the branch of hypoglossal nerve innervating genioglossus results in broadening of airway lumen and an increase in stiffness of their walls. [7,8,9] Stimulation of the whole hypoglossal nerve results in stimulation of extrinsic and intrinsic muscles of tongue. In a longer period, nonselective stimulation may result in their excessive fatigue. According to Friedman et al. selective stimulation of the branches of the 12th nerve should be aimed for to achieve desired therapeutic effect and minimalize side effects. It allows to avoid the activation of intrinsic muscles of tongue which have no influence on its position. [9] [FIG 1]

Genioglossus is built from horizontal and vertical fibers. A contraction of vertical fibers causes depression of the tongue without influencing the airways and a contraction of horizontal fibers causes protrusion of tongue and broadening of the lumen of airways and improves the tone of the anterior part of the throat. [2,4,14] In the studies of Eastwood et al. and Schwarz et al. it was found that stimulation of the branch of hypoglossal nerve innervating genioglossus leads to its contraction and occurs without awakening the patient from sleep. [6,25].

TECHNOLOGY

Nowadays four systems offering devices for HGNS are available: ImThera aura6000™ Stimulation System, Inspire® II Upper Airway Stimulation System, Apnex Medical Device, being currently in the phase of clinical trials, and Nyxoah SAT System, also being in the phase of clinical trials.

The ImThera THN System is characterized by a constant stimulation of hypoglossal nerve independent of the respiratory cycle of the patient. 6 ring electrodes placed on the main trunk of the hypoglossal nerve and a subcutaneously implanted neurostimulator are parts of the system. The functioning is based on sending the impulses which lead to an increase in muscle tone during the time of system activity. Stimulator is charged inductively every 1-2 days, the battery life according to manufacturer is assessed at 10-12 years. The system is in the 2nd phase of clinical trials and has the CE certificate. Its efficiency in the reduction of AHI is evaluated as 53% after 12 months of use.

The Inspire System consists of three elements: electrodes, stimulator and breathing sensors. The electrodes are placed on the distal part of the hypoglossal nerve, on its medial branches. The functioning of the system is based on the prevention of tongue collapsing which occurs in synchronization with the patient's breath. As opposed to the ImThera THN System, it does not need charging and the battery life is assessed at 10.7 years. The system is currently in the 3rd/4th phase of clinical trials, it has CE and FDA certificates. The effectiveness is evaluated as 68% after 36 months of use (Heiser et al.). The stimulator is launched after approximately one month from implantation and requires calibration by a doctor. [12]

The Apex Medical Device consists of electrodes and neurostimulator which is implanted subcutaneously in the subclavicular region. Electrical impulses sent to the hypoglossal nerve come from the wire ending with an electrode. Breathing sensors are on the both sides of chest and their action is based on the bioimpedance measurement which enables detection of the initiation of breath. Hypoglossal nerve stimulation starts directly before the breath and lasts throughout breathing in, which results in maintaining the width of airway lumen and their tone. Parts of the device are: neurostimulator, breathing sensors and electrode, which stimulates hypoglossal nerve. [6,14] Using this device, Kezirian et al. showed reduction of AHI from 45.4/h ±17.5 to 25.3/h ± 20.6 during the time of 12 month observation. The system is still in the phase of testing and is not allowed in Europe and in the USA. [17]

The most recent system which has been described is, being in the phase of testing, Nyxoah SAT system [Nyxoah SA, Mont-St-Guibert, Belgium]. The functioning is based on a constant stimulation of hypoglossal nerve without synchronization with breathing rhythm. Electrodes are placed on the medial fibers of the 12th nerve, adjacent to genioglossus. In contrast to the other systems, it does not prevent conducting magnetic resonance imaging (MRI) examination. Due to lack of clinical tests, there is no data confirming its effectiveness. [13]

SURGERY

Qualification for operation is based on the extensive analysis of clinical picture of the patient's medical history, endoscopic evaluation of upper airways and polysomnographic examination. The exclusion criteria comprise neuromuscular disorders and diseases, pulmonary hypertension, severe pulmonary embolism, myocardial infarction (up to 6 months) and psychiatric disease. [15]

Cetral et al. showed that in spite of lack of clear indications, patient should have BMI under 32 kg/m^2, AHI between 20 and 50/h. In patients whose tongue is of larger dimensions better response to therapy was found. It is thought that qualification of patient to the surgery should be preceded by fiberoscopic examination during induced sleep - DISE (drug-induced sleep endoscopy). [12,26] Its aim is to determine the type of collapsing of the airways. The studies by Vanderveken et al. showed that in case of collapsing in the anterior-posterior dimension, treatment with the use of HGNS leads to reduction of AHI from 37.6/h ± 11.4/h to 11.6/h ± 11.7/h after 6 months of use. In patients in whom a concentric type of collapsing was found the HGNS treatment was not effective. [12,26]

Depending on the system used, the procedure of electrode and stimulator implantation may differ. The differences mainly result from the placement of electrodes on the 12th nerve and from the presence of breathing sensors which are not present in every system. The surgical procedure itself is similar and the access to the 12th nerve is gained by the neck incision, localized submandibularly.

The procedure of stimulator implantation is conducted in the general anesthesia. After performing an incision parallel to the inferior rim of the mandible (approx. 4 cm), the nerve is being localized under the submandibular salivary gland, above the tendon of digastric muscle. The electrode is placed on the distal branch of hypoglossal nerve, on its lateral branch. The nerve response is controlled intraoperatively. The wire of neurostimulator is placed under the platysma. The stimulator itself is localized subcutaneously in the subclavicular region on the same side. The additional elements are two breathing sensors localized subcutaneously on the left and the right side, along the rib edge. [6,14] A silicone cuff on the electrode prevents constant irritation of the nerve. Neurostimulator is launched approx. 30 minutes after the procedure of implantation. To adjust the amplitude, amperage and frequency of the impulses, the patient undergoes an overnight (polysomnographic) examination, during which the parameters are determined so that the impulses will not awaken the patient during sleep. The stimulator system also includes a remote controller which

allows controlling the device by the patients themselves. [6] [FIG 2] [FIG 3]

In the case of Inspire II System implantation a submandibular incision is being made. Hypoglossal nerve is being localized and under the control of neuromonitoring an electrode is being attached to the branches responsible for tongue protrusion. The second incision is being made under the clavicula, above the pectoralis major, where a pocket for the neurostimulator (implanted pulse generator- IPG) is being created. The electrodes monitoring breathing are placed in the created tunnel, between internal and external intercostal muscles, on the right side of the chest. The wires of the electrodes are led in the subcutaneous tunnel reaching to the stimulator. [13]

SUMMARY

Stimulation of hypoglossal nerve is a new method of treatment of OSA. Stimulators are considered as a good alternative for patients with moderate or severe OSA in whom CPAP treatment did not bring desired results or was badly tolerated. It is an invasive method of treatment which requires selection of the chosen group of patients. Treatment of the obstructive sleep apnea with the use of HGNS gives very promising results, yet still requires research on safety in the long period of use, influence of chronic stimulation on the function and anatomical build of the tongue and also on the genioglossus itself. [5,9,18]

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