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Original Research

Real-world data on polysomnography- and patient-reported outcomes in hypoglossal nerve stimulation and auto-titrating positive airway pressure therapy for obstructive sleep apnea

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ABSTRACT

Background: Few data are available comparing first-line positive airway pressure (PAP) therapy of obstructive sleep apnea (OSA), especially auto-adjusting PAP (aPAP), with second-line hypoglossal nerve stimulation (HGNS) therapy. The aim of this study was to directly compare these therapeutic options by standard polysomnography (PSG)-related parameters and patient-reported outcomes in comparable groups.

Methods: 20 patients (aged 57.30 ± 8.56 years; 6 female) were included in the HGNS and 35 patients (aged 56.83 ± 9.20 years; 9 female) were included in the aPAP group. In both groups participants had to fit the current guideline criteria for HGNS treatment. Groups were compared by analysis of covariance (ANCOVA) using inverse propensity score weighting.

Results: Propensity scores did not differ between groups. Pre-therapeutic AHI (HGNS: 40.22 ± 12.78/h; aPAP: 39.23 ± 12.33/h) and ODI (HGNS: 37.9 ± 14.7/h, aPAP: 34.58 ± 14.74/h) were comparable between the groups. After 413.6 ± 116.66 days (HGNS) and 162.09 ± 140.58 days (aPAP) of treatment AHI (HGNS: 30.22 ± 17.65/h, aPAP group: 4.71 ± 3.42/h; $p < 0.001$) was significantly higher in the HGNS group compared to the aPAP group. However, epworth sleepiness scale (ESS) was post-interventionally significantly lower in the HGNS group compared to the aPAP group (pretherapeutic: HGNS: 13.32 ± 5.81 points, aPAP: 9.09 ± 4.71 points; posttherapeutic: HGNS: 7.17 ± 5.06 points; aPAP: 8.38 ± 5.41 points; $p < 0.01$).

Conclusion: These are novel real-world data. More research on the key parameters regarding titration of the HGNS neurostimulation parameter tuning and on the impact of factors influencing HGNS adherence is needed.

1. Introduction

Obstructive sleep apnea (OSA) is the most common sleep disorder with almost a seventh of the world's population suffering from [1]. Therefore, there is relevant need for optimal OSA therapy. Positive airway pressure (PAP) therapy represents the gold standard in OSA treatment [2]. Autotitrating-cPAP (aPAP) has been developed and established as an alternative to the fixed continuous PAP (cPAP) therapy. Over the years it has evolved to one of the leading modes of PAP delivery [3]. aPAP therapy needs lower mean pressures since therapy pressures are adapted to patient's needs [4,5]. Higher pressures are applied in upper airway collapse registered by upper airway resistance, lower pressures are applied in an open airway registered by missing upper airway resistance. Therefore, aPAP therapy was thought to be an alternative for patients not tolerating a fixed cPAP therapy [6,7]. A meta-analysis comparing the outcomes of patients treated with an aPAP and with a fixed cPAP-model found no significant differences regarding the apnoea-hypopnea-index (AHI) and daytime sleepiness detected by the Epworth Sleepiness Scale (ESS) questionnaire [8]. However, patients significantly preferred an aPAP device [5] resulting in a significantly higher compliance [8]. In some sleep society guidelines on adult sleep-related breathing disorders, aPAP and cPAP therapy are recommended as equivalent therapeutic options [9]. PAP therapy compliance remains challenging. Many patients do not tolerate PAP-therapy, which

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results in non-adherence as a major therapy limitation. A meta-analysis from studies over twenty years proved that over a third of patients treated with cPAP were non-adherent based on a 7-h/night total sleep time [10]. For these patients, alternative treatments are required including surgery such as velar/oropharyngeal soft tissue or maxilla-mandibular surgery and conservative therapy such as weight loss, mandibular advancement devices and positional therapy. In the last decade hypoglossal nerve stimulation (HGNS) has been established as a second-line therapy of OSA in patients not tolerating PAP-therapy. Among multicentred approval studies [11,12] further studies [13–15] have demonstrated inspiration-coupled HGNS as a safe and effective therapeutic alternative. So far studies comparing the therapeutic outcomes of PAP therapy and HGNS therapy in clinical routine are largely missing. Previously one study aimed to compare HGNS and PAP treatment including cPAP, aPAP, and bilevel PAP using sleepiness, AHI and effectiveness after 12 months of treatment as endpoints [16]. No significant difference was observed in the reduction of AHI between the PAP and HGNS cohort. The reduction of daytime sleepiness measured by the ESS questionnaire significantly differed between the PAP and HGNS cohort with higher reduction in the HGNS cohort. Overall effectiveness was comparable between the PAP and HGNS cohort [16]. Another study showed that patient-reported outcomes such as daytime sleepiness, insomnia and functional Outcomes of Sleep did not significantly differ between a PAP cohort at 3 months and a HGNS cohort at 12 months [17]. Since only few real-world data are available comparing the first-line PAP therapy in clinical routine, specifically aPAP, with second-line HGNS therapy the aim of this study was to directly compare these therapeutic options by core polysomnography (PSG) - related parameters such as apnea/hypopnea index (AHI), apnea index (AI), hypopnea index (HI), snoring index (SI), oxygen desaturation index (ODI) and arousal index and patient-related outcomes such as reported insomnia and daytime sleepiness symptoms.

2. Methods

All patients treated with inspiration-coupled HGNS (produced by Inspire Medical Systems, Inc., Golden Valley, MN, US) in our tertiary care otorhinolaryngology department between February 2020 and December 2022 were retrospectively assessed. In order to be included, participants had to fit the current guideline criteria for HGNS treatment such as intolerance to PAP therapy, body mass index (BMI) < 35 kg/m^2, the absence of complete velar concentric collapse on drug-induced sleep endoscopy (DISE), AHI 15–65/ h with <25 % central apneas on PSG, and the absence of chronic major psychiatric or neurodegenerative disease [18]. Therefore, PSG according to the American Academy of Sleep Medicine (AASM) standard guidelines and DISE were performed before implantation of HGNS. 413.60 ± 116.66 days after activation of the device a further PSG according to AASM standard guidelines was performed. Patients' baseline clinical parameters including sex, age and BMI were evaluated. Furthermore, the following PSG related parameters were evaluated: AHI, AI, HI, cumulative time of apnoea and hypopnea during sleep, snoring index, ODI, mean oxygen desaturation, percentage of oxygen desaturation lower than 90 % (t90) and number of arousal events per hour (arousal index).

The Insomnia Severity Index (ISI) was used to assess insomnia-related symptoms [19]. The ISI is a questionnaire containing seven items covering the different aspects of insomnia. Each item is scored on four-point Likert scale from 0 = no problem to 4 = very severe problem resulting in a total score ranging between 0 and 28 points. Zero to 7 points corresponds to no clinically significant insomnia, 8–14 points to a sub-threshold clinical insomnia, 15–21 to a moderately severe insomnia and 22–28 to a severe clinical insomnia. Daytime sleepiness was evaluated by the Epworth Sleepiness Scale (ESS) [20]. The ESS is a questionnaire containing 8 items on a four-point Likert scale resulting a total score between 0 and 28. Higher ESS score values are associated with more pronounced daytime sleepiness.

Patients included in the aPAP group were assessed retrospectively and they had been treated between 2018 and 2022. Only patients aged over 18 years were included. All patients were selected in accordance with the above-mentioned guideline criteria for HGNS therapy: body BMI <35 kg/m^2, AHI 15–65 h with <25 % central apneas on PSG, and the absence of chronic major psychiatric or neurodegenerative disease. 35 patients with these criteria could be included. The same PSG according to AASM standards were performed in the HGNS group as well as in the aPAP group before and under therapy.

In both groups the following main comorbidities were assessed: cardiovascular diseases (e.g. arterial hypertension), respiratory diseases (e.g. bronchial asthma, chronic obstructive pulmonary disease), psychiatric diseases (e.g. depression) and endocrinological diseases (e.g. diabetes mellitus). Furthermore, both groups were divided in patients with no regular pharmacological treatment, regular use of one to three medicaments and regular use of over three medicaments.

2.1. Statistical analysis

SPSS 27 (IBM, Armonk, NY, USA) and SAS version 9.4 (SAS Institute Inc., Cary, NC, USA.) were used for statistical analysis. Groups were compared by analysis of covariance (ANCOVA) using inverse propensity score weighting. Propensity scores for belonging to a HGNS or aPAP were calculated by a logistic regression model with gender, baseline AHI scores and baseline BMI values as the independent variables. For AHI and ODI the post-hoc power was calculated by using a *t*-test and a two-sided significance level of alpha = 5 % using the observed sample sizes. The observed Pre/Post differences were used as the true effects and the average observed standard deviation at baseline served as common standard deviations. Calculations were done by SAS, Version 9.4. Inner-group comparisons were analyzed using the Wilcoxon's signed rank test. $p < 0.05$ was considered as a statistically significant result.

Ethical statement

In this study, only health data that is collected in the clinical routine was analyzed retrospectively. So-called "third parties" did not have access to the data and publication occurs exclusively in anonymized form. The Ethics Committee of the Rhineland-Palatinate Medical Association refrains from providing advice in such cases, citing the State Hospital Act (§36 and §37) (see also: https://www.laek-rlp.de/ausschuesse-kommissionen/ethikkommission/).

3. Results

Twenty patients (6 female) were included in the HGNS and 35 (9 female) were included in the aPAP group. Propensity scores did not differ between groups pointing to non-predictive baseline parameters. For AHI and ODI a post -hoc power of >99 % was calculated, resulting in post-hoc sample sizes of 12 in total for AHI and 22 for ODI with a two-sided significance level of 5 %, a power of 80 % and by using a *t*-test with equal group sizes.

After treatment AHI (n/h), AI (n/h), HI (n/h), cumulative apnea and hypopnea time (min), ODI (n/h), snoring index and arousal index (n/h) were significantly higher in the HGNS group compared to the aPAP group. Mean oxygen saturation (%) and ESS score was significantly lower in the HGNS group compared to the aPAP group. ISI score and t90 % did not differ significantly after treatment between HGNS and aPAP group (Table 1).

Within the HGNS group the following respiratory parameters were significantly reduced after HGNS treatment: AHI (n/h), HI (n/h), cumulative apnea and hypopnea time (min), ODI (n/h), ISI and ESS score. AI, snoring index, mean oxygen saturation (%), t 90 (%) and arousal index (n/h) did not differ significantly (Table 1).

Within the aPAP group the following respiratory parameters were significantly reduced after aPAP treatment: AHI (n/h), AI (n/h), HI (n/

Table 1
Pretherapeutic and post-therapeutic results of age, BMI, PSG-parameter, ISI and ESS with inner- and intragroup comparison.

	HGNS pre	PAP pre	HGNS post	PAP post	P (HGNS post vs. PAP post)	P (HGNS pre vs. HGNS post)	P (PAP pre vs. PAP post)
BMI (kg/m^2)	29.10 ± 4.77	28.65 ± 3.93					
Age (years)	57.30 ± 8.56	56.83 ± 9.20					
AHI (n/h)	40.22 ± 12.78	39.23 ± 12.33	30.22 ± 17.65	4.71 ± 3.42	<0.001	0.01	<0.001
AI (n/h)	13.47 ± 11.04	18.90 ± 12.68	11.28 ± 11.96	1.60 ± 1.91	<0.001	0.17	<0.001
HI (n/h)	26.72 ± 9.08	20.31 ± 9.72	18.94 ± 11.25	3.11 ± 3.11	<0.001	0.01	<0.001
Cumulative apnea and hypopnea time (min)	78.15 ± 30.79	91.74 ± 43.40	54.25 ± 29.46	9.69 ± 10.44	<0.001	0.01	<0.001
Snoring index (n/h)	259.82 ± 172.56	273.16 ± 223.21	201.34 ± 174.22	98.15 ± 105.32	0.01	0.22	<0.001
ODI (n/h)	37.90 ± 14.70	34.58 ± 14.74	31.44 ± 20.24	8.73 ± 9.00	<0.001	0.04	<0.001
Mean oxygen saturation (%)	93.00 ± 1.86	93.37 ± 1.54	93.43 ± 1.46	94.77 ± 1.31	<0.001	0.23	<0.001
t90 (%)	8.82 ± 11.21	7.50 ± 10.25	4.78 ± 6.86	1.35 ± 4.92	0.05	0.30	<0.001
Arousal index (n/h)	20.82 ± 10.60	20.62 ± 9.78	19.76 ± 10.47	13.74 ± 8.03	0.03	0.87	<0.001
ISI	19.74 ± 5.06	11.52 ± 5.42	10.08 ± 7.13	8.56 ± 6.25	0.09	<0.01	<0.01
ESS	13.32 ± 5.81	9.09 ± 4.71	7.17 ± 5.06	8.38 ± 5.41	<0.01	<0.01	0.06

Table 2
Main clinical (comorbidities), anthropometric characteristics and regular pharmacological treatments in HGNS and aPAP groups.

	HGNS	aPAP
BMI (kg/m^2)	29.10 ± 4.77	28.65 ± 3.93
Age (years)	57.30 ± 8.56	56.83 ± 9.20
Female/male	6/14	9/26
Psychiatric diseases number/study population	7/20	4/35
Endocrinological diseases number/study population	1/20	2/35
No pharmacological treatment number/study population	1/20	13/35
Pharmacological treatment (1–3) number/study population	13/20	16/35
Pharmacological treatment (>3) number/study population	6/20	6/35

Table 2: Main clinical (comorbidities), anthropometric characteristics and regular pharmacological treatments in HGNS and aPAP group; cardiovascular diseases such as arterial hypertension, respiratory diseases such as asthma and chronic obstructive pulmonary disease, psychiatric diseases such as depression and endocrinological diseases such as diabetes mellitus.

h), cumulative apnea and hypopnea time (min), snoring index (n/h), ODI (n/h), mean oxygen saturation (%), t 90 (%), arousal index (n/h) and ISI-score. ESS score did not differ significantly before and after aPAP treatment (Table 1).

Table 1: Pretherapeutic and post-therapeutic results of age n (HGNS) = 20; n (aPAP) = 35, BMI n (HGNS) = 20; n (aPAP) = 35, PSG-parameter n (HGNS) = 20; n (aPAP) = 35, ISI (pretherapeutic) n (HGNS) = 19; n (aPAP) = 31, ISI (posttherapeutic) n (HGNS) = 12; n (aPAP) = 27, ESS (pretherapeutic) n (HGNS) = 19; n (aPAP) = 35 and ESS (post-therapeutic) N (HGNS) = 12; n (aPAP) = 29, with inner- and intragroup comparison.

Comorbidities and regular pharmacological treatment are shown on Table 2.

4. Discussion

In the present report we provide evidence that both AHI and ODI are significantly less reduced by treatment with HGNS compared to aPAP in OSA patients. However, daytime sleepiness, as depicted by the ESS, was significantly lower after treatment with HGNS compared to treatment with aPAP. After treatment AHI (n/h), AI (n/h), HI (n/h), cumulative apnea and hypopnea time (min), ODI (n/h), snoring index and arousal index (n/h) were significantly higher in the HGNS group compared to the aPAP group. Mean oxygen saturation (%) and ESS score was significantly lower in the HGNS group compared to the PAP group. ISI score and t90 % did not differ significantly after treatment between HGNS and PAP group.

Our observed results within the aPAP group are in line with previous studies. In the aPAP group an 88 % AHI reduction and an 82 % t90 reduction was observed. A previous study with comparable baseline AHI of 45.8/h and t90 of 12.6 % showed a significant 87 % AHI reduction and a 93 % t90 reduction [21]. Another study with a baseline AHI of 47.2/h, arousal index of 17.3/h, ODI of 53/h and minimum O2 saturation of 67.8 % demonstrated a significant AHI reduction of 72 % compared to 88 % in our study, a significant arousal index reduction of 66 % (compared to 33 % in our study), a significant ODI reduction of 72 % (compared to 75 % in our study) and a significant increase of the basal O2 saturation of 4 % (compared to 1.5 % in our study) [22]. Another study including patients suffering mild or moderate OSAS with a baseline AHI of 14.7/h proved a significant reduction of AHI, total desaturation and significant improvement in mean SaO2 % and minimum SaO2 % [23]. Even if PAP therapy is not the gold standard for snoring treatment it is well known that snoring can be effectively treated with PAP therapy as well [24,25].

Within the HGNS group a 25 % reduction of AHI was found post-operatively in the present cohort. In previous studies [11,26] higher AHI reduction was reported, up to an 82 % AHI reduction [27]. However, the baseline AHI in our HGNS cohort was much higher, namely 40.22/h. Furthermore, in contrast to the aforementioned studies, no in-night titration of the neuro-stimulation parameters was performed during the post-operative PSG in our patients [11,12,15,28,29]. As a result, the PSG-results in the present study may much better depict the real-life situation and therefore better resemble the condition in the home settings of these patients. Our patients' neuro-stimulation parameters were

titrated and adapted in the awake patients in the morning after a three months' follow-up PSG (again without in-night intra-lab titration) after the initial device activation while in parallel educating patients in use of the device. Existing studies do not actively report on the exact titration protocol used for intra-lab PSG-based titration [11,12,15,28,29]. Titration of the neurostimulation parameters seems to be a key determinant of therapeutic success, despite the largely missing published scientific evidence concerning details of the procedures guiding intra-laboratory titration.

To the best of our knowledge, only one study aimed to date to compare HGNS therapy to PAP therapy in matched OSA patients [16]. This study focused on daytime sleepiness, objective adherence and AHI as endpoints. An AHI reduction of 30.9 ± 21.9/h was observed in the cPAP cohort compared to an AHI reduction of 34.52 ± 13.24/h in our aPAP group. Pretherapeutic AHI in the cPAP group was comparable with 39.6 ± 26.7/h compared to 39.23 ± 12.33/h in our aPAP group. Therefore, patients in our aPAP group performed better concerning posttreatment AHI improvement than patients in the former report [16]. Regarding the HGNS group, an AHI reduction of 23.0 ± 13.0/h was observed [16], compared to 10.0 ± 14.94/h in our HGNS cohort. The reduction of AHI did not significantly differ between HGNS and PAP group ($p = 0.075$) [16], while our study proved a significant lower postinterventional AHI in the aPAP group compared to the HGNS group. Therefore, the significantly lower AHI in the aPAP group compared to the HGNS group in our study is due to both the better outcome in our aPAP group and the worse outcome in our HGNS group compared to the data in the above mentioned study [16]. In addition, it should be noted that preoperative AHI in the former study [16] was lower with 36.5 ± 14.8/h compared to 40.22 ± 12.78/h in the HGNS group of the present study.

Of note, daytime sleepiness was significantly improved after HGNS therapy measured by ESS (HGNS: preoperative ESS: 13.32 ± 5.81 points; HGNS: postoperative ESS: 7.17 ± 5.06) but not in the aPAP group (aPAP preoperative ESS: 9.09 ± 4.71 points; aPAP postoperative ESS: 8.38 ± 5.41) despite a higher improvement of core PSG-related parameters observed in our aPAP group. This dissociation between ESS outcomes and either AHI- or ODI- outcomes in OSA is in line with previous evidence from larger cohorts of OSA patients in which no correlation between ESS and either AHI, minimal SpO2 or ODI could be proven [30]. In addition, the present findings are in line with results from previous studies [16,17] in which a higher improvement in ESS in patients treated with HGNS was described. This fact is surprising, since important core PSG-related parameters which would have been expected to have a major impact on daytime sleepiness (such as AHI, AI, HI and mean oxygen saturation) were postoperatively much more significantly improved in the aPAP group compared to the HGNS group in our cohort. Notably, one study proved that desaturation severity, depicted by the sum of areas of all desaturation events normalized by total sleep time, to be better associated with daytime sleepiness than AHI and ODI [31]. It should be stressed that t90 was not significantly improved in the aPAP group compared to the HGNS group. A much higher reduction in daytime sleepiness was observed in the HGNS group compared to the PAP group. Based on evidence of the present study, the arousal index is not a key predictor of ESS improvement in OSA patients treated by either aPAP or HGNS. This fact suggests that daytime sleepiness may be highly influenced by other factors beyond the standard PSG-metrics [32,33] and that investigations regarding further potential, neurophysiologic or other, surrogate markers that may better capture subjective daytime sleepiness are therefore needed in the future.

PAP therapy adherence is very low with 54 %–17 % adherence when applying stricter recommendation criteria for daily PAP use [34]. Therefore, a potential higher therapy adherence in HGNS treated patients compared to PAP treated patients [16] could be an explanation for the higher daytime sleepiness improvement in the HGNS group compared to the PAP group. The HGNS group showed a much higher pre-inetrventional ISI score than the aPAP group. Insomnia is well-known to lead to lower adherence to PAP therapy [35]. For implantation of a HGNS system an intolerance for PAP therapy is a prerequisite [18]. Therefore, it is not surprising, that patients treated with HGNS tend to suffer from more severe insomnia. Postinterventional insomnia-related symptoms did not differ significantly between the HGNS and aPAP group. However, in both groups the ISI score was significantly improved. In the HGNS group the mean of ISI score decreased from 19.74 ± 5.06 points to 10.08 ± 7.13 and in the aPAP group from 11.52 ± 5.42 to 8.56 ± 6.25. In a previous report an ISI score decrease from 15.16 (95 % CI, 13.71–16.62) to 9.17 (95 % CI, 7.38–10.96) was found [17], with a comparable range of ISI-score reduction with a higher baseline ISI. However, this study could demonstrate a higher percentage of patients with a clinically meaningful reduction in ISI score of at least 6 points in the HGNS group with 46.9 % compared to 36.4 % in the PAP group [17].

Relevant limitations of our study are the relatively small sample size, the retrospective nature of this study and the differences in the follow-up time for the HGNS and aPAP group for PSG after the start of the treatment.

Only 20 patients were included in the HGNS group and only 35 patients were included in the aPAP group. So far there exists one study matching 126 patients one to one to either HGNS group or to PAP group [16]. Studies investigating only the outcome of HGNS therapy have included 301 patients [12] and a pooled cohort analysis of 4 observational cohorts comprised 584 patients [14]. Against this background, the sample size in our study may appear small. Nonetheless, the post-hoc power, calculated by using a *t*-test and a two-sided significance level of alpha = 5 % using the observed sample sizes, was >99 % for AHI and ODI.

Due to the retrospective nature of this study not all relevant baseline variables could be perfectly matched between the HGSN and aPAP groups, such as daytime sleepiness (ESS scores) and insomnia-related symptoms. Furthermore, the comorbidities as well as regular medication (including adherence to it) could not be matched. These could present confounding factors. Patients with more comorbidities and on multiple pharmacological treatments could show lower adherence rate to both HGNS and aPAP-therapy. Further studies are needed to prove if any and what kind of confounding factors impact the final outcomes.

However, the gathered data are of high quality and provide new information regarding the comparison of two major therapeutic options for OSA patients.

This is a clinically relevant study. It is the first study comparing HGNS- and aPAP-therapy in a clinical routine setting. Furthermore, it is the first study to emphasise the position of aPAP therapy as a standard therapy in OSA. There may be several reasons for this. First, there is a certain mismatch between patients treated with aPAP compared to patients not tolerating aPAP therapy. It seems that insomnia-related symptoms are more prevalent in patients not tolerating aPAP. Our study proved that compliant aPAP - treated patients suffered pretherapeutically from much less insomnia than those treated with HGNS therapy. Especially comorbid insomnia is associated with poorer therapeutic outcome in OSA treatment [36] and may therefore be a major confounding factor in HGNS treatment. Furthermore, HGNS therapy requires more personal initiative over control of the neurostimulation parameters than aPAP therapy does. Patients treated with HGNS are encouraged to individually titrate the stimulation parameters during quite some time.

We propose that future studies should focus on insomnia-related symptoms in patients requiring HGNS therapy. Especially studies investigating the addition of cognitive behavioural therapy in patients requiring HGNS therapy with insomnia-related symptoms are necessary. An additional cognitive behavioural therapy could improve the outcome of those patients by improving therapy compliance. Furthermore, there is a need to enlarge the evidence base regarding detailed procedures for the titration of HGNS neurostimulation parameters. Titration of neurostimulation parameters of HGNS therapy seems to be a major determinant of therapeutic success.

5. Conclusion

Following intervention, PSG-related parameters, such as AHI, apnea- and hypopnea-index, cumulative apnea and hypopnea time, ODI and mean oxygen saturation were significantly improved in the aPAP group compared to the HGNS group. However, higher improvement in patient-reported outcomes regarding daytime sleepiness and insomnia was observed in the HGNS group compared to the aPAP group. HGNS is a very good therapeutic option for patients not tolerating aPAP therapy. Titration details of neurostimulation parameters under HGNS therapy and insomnia-related features may be key factors influencing HGNS therapeutic outcomes.

Data availability

Please contact the authors for data requests.

Ethics approval and consent to participate

In this study, only health data that is collected in the clinical routine was analyzed retrospectively. So-called "third parties" did not have access to the data and publication occurs exclusively in anonymized form. The Ethics Committee of the Rhineland-Palatinate Medical Association refrains from providing advice in such cases, citing the State Hospital Act (§36 and §37) (see also: https://www.laek-rlp.de/ausschuesse-kommissionen/ethikkommission/).

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CRediT authorship contribution statement

Johannes Pordzik: Writing – review & editing, Writing – original draft, Methodology, Data curation, Conceptualization. **Katharina Ludwig:** Writing – review & editing, Methodology, Conceptualization. **Christopher Seifen:** Writing – review & editing, Methodology, Conceptualization. **Christian Ruckes:** Writing – review & editing, Methodology, Data curation. **Tilman Huppertz:** Writing – review & editing, Methodology, Conceptualization. **Katharina Bahr-Hamm:** Writing – review & editing, Methodology, Conceptualization. **Berit Hackenberg:** Writing – review & editing, Methodology. **Christoph Matthias:** Writing – review & editing, Methodology, Conceptualization. **Haralampos Gouveris:** Writing – review & editing, Writing – original draft, Methodology, Data curation, Conceptualization.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Haralampos Gouveris reports a relationship with Inspire Medical Systems Inc that includes: funding grants and speaking and lecture fees. If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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