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SCIENTIFIC INVESTIGATIONS

Mandibular advancement device as treatment trial for catathrenia (nocturnal groaning)

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Study Objectives: Catathrenia is a rare disease, classified as isolated symptoms and normal variants under sleep-related breathing disorders in the International Classification of Sleep Disorders, Third Edition. Because of its rarity, the research on its pathogenesis and treatment is insufficient. This study aimed to evaluate whether the mandibular advancement device (MAD) could be considered an alternative treatment trial and if so, to explore factors predicting its effectiveness.

Methods: Thirty patients (12 males and 18 females, aged 16 to 67 years) with catathrenia participated in the study. They underwent standard clinical evaluation, questionnaires, physical examinations, craniofacial evaluations, video-polysomnography, and imaging of the upper airway before and after the insertion of the MAD. Groaning index (GI, groaning episodes per hour of sleep) and apnea-hypopnea index (AHI) were evaluated and anatomic factors predicting effectiveness were explored.

Results: The sleep efficiency of most patients was higher than 80% and groaning was present throughout all stages of sleep. With the insertion of MAD, GI decreased significantly from 5.8 (2.7, 14.3) to 2.8 (1.3, 12.2) events/h ($P = 0.014$). Age had a negative effect on efficacy. Mandibular repositioning of MAD, especially the amount of vertical opening and changes of cross-sectional area of hypopharynx, was positively related with efficacy.

Conclusions: The MAD could be considered a possible treatment trial for those seeking treatment for groaning.

Clinical Trial Registration: Registry: Chinese Clinical Trial Registry; URL: http://www.chictr.org.cn/showproj.aspx?proj=22286; Identifier: ChiCTR-IND-17013239

Keywords: cone beam computed tomography; nocturnal groaning; oral appliance; treatment efficacy

BRIEF SUMMARY

Anatomic characteristics are different among patients with catathrenia and those with obstructive sleep apnea. The oral appliance for obstructive sleep apnea can be applied to patients with catathrenia by adjusting the vertical opening slightly. The MAD could improve symptoms and decrease groaning episodes.

INTRODUCTION

Catathrenia, also known as sleep-related groaning, is characterized by a deep inspiration and long expiratory groan. The first case was described as early as 1983 in a brief case report;[1] however, there have been fewer than 230 cases in total (conference abstracts excluded) reported in the literature thus far. A rare disease, catathrenia affects only 0.063% to 0.54% of patients admitted to sleep centers.[2-5] Nevertheless, a population-based telephone interview reported that the prevalence of sleep-related groaning was as high as 31.3%.[6] The etiology of catathrenia still remains controversial, with the proposal of several mechanisms, from the involvement of neurologic structures[7, 8] to sleep-related narrowing or obstruction of the upper airway.[9-12] The polysomnographic findings of nocturnal groaning are also inconsistent. Catathrenia was originally reported to occur predominantly or exclusively during rapid eye movement (REM) sleep,[1, 2, 9, 10] yet a different type of predominance during nonrapid eye movement (NREM) also has been found.[7, 11, 13]

Several treatment trials have been conducted; however, there was a poor response to various medication including clonazepam and trazodone.[2, 10] A better response was observed with interventions for sleep-disordered breathing (SDB). Continuous positive airway pressure (CPAP) at 4 to 12 cm H_2O was found to be effective in reducing groaning episodes.[3, 4, 7, 11, 12, 14-18] Thus, catathrenia was reclassified under sleep-related breathing disorders in the International Classification of Sleep Disorders, Third Edition (ICSD-3).[19]

The mandibular advancement device (MAD), as an alternative treatment for CPAP for SDB, was mentioned in only a few cases, resulting in difficulties in statistical analysis.[5, 11, 16, 20] The self-report effect was also subjective, leading to inconsistent findings.

SDB constitutes a category of disease and MADs are mostly involved with the management of patients with obstructive sleep apnea (OSA).[21] However, patients with catathrenia had craniofacial characteristics that were different from those in patients with OSA;[22] therefore, the differences in the application of the MAD for catathrenia should be evaluated. With respect to anatomic etiology, the goal of this study was to investigate both the objective efficacy of the MAD for catathrenia and the factors predicting its effectiveness in order to verify the hypothesis that use of the MAD would reduce the groaning index (GI) by at least 5 events/h.

METHODS

This study is designed as a self-controlled case series. Intergroup comparison between patients with catathrenia and those with OSA was also applied. The study was registered in Chinese Clinical Trial Registry (No. ChiCTR-COC-17013239). It was approved by the committee of the Institutional Review Board of Peking University School of Stomatology (No. 201631128) and written informed consent was obtained from all patients. The procedures used in this study adhere to the tenets of the Declaration of Helsinki.

Patients

A true difference of GI of 5 events/h, a standard deviation of GI of 7 events/h (based on pilot study), a dropout rate of 20%, a two-sided significance of 0.05, and power of 90% were considered for the sample size calculation.[23] A total of 30 patients was required for the study. From August 2014 to March 2019, 30 patients (12 males and 18 females, aged 16 to 67 years) in whom catathrenia was diagnosed in a certified sleep center and who were seeking improvement of groaning sounds were recruited. Standard clinical evaluation, questionnaires, and physical examinations were carried out and cone-beam computed tomography (CBCT) of the upper airway was performed.

Polysomnography

All patients underwent full-night video polysomnography using the Alice 5 Polysomnography System (Philipis Respironics, Pennsylvania, USA) at Sleep Center of Peking University People's Hospital. Recordings included a three-channel electroencephalogram (central and occipital), a two-channel electrooculogram, a two-channel electromyogram (submental and anterior tibialis muscles), and an electrocardiogram with surface electrodes. Nasal air pressure monitors, pulse oximeters, piezoelectric bands, and body position/respirator sensors were also used.

Figure 1—Custom-fitted mandibular advancement device.

Design features of the appliance are separate upper and lower appliances connected at the posterior region of dental arches; and full coverage of all surface of teeth to increase anchorage.

Time-synchronized video recordings were performed and audio was captured by a microphone positioned approximately 15 cm from the mouth and slightly below the chin to reduce airflow effects.

Sleep architecture was manually scored in sequential 30-second epochs and sleep staging was interpreted according to the American Academy of Sleep Medicine scoring manual. Apneas and hypopneas were also scored to calculate apnea-hypopnea index (AHI). A groaning event was defined as a sharp inspiration followed by a prolonged expiration, without any paradoxical movement of the chest and abdomen during the event, together with the presence of vocal sounds detected by the microphone which indicated ongoing breathing. Groaning events often occurred in clusters but were scored separately under the guideline of ICSD-2 in order to determine the groaning index (GI, groaning episodes per hour of sleep). All the records were scored manually by certified technicians and verified by a researcher. The technicians and researcher who scored the polysomnographic records did not participate in data measurement.

Mandibular Advancement Device

Patients underwent detailed dental evaluation to determine their suitability for MAD therapy, including assessment of overjet, overbite, maxillofacial morphology, and periodontal disease conditions, and temporomandibular joint disorders. The occlusal relationship was examined with each patient seated upright in a natural head position. Intercuspid position, maximal mandibular protrusion, and the freeway space were assessed. The bite registration was set at approximately two-thirds of maximum mandibular protrusion and 3 to 6 mm of vertical opening between the incisal edges and adjusted according to each patient's adaptation and craniofacial morphology.

After impression making and the preparation of cast models, a 3-mm-thick thermoforming plastic sheet was used for a custom-fitted MAD (Kombiplast soft D-420017, DreveDentamid GmbH, Unna, Germany). The MAD is shown in Figure 1. It was designed to advance the mandible and its associated soft tissues slightly forward and to open the bite.

Polysomnography was repeated with the MAD in place at least 1 month after the patient was fitted with the MAD.

CBCT of the Upper Airway

CBCT has become a popular modality in the evaluation of the upper airway because it offers high diagnostic value with a relatively low radiation dose of short duration. It has also been proven to be an accurate and reliable method for three-dimensional analysis of the upper airway.[24] Informed choices were made by patients to undergo CBCT of their upper airway with and without insertion of the MAD.

All images were obtained on a CBCT scanner VATECH (DCTPRO-050Z, VATECH Co, Ltd, Korea). The scanning protocol was 120 kV, 5 mA, 13 17 cm field of view, 0.25 mm voxels, and a scanning time of 40 seconds. The scans were obtained with patients seated in an upright position. A rigid cervical collar and a plumb line were used to ensure that the soft-tissue Frankfort plane (the line through the superior point of external auditory canal and the infraorbital margin) remained parallel to the ground. All patients were asked to maintain centric occlusion, or with MAD placement, to breathe evenly and to refrain from swallowing.

The Digital Imaging and Communications in Medicine images for each patient were assessed using Dolphin Imaging (Version 11.8 Premium; Dolphin imaging, Chatsworth, California). Once imported, three-dimensional reconstructions were oriented so that the Frankfort horizontal plane was parallel to the axial plane. The midsagittal plane was oriented to the patient's midline. The coronal plane was oriented so that it passed through both the left and the right porion points. Volume, average cross-sectional area, and anteroposterior and lateral diameter of the velopharynx, oropharynx, and hypopharynx were measured.

A cephalometric radiograph could be made from CBCT. The cephalometric reference points of the craniofacial structures, upper airway, and surrounding tissues are shown in **Figure 2**. Vertical opening represented changes of distance from lower incisor edge (L1) to Frankfort plane. Sagittal advancement was defined as changes of distance of lower incisor edge (L1) along occlusal plane.

All measurements were performed twice in a 2-week interval by the same examiner. Intrareliability was tested by intraclass correlation coefficient with results from 0.85 to 1.00 (>0.75).

Statistical Analysis

The statistical analysis was performed using SPSS 26.0 (IBM Corporation, IBM SPSS Statistics for Mac, Version 26.0. Armonk, New York). Parameters of normal distribution were verified by the Shapiro-Wilk test and summarized as mean standard deviation, otherwise as median (interquartile range). The comparisons before and after MAD insertion in each patient were performed using paired-sample t-test and two related samples nonparametric tests for normally distributed and skewed distributed parameters, respectively. The intergroup differences were performed with univariate analysis (multiple comparisons not corrected). Logistic regression was performed for multivariate analysis. Statistical significance was considered with value of $P < 0.05$.

RESULTS

Clinical characteristics

Twelve men and 18 women (median age, 31.0 years) were included in the study. The median age of recalled symptom onset was 18 years. All the patients had a normal body mass index (average 22.0 ± 2.7 kg/m^2). None of the patients had special medical history. The most frequently reported symptoms were groaning noises during sleep (100%), unrefreshing sleep (36.7%), daytime fatigue (23.3%), and decreased memory and concentration (20%). A total of 14 patients (46.7%) had an Epworth Sleepiness Scale (ESS) score higher than 10.

Cephalometric findings

The detailed measurements of maxillofacial structures, upper airway and its surrounding soft tissue are shown in **Table 1**. Compared with normal reference, the maxilla and mandible of patients with catathrenia were within normal range; however, the mandibular plane angle was significantly lower. Not only were none of the patients noted to have narrowing of the upper airway on lateral cephalogram, but also the retropalatal airway space (SPP-SPPW) of patients with catathrenia was significantly larger than normal reference. These patients also had a higher hyoid bone and shorter tongue length compared with normal values in Chinese patients.[25, 26]

Polysomnographic characteristics

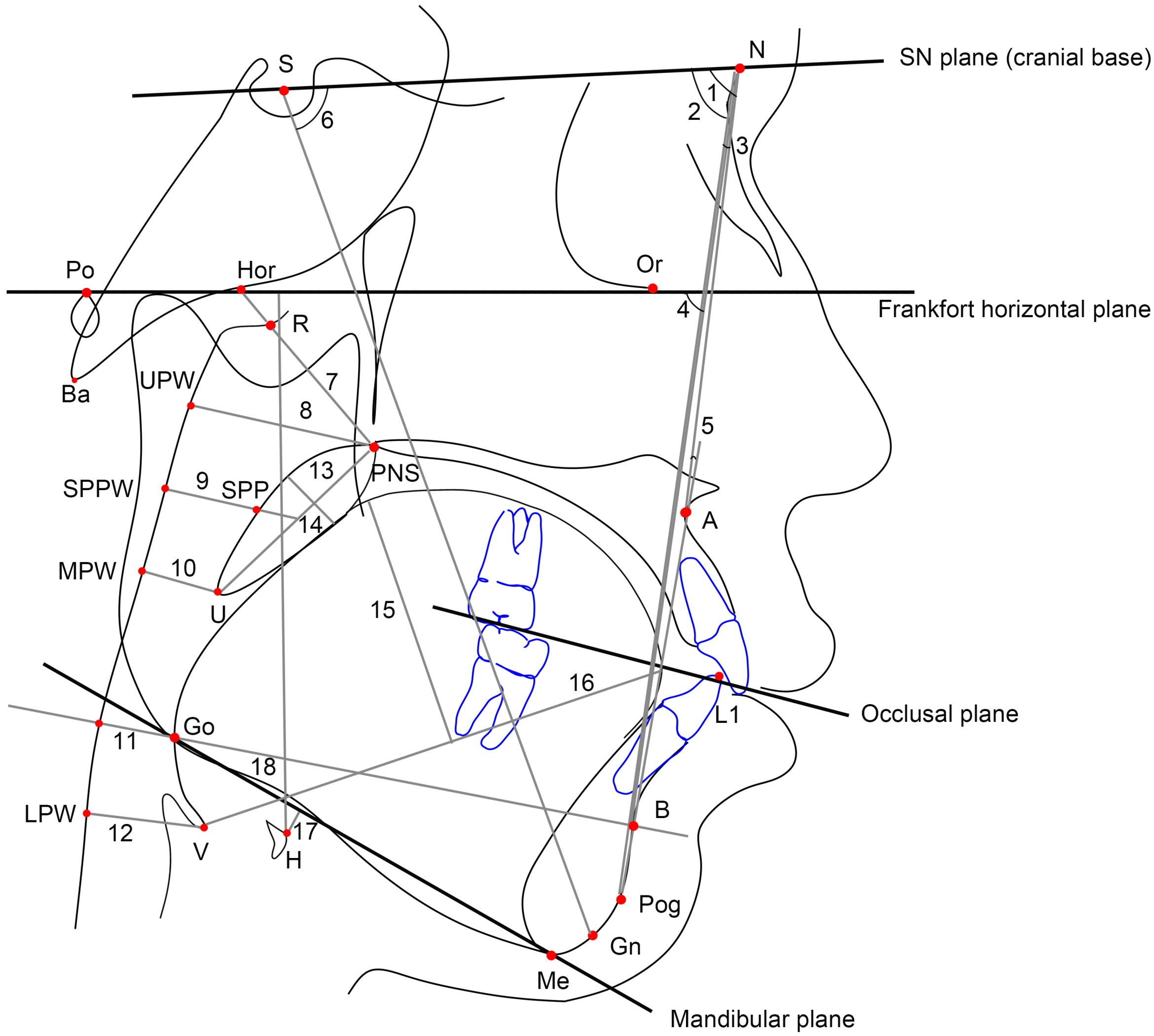
The detailed record of polysomnography is shown in **Table 2**. Sleep efficiency in most patients was higher than 80%. Groaning was characterized by a deep inspiration, followed by a prolonged expiration with monotonous vocalization. These episodes often occurred in clusters, with a sharp inspiration as an interval. Groaning was not associated with a discernible decrease in oxygen saturation but was accompanied by a slight decrease in respiratory frequency and heart rate. Catathrenia events occurred predominantly during REM sleep in 11 patients (36.7%) and occurred mainly during NREM sleep in 15 patients (50%). The remaining 4 patients (13.3%) had groaning episodes distributed evenly in REM and NREM sleep stages. Initial GI ranged from 0.53 to 57.6 events/h. There were 14 patients (46.7%) with GI lower than 5 events/h and 14 patients (46.7%) with GI from 5 to 15 events/h. AHI ranged from zero to 15.2 events/h. In six patients, OSA was diagnosed as mild in five and of moderate severity in one.

Efficacy of MAD

Approximately 70% of the patients reported an improvement in sleep quality and decreased nocturnal groaning noises as evaluated by their roommates or bed partners. ESS score improved from 9.4 ± 4.2 to 6.9 ± 2.8 with MAD ($P = 0.009$).

As Table 2 shows, there was no statistical change in sleep efficiency after MAD insertion. A decreased duration of sleep latency and REM latency was observed with the MAD; no significant difference was shown. GI decreased significantly from 5.8 (2.7, 14.3) to 2.8 (1.3, 12.2) events/h ($P = 0.014$).

Figure 2—Cephalometric measurements of maxillofacial, upper airway, and surrounding structures



S Sella, midpoint of sella turcica; N Nasion, most anterior point on frontonasal suture; A Subspinale, most concave point of anterior maxilla; B Supramental, most concave point on mandibular symphysis; Pog Pogonion, most anterior point of mandibular symphysis; Gn Gnathion, point located perpendicular on mandibular symphysis midway between pogonion and menton; Me Menton, lowest point on mandibular symphysis; Go Gonion, most posterior inferior point on angle of mandible; Ba Basion, most anterior point on foramen magnum; PNS, posterior nasal spine, posterior limit of bony palate or maxilla; Hor, the intersection between the greater wing and the body of the sphenoid bone; R, the intersection between posterior pharyngeal wall and PNS-Hor line; UPW, the intersection between posterior pharyngeal wall and PNS-Ba line; U, tip of soft palate; MPW, foot point at the posterior pharyngeal wall of perpendicular line from point U; V, base of epiglottis; LPW, foot point at the posterior pharyngeal wall of perpendicular line from point V; H, most superior and anterior point on the body of hyoid bone; L1, the ridge of lower first incisor.
SN plane, the anterior cranial base and is formed by projecting a plane from the sella-nasion line; Frankfort horizontal plane, FH plane, the line through the superior point of the auditory canal (Po) and the inferior point of the optic fossa (Or); Occlusal plane, the plane connecting the overlap of the first permanent molars and incisors; Mandibular plane, MP plane, the line through Go and Me;

1. SNA, the relative anteroposterior position of the maxilla to the cranial base; 2. SNB, the relative anteroposterior position of the mandible to the cranial base; 3. ANB, the relative anteroposterior position of the maxilla to the mandible; 4. facial angle(FH-NPog), the degree of protrusion or retrusion of the mandible; 5. convexity(NA-APog), convexity or concavity of skeletal profile; 6. Y-axis(NS-SGn), the degree of downward, rearward or forward position of the chin in relation to the upper face; 7. PNS-R; 8. PNS-UPW; 9. SPP-SPPW; 10.U-MPW; 11. PAS, posterior airway space along the Go-B line; 12. V-LPW; 13. soft palate length; 14. soft palate thickness; 15. tongue height; 16. tongue length; 17. H-MP, distance from hyoid to mandibular plane; 18. H-FH, distance from hyoid to Frankfort horizontal plane.

Table 1-- Comparisons of cephalometric measurements between catathrenia and Chinese normal reference. (M±SD)

Parameters	Catathrenia	Chinese normal reference[1, 2]	t[3]	*p*
Maxillofacial structures				
SNA(°)	81.7±4.0	82.8±4.0	-1.370	0.172
SNB(°)	78.8±4.5	80.1±3.9	-1.616	0.108
ANB(°)	2.9±2.4	2.7±2.0	0.481	0.631
Facial angle(FH-NP)(°)	87.1±3.8	85.4±3.7	2.279	0.024*
Convexity(NA-AP)(°)	4.7±5.8	6.0±4.4	-1.160	0.254
MP-SN(°)	35.4±6.5	32.5±5.2	2.295	0.027*
MP-FH(°)	27.5±5.6	31.1±5.6	-3.203	0.002**
Y-axis(°)	62.4±6.0	66.3±7.1	-2.805	0.006**
Upper airway[4]				
PNS-R(mm)	23.7±3.7	23.1±3.1	0.888	0.376
PNS-UPW(mm)	29.6±3.4	28.6±3.1	1.515	0.132
SPP-SPPW(mm)	20.4±3.7	13.6±2.8	9.299	0.000***
U-MPW(mm)	12.7±4.4	12.4±3.2	0.347	0.731
PAS(mm)	14.3±5.6	13.7±3.6	0.554	0.583
V-LPW(mm)	19.2±5.5	20.1±4.5	-0.911	0.364
Soft palate				
Length(mm)	37.8±4.7	36.6±3.6	1.290	0.205
Thickness(mm)	9.8±1.9	10.2±1.8	-1.054	0.294
Tongue				
Height(mm)	37.9±4.0	37.1±3.7	1.019	0.310
Length(mm)	66.6±8.7	79.0±7.0	-8.029	0.000***
Hyoid bone position				
H-MP(mm)	9.0±5.0	12.6±5.0	-3.459	0.001**
H-FH(mm)	85.8±8.0	94.5±9.7	-4.474	0.000***

SNA, the relative anteroposterior position of the maxilla to the cranial base; SNB, the relative anteroposterior position of the mandible to the cranial base; ANB, the relative anteroposterior position of the maxilla to the mandible; Facial angle(FH-NP), the degree of protrusion or retrusion of the mandible; Convexity(NA-AP), convexity or concavity of skeletal profile; MP-SN and MP-FH, relation of mandibular plane to cranial base and Frankfort horizontal plane; Y-axis, the degree of downward, rearward or forward position of the chin in relation to the upper face; H-MP and H-FH, the distance from hyoid bone to mandibular plane and Frankfort horizontal plane. [1] Fu MK, Mao XJ. Cephalometric analysis on 144 Chinese with normal occlusion. *Journal of Beijing Medical School*. 1965;4:251-56. [2] Liu Y, Zeng X, Fu M, Huang X. X-ray cephalometry study of normal people's upper airway structure orthodontics. *Chin J Orthod*. 1997;4(1):10-14. [3] summary independent samples t-test; 4 posterior airway space from PNS (posterior nasal spine) to V (base of epiglottis) * p<0.05; ** p<0.01;*** p<0.001.

However, none of the patients were observed to have complete elimination of groaning sounds, and an absolute change of GI to 5 events/h was not reached. MAD use also did not alter GI distribution through sleep stages. For the six patients who also had OSA, AHI decreased from 10.0 3.9 to 3.2 3.5 (P = 0.001) and GI decreased from 12.8 (0.8, 34.4) to 1.6 (1.2, 26.5) (P = 0.116).

Following MAD placement (**Table 3**), the total volume of the upper airway remained unchanged (P > 0.05). The lateral diameter increased, with the most significant change in velopharynx (P = 0.001). The ratio of anteroposterior to lateral diameter decreased (P < 0.05), indicating a change in morphology of the upper airway.

Factors predicting effectiveness of MAD placement

In order to explore anatomic factors predicting effectiveness, patients were assigned to two groups according to GI changes: good responders, defined by GI reduction ≥ 50% (n = 11), and

Table 2-- Comparisons of polysomnographic characteristics of catathrenia, before and after insertion of mandibular advancement device (n=30)

	Initial	MAD insertion	
	M±SD/MED(IQR)	M±SD/MED(IQR)	*p*
TST (min)	426.9±43.6	399.5±68.7	0.224
SE (%)	87±9	83±5	0.598
Sleep LAT (min)	27±34	14±11	0.621
REM LAT (min)	134±51	111±47	0.651
REM (%)	14±7	15±5	0.943
AHI[1](events/h)	1.8(0.4, 4.2)	0.2(0, 1.8)	0.002**,[3]
AHI[2](events/h)	10.0±3.9	3.2±3.5	0.001**,[4]
SpO_2(%)	96.5±0.9	96.6±0.9	0.842
GI (events/h)	5.8(2.7, 14.3)	2.8(1.3, 12.2)	0.014*[3]

MAD, mandibular advancement device; TST, total sleep time; SE, sleep efficiency; Sleep LAT, sleep latency; REM LAT, stage R latency; AHI, apnea-hypopnea index; SpO_2: mean oxygen saturation; GI, groaning index, groaning episodes per hour of sleep. [1] AHI of all included subjects; [2] AHI of patients combined with OSA; [3] 2 related samples nonparametric test; [4] paired-samples *t*-test; $*p<0.05$;$**p<0.01$.

poor responders, defined by GI reduction < 50% (n=19). Intergroup changes were explored, including demographic characteristics (age, onset age, sex, body mass index, and ESS score), PSG findings (initial GI, AHI; GI distribution), cephalometric parameters, two-dimensional and three-dimensional upper airway parameters, and mandibular repositioning (sagittal, vertical, and total).

In univariate analysis, there was a significant difference in patient age, hypopharynx changes with MAD placement, and mandible repositioning. After stepwise logistic regression, only the vertical opening remained significantly different between responders and nonresponders.

A significant intergroup age difference was present (P = 0.007). Good responders (median 23.0 years) were younger than poor responders (median 34.0 years). Initial groaning severity was not statistically different between groups (P = 0.672), nor was initial AHI (P = 0.497). Maxillofacial structures on lateral cephalometric analysis were fairly consistent between groups. Mandibular repositioning, particularly vertical opening, was significantly different between the two groups. The average vertical opening was 8.4 ± 1.8 mm in good responders and 5.9 ± 1.8 mm in poor responders (P = 0.005). The total repositioning (vertical opening and sagittal advancement) was 13.8 ± 3.2 mm and 10.4 ± 2.3 mm for good responders and poor responders, respectively (P = 0.010). In addition, CBCT analysis of upper airways changes with the MAD in place demonstrated a more significant improvement of the hypopharynx of good responders, with an average 1.9-mm increase in lateral diameter (P = 0.044) and an average 25-mm^2 increase in cross-sectional area (P = 0.046).

With the aforementioned significant variables between groups, forward stepwise logistic regression was implemented. The vertical opening was the only variable entered into the equation (**Table 4**).

DISCUSSION

Sleep-related groaning is a rare disease, with onset usually in adolescence or early adulthood.[17, 27] Catathrenia was reported to be more common in men,[19] whereas in our study there were slightly more female patients. Patients usually have no recollection of the sound but may experience unrefreshing sleep, fatigue, and decreased daytime alertness.[27]

In our study, distribution of groaning episodes through sleep stages varied across individuals. MAD treatment did not seem to affect such distribution. Groaning was originally characterized by REM sleep predominance,[1, 2, 4, 9, 10, 28] but later NREM-sleep related cases [3, 7, 11, 13] and even cases independent of sleep stages[15, 29] were reported. Although sound analysis did not show any differences in the regularity of catathrenia waveforms between REM and NREM sleep,[30] subtypes or variants of catathrenia have been proposed.[31]

In our study, although no obvious upper airway obstruction was present on radiographs when patients were awake and in the sitting position, a better treatment response could be ascribed to more increases in obstruction in the hypopharynx, supporting the hypothesis of sleep-related obstruction of the upper airway. Vetrugno et al. observed that endoesophageal pressure during groaning swung positively at the initial phase of expiration,[9, 29] also suggesting sleep-related obstruction of the upper airway.[1, 10, 12, 17] Groaning may therefore represent a positive end-expiratory pressure maneuver to maintain airway patency at end expiration.[11] Other assumptions have been made. The formants and harmonics noted with the groaning sounds indicated that the generator of catathrenia might be adjacent to the vocal cord region.[30] Therefore, the groaning might derive from the partial or intermittent closure of the glottis and reactive forced prolonged expiration to overcome

Table 3-- Changes of upper airway parameters after insertion of mandibular advancement device on CBCT. (M±SD)

	Overall (n=30) MAD insertion -initial	t	p^1	Good responders (n=11) MAD insertion -initial	Poor responders (n=19) MAD insertion - initial	t	p^2
Average cross sectional area (mm^2)							
Velopharynx	14.2±54.9	1.068	0.301	12.5±41.0	15.8±67.5	-0.121	0.906
Oropharynx	-45.8±114.6	-1.648	0.119	-19.8±68.4	-68.9±144.6	0.874	0.396
Hypopharynx	-18.2±86.4	-0.867	0.399	25.0±40.6	-56.5±99.8	2.248	0.046*
Average anteroposterior diameter (mm)							
Velopharynx	-0.5±1.6	-1.306	0.210	-0.3±1.3	-0.7±1.9	0.519	0.611
Oropharynx	-2.0±3.4	-2.423	0.028*	-1.2±1.9	-2.7±4.3	0.918	0.373
Hypopharynx	-1.1±2.8	-1.589	0.132	0.0±1.6	-2.0±3.3	1.577	0.136
Average lateral diameter (mm)							
Velopharynx	2.7±2.7	4.014	0.001**	2.6±2.6	2.7±3.0	-0.044	0.966
Oropharynx	0.3±4.0	0.320	0.753	0.9±4.2	-0.2±4.1	0.549	0.591
Hypopharynx	0.5±2.7	0.762	0.457	1.9±1.2	-0.7±3.2	2.291	0.044*
Anteroposterior/lateral diameter							
Velopharynx	-0.05±0.04	-5.921	0.000***	-0.04±0.03	-0.07±0.04	1.252	0.230
Oropharynx	-0.07±0.07	-4.146	0.001**	-0.05±0.04	-0.08±0.08	1.001	0.333
Hypopharynx	-0.04±0.07	-2.339	0.033*	-0.03±0.04	-0.05±0.08	0.699	0.497

CBCT, cone beam computed tomography; MAD, mandibular advancement device. [1] paired samples *t*-test; [2] independent samples *t*-test; * $p<0.05$;** $p<0.01$;*** $p<0.001$.

Table 4 – Variables of forward stepwise logistic regression

Variables	B	S.E.	Sig.	Exp(B)	95% C.I.for EXP(B) Lower	95% C.I.for EXP(B) Upper
Vertical opening	0.795	0.367	0.030	2.214	1.078	4.547
Constant	-5.659	2.626	0.031	0.003		
Age	3.664		0.056			
Total repositioning	1.341		0.247			
Changes of average lateral diameter of hypopharynx	0.737		0.391			
Changes of average cross sectional area of hypopharynx	0.666		0.414			

S.E., standard error; C.I., confidence interval; EXP(B), the exponentiation of the B coefficient this resistance.[1, 2] In one study, a subtotal closure of the glottis, causing the groan, was seen during laryngoscopy in a patient under deep sedation.[14] Involvement of postinspiratory neurons was suggested by several investigators.[1, 7] A report of catathrenia provoked by sodium oxybate treatment for narcolepsy with cataplexy suggested instability of the neural structures controlling ventilation during sleep.[8] One study has shown close association between arousals and groaning episodes and that arousal mechanisms may be involved in the pathogenesis of nocturnal groaning.[5]

Several treatment trials have been conducted for catathrenia. Response to various medication including clonazepam, trazodone, paroxetine, and dosulepine was poor,[2, 32] and gabapentin had only a transitory effect on the disappearance of groaning.[10] Catathrenia is classified under sleep-related breathing disorders in ICSD-3. Considering that CPAP might keep the glottis open and maintain airway patency, especially for patients who also experience SDB, it was used as an exploratory treatment. A review of the literature showed that CPAP was mentioned as a therapeutic approach in 16 articles (conference abstracts excluded). As **Table 5** shows, most patients reported clinical improvement with CPAP with positive airway pressure from 4 to 12 cm H_2O,[2-5, 7, 11-15, 17, 18, 20, 28, 33-35] and some investigators found it more effective with higher pressure.[36] However, a universal response of CPAP treatment has not been identified.[13, 28, 32]

However, as an alternative treatment for SDB, the MAD was reportedly used in a treatment trial for catathrenia in fewer than 10 patients and the findings were inconsistent, ranging from no clinical improvement[20] to self-reported subjective resolution.[5] Our study is one of the few studies to evaluate the objective effect of the MAD on patients with catathrenia. An overall significant reduction of GI was observed; however, similar to CPAP, MAD could not completely eliminate groaning sounds. In addition, responses to treatment fluctuated among patients. This therapeutic response was completely different from that applied to OSA.

Individual differences in response to treatment inspired us to explore the factors affecting efficacy. Several factors might be associated with the prediction of efficacy based on univariate analysis: the patient's age, hypopharynx changes with MAD placement, and mandible repositioning. However, only the vertical opening remains statistically significant in multivariate analysis. It seemed that the greater the vertical opening with MAD placement, the more likely there would be a better response for nocturnal groaning. This finding is consistent with the efficacy of CPAP to some extent, that higher pressures are recommended.[11, 12, 36] However, these factors need to be interpreted with caution because of the small sample size and the lack of a control group in this study.

In our research, for those patients with OSA, MAD therapy was quite effective. The purpose of MADs in the treatment of OSA was mainly to increase the upper airway dimension, dimension, especially in the velopharynx and hypopharynx and specifically in the lateral dimension.[37] The upper airway configuration of patients with catathrenia was broader than that of healthy control,[22] and therefore no significant increase in airway size after the insertion of the MAD was observed in our study except for that in the lateral dimension in the velopharynx. Furthermore, MAD use may also tense palatal muscles and activate respiratory-related genioglossus electromyographic activity.[38] Changes of the shape of the upper airway will tend to tilt the balance of forces acting on the upper airway in favor of improved patency, which may explain the efficacy of MADs in reducing groaning sounds.

The amount of advancement is considered to contribute to the degree of effectiveness of MAD treatment for OSA and mandibular opening should be kept to a minimum.[39] On the contrary, in our study, the amount of vertical opening seemed to be contribute more to the degree of effectiveness of treatment for nocturnal groaning. Patients with catathrenia have craniofacial and occlusal characteristics that are different from those of patients with OSA.[22] Typically, patients with OSA have a higher mandibular plane angle and the glenoid fossa of these patients may result in a clockwise rotation of the mandible, which tends to rotate the genioglossus and hyoid musculature closer to the oropharyngeal airway.[40] However, patients with catathrenia have lower mandibular planes; therefore, an increase in the vertical reposition of the mandible seems to be acceptable.

Our study has some limitations. The sample size is small because of the low prevalence of catathrenia, resulting in low statistical power. We examined the upper airway when patients were awake and seated, whereas catathrenia occurs at night when patients are lying down. Participants in this study were disturbed by groaning sounds and sought symptom relief; therefore, the control group might not see any benefit. With unknown long-term effects of the disease, patients were not willing to participate in a time-consuming study; thus, changes in upper airway configuration from chronic use of MADs are not discussed. Because of the maxillofacial characteristics in different ethnic groups, the findings in our study might be limited.

Summary

The MAD could be considered as a possible treatment trial for patients with catathrenia. However, mandibular repositioning might be different for those with OSA. For nocturnal groaning, MAD seemed to be more beneficial from a vertical opening. A better response of the hypopharynx seems to be associated with better treatment efficacy. Caution should be exercised when interpreting this study. A longitudinal study with a large sample size and a control group is needed in the future.

Table 5 -- Summary of catathrenia subjects with treatment trial described in prior studies

Study	Year	Age(y)	Sex	Treatment trial	Response
Pevernagie, et al	2001	29	M	Trazodone 50 mg at bedtime	Not available
				Clonazepam 0.5 mg at bedtime	Bradypneic events unchanged
				Clonazepam 2 mg at bedtime	Not available
		22	M	Clonazepam 0.5 mg at bedtime	Not available
				Clonazepam 1.5 mg at bedtime	Bradypneic events unchanged
		27	M	Clonazepam 0.5 mg at bedtime	Bradypneic events unchanged
				Clonazepam 2 mg at bedtime	Not available
		38	M	Paroxetine 20 mg at bedtime	Not available
		29	M	Dosulepine 75 mg at bedtime	Not available
		40	M	Trazodone 100 mg at bedtime	Not available
		20	F	Dosulepine 75 mg at bedtime	Not available
		49	F	Nasal CPAP (8 cmH_2O)	Bradypneic events unchanged
		36	M	Nasal CPAP (8 cmH_2O)	Bradypneic events reduced
Grigg-Damberger, et al	2006	12	M	CPAP 8cmH_2O	Resolution of catathrenia
Iriarte, et al	2006	62	F	CPAP 6cmH_2O	The noise disappeared almost completely
Guilleminault, et al	2008	23	F	CPAP 7cmH_2O+MAD	Resolution
		34	F	CPAP 9cmH_2O	Resolution
		28	F	CPAP 8cmH_2O+MAD	Resolved
		20	F	CPAP 8cmH_2O	Resolution
		31	F	CPAP 10cmH_2O	Resolution
		26	F	CPAP 10cmH_2O+MAD	Resolved
		25	F	CPAP 7cmH_2O	Resolution
Manconi, et al	2008	31	M	CPAP up to 14cmH_2O	Non-effective
Songu, et al	2008	40	F	CPAP 11mBar	The groaning sound disappeared completely
Steinig, et al	2008	33	M	CPAP	Subjective improvement was mild and not long-lasting
Ott, et al.	2011	29	F	CPAP 8cmH_2O	Significant reduction in groaning
Abbasi, et al	2012	30	M	CPAP 5cmH_2O	143 catathrenia events decreased to 2 events
		76	M	CPAP 7cmH_2O	26 catathrenia events decreased to 5 events
		30	F	CPAP 10cmH_2O	137 catathrenia events decreased to 38 events
		47	M	CPAP 10cmH_2O	40 catathrenia events decreased to 4 events
Øverland, et al	2012	29	M	automatic CPAP	Groaning index reduced from 4.2/h to 3.4/h
Neutel, et al	2014	32	M	CPAP 4-12cmH_2O	Resolution of complaints
Dias, et al	2017	40	F	CPAP 7cmH_2O	0 catathrenia event remained
		25	F	CPAP 6cmH_2O	0 catathrenia event remained
		37	F	CPAP 6cmH_2O	0 catathrenia event remained
		30	F	CPAP 8cmH_2O	0 catathrenia event remained
		31	M	CPAP 9cmH_2O	0 catathrenia event remained
		32	M	CPAP 12cmH_2O	9 catathernia events remained
		36	F	CPAP 8cmH_2O	0 catathrenia event remained
		34	F	CPAP 7cmH_2O	0 catathrenia event remained
Drakatos, et al	2017	33.1 ±7.7	M/F =23/15	CPAP (n=9)	Self-report subjective resolution
				MAD (n=6)	Effective with follow-up

Table 5 -- Summary of catathrenia subjects with treatment trial described in prior studies, continued

Xiang, et al	2019	22	F	CPAP	Groaning events reduced
		27	F	CPAP	No improvement
Petitto, et al	2019	7	M	CPAP 7cmH_2O	Resolution of events
		14	M	CPAP 8cmH_2O	Resolution of events
		12	M	CPAP 6cmH_2O	Resolution of events
Gomez, et al	2020	22	F	CPAP 4cmH_2O	Catathrenia events reduced from 38 to 8 (polygraphy test)

CPAP, continuous positive airway pressure; MAD, mandibular advancement device.

ABBREVIATIONS

AHI, apnea-hypopnea index
CBCT, cone beam computed tomography
CPAP, continuous positive airway pressure
ESS, Epworth Sleepiness Scale
GI, groaning index
ICSD, International Classification of Sleep Disorders
MAD, mandibular advancement device
NREM, nonrapid eye movement
OSA, obstructive sleep apnea
REM, rapid eye movement
SDB, sleep-disordered breathing

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DISCLOSURE STATEMENT

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