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Clinical Characteristics of Patients with Persistent Apogeotropic and Persistent Geotropic Direction-Changing Positional Nystagmus

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Background and Purpose This study aimed to determine the clinical features, diagnosis, and treatment of patients with persistent geotropic (pG) and persistent apogeotropic (pAG) direction-changing positional nystagmus (DCPN).

Methods This retrospective study included 30 patients with pG-DCPN and 44 patients with pAG-DCPN. All patients underwent neurological and neurotological examinations, including an evaluation of gaze-evoked nystagmus, eye-movement tests, and assessments of limb ataxia and balance, as well as magnetic resonance imaging to exclude central causes. The characteristics of positional nystagmus were detected using the supine roll test (SRT) and bow-and-lean test (BLT). The null point (NP) at which the nystagmus disappeared was determined. All patients were treated with the barbecue maneuver, and treatment efficacy was evaluated immediately, 1 week, and 1 month after treatment.

Results The history of diseases associated with atherosclerosis, peripheral vestibular disorders, otological disease, and migraine differed significantly between patients with pG-DCPN and pAG-DCPN. The affected sides of persistent horizontal DCPN can be determined using the SRT and the BLT, while determining the second NP and vestibular function as well as performing an audiological evaluation can be used to assist in identifying the affected side. The efficacy rates immediately and 1 week after treatment with the barbecue maneuver were higher in patients with pAG-DCPN than in patients with pG-DCPN.

Conclusions pAG-DCPN was more compatible with the characteristics of cupulolithiasis, and pG-DCPN was more likely to be associated with a light cupula rather than canalolithiasis. pAG-DCPN was more likely to be accompanied by a disease associated with atherosclerosis, while pG-DCPN was often accompanied by autoimmune-related diseases and a history of migraine. The associations between pAG-DCPN, pG-DCPN, and the above-mentioned diseases need to be clarified further. The canalith-repositioning maneuver was effective in patients with pAG-DCPN and ineffective in patients with pG-DCPN, but most cases of pG-DCPN are self-limiting.

Key Words benign paroxysmal positional vertigo, nystagmus, antibodies.

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INTRODUCTION

Benign paroxysmal positional vertigo (BPPV) accounts for approximately 90% of all patients with positional vertigo and is the most common peripheral vestibular disease.[1] Horizontal-canal BPPV (HC-BPPV) reportedly accounts for 5−30% of BPPV cases.[2,3] Geotropic or apogeotropic nystagmus [i.e., direction-changing positional nystagmus (DCPN)] induced by the supine roll test (SRT) is a typical characteristic of HC-BPPV.[4] Generally, canalolithiasis of the posterior arm of the HC is considered if geotropic DCPN lasts for less than

1 min, and canalolithiasis of the anterior arm of the HC is considered if apogeotropic DCPN lasts for less than 1 min. Canalolithiasis has been attributed to degenerative otoconial debris floating freely in the endolymph of a semicircular canal, and when the head is in the provoking position, the movement of the otolith causes the flow of the lymph fluid to push against the cupula so as to cause cupula displacement, thereby inducing vertigo and nystagmus.[5]

Cupulolithiasis has been attributed to the detached otoconia observed on the surface of transitional and dark cells surrounding the maculae in the utricle that are generally absorbed by dark cells. However, when a vestibular disorder is present, the number of detached otoconia increases such that they cannot be absorbed by dark cells, which deposit on the cupula of the semicircular canal and interfere with the balance between the cupula and the endolymph, thereby creating a heavy cupula that makes the cupula of the crista ampullaris sensitive to gravity.[6-8] If geostrophic DCPN lasts for more than 1 min without latency or the induction of fatigability, it is considered that a light rather than a heavy cupula has been produced.[9-11] The pathogenesis of a light cupula is currently mainly attributed to the attachment of light debris to the cupula[7,10,12] and an increased specific gravity of the endolymph.[8,13,14] One study found that a light cupula accounted for about 14% of all patients showing geotropic DCPN.[7]

A heavy cupula of the HC is a quite-common clinical condition, but diagnosing and treating a light cupula has recently also attracted the attention of clinicians. Previous studies[7,9,11,15-17] found that both light and heavy cupulae were associated with the presence of a null point (NP), with the direction of the nystagmus being opposite on the two sides of the NP. Generally, for cases of persistent horizontal DCPN (pH-DCPN), determining the affected side mainly relies on the nystagmus intensity on both sides in the SRT. However, the nystagmus cannot be measured accurately due to variations in the speed and amplitude applied during the procedure and some vertigo clinics not being equipped with videonystagmography (VNG) testing. Some studies have proposed new position tests such as the bow-and-lean test (BLT) to assist in diagnosing the affected side in patients with pH-DCPN.[14,16,18,19]

Previous studies of light and heavy cupulae have largely focused on the clinical symptoms and nystagmus characteristics. However, data on the etiologies of light and heavy cupulae and the follow-up diagnosis of such patients are still insufficient, and the relationship between light and heavy cupulae and HC-BPPV needs to be further clarified. The present study analyzed the clinical features, diagnosis, treatment, and prognosis of patients with pH-DCPN, and investigated the value of the SRT, BLT, and NP in diagnosing the affected side.

METHODS

Subjects

We conducted a retrospective study of 30 patients presenting with persistent geotropic DCPN (pG-DCPN) and 44 patients presenting with persistent apogeotropic DCPN (pAG-DCPN) using the SRT who were treated in the vertigo department of Aerospace Center Hospital from July 2017 to February 2020. All patients underwent neurological and neurotological examinations, including an evaluation of gaze-evoked nystagmus, eye-movement tests (gaze test, saccade test, smooth-pursuit test, and optokinetic nystagmus test), and assessments of limb ataxia and balance to confirm the absence of a central lesion. Magnetic resonance imaging (MRI) was also performed in all patients, which did not reveal any central lesions. Bithermal caloric tests, the vestibular evoked myogenic potential (VEMP), the video head impulse test (vHIT), and positional tests including the SRT, Dix-Hallpike test (D-HT), and BLT were performed in all patients. The nystagmus was recorded using a VNG system (Interacoustics, Assens, Denmark). Several immune-related indicators were evaluated, including antinuclear antibody (ANA), rheumatoid factor (RF), thyroglobulin antibody (TGAb), and thyroid peroxidase antibody (TPOAb). All patients signed informed-consent forms, and the study was approved by the Ethics Committee of our hospital (20171206-YN-07).

Positional tests

In the SRT, the patient was placed in a supine position with the head tilted forward by 30°, the presence or absence of nystagmus was observed, and the head was then rapidly rotated 90° to one side, with this position maintained to observe the presence or absence of vertigo and nystagmus. The patient was then returned to the supine position, the head was rapidly rotated 90° to the opposite side, with this position maintained to again observe the presence or absence of vertigo and nystagmus. Finally, the patient was returned to the supine position. If nystagmus was present, the patient should be maintained in this position for 2 min.

In the D-HT, the patient was placed in a sitting position on the examination bed with the head turned to one side by 45°, and then rapidly laid down with the head hanging 30° below horizontal over the edge of the bed, with nystagmus in this position observed and recorded until it disappeared. The patients was then rapidly returned to the sitting position. The D-HT was performed on other side in the same manner in order to exclude patients with other types of nystagmus.

Choung et al.[18] proposed using the BLT test to determine the affected side. The SRT was first performed to determine whether the HC-BPPV was the canalolithiasis or cupulolithi-

asis form in the supine position. In the sitting position, the patient bowed their head forward by more than 90° and the direction of bowing nystagmus (BN) was observed, and then the head was tilted backward by more than 45° and the direction of leaning nystagmus (LN) was observed.

Kim et al.[14] proposed three NPs. If the patient had spontaneous nystagmus, and the nystagmus disappeared when the head was bowed in the pitch plane, this point was determined as the first NP. The second NP, in which the nystagmus disappeared, was identified when the patient's head was rotated to the left or right while in the supine position with the head tilted forward by 30°. When the patient bowed their head forward by 90° and the nystagmus disappeared when the head was turned to the left or right, this point was determined to be the third NP.

Immune-related laboratory tests

ANA was detected by immunoblotting using an ANA detection kit [Diagnostic Kit for ANA Profile; Werfen Medical Equipment Trading (Beijing) Co., Ltd., Beijing, China] to detect IgG antibodies toward nucleosome, dsDNA, histone, SmD1, PCNA, P0, SARO60kD, SSA/RoS2D, SSB/La, CenpB, Scl70, UI-snRNP, AMA-M2, Jo-l, PM-Scl, Mi-2, and Ku in patient serum. RF in patient serum was detected using the immune turbidimetric assay with an RF detection kit (Shenzhen YHLO Biotech Co., Ltd., Shenzhen, China). TGAb and TPOAb were detected using a two-step sandwich chemiluminescence immunoassay with the appropriate detection kits (Shenzhen Mindray Bio-Medical Electronics Co., Ltd., Shenzhen, China).

Treatments and outcomes

All patients were treated with the barbecue maneuver.[20] Specifically, the patient was laid in the supine position with the head tilted forward by 30°, the head and whole body were rotated 90° to the unaffected side, and then a further 90° rotation of the head and whole body toward the unaffected side was performed (with the patient lying in the prone position). The head and whole body were then rotated 90° to the unaffected side, and finally a further 90° rotation was performed and the patient was turned to the supine position. Each position was maintained for a certain period of time until the nystagmus or vertigo had been alleviated or disappeared.[21]

The efficacy of the barbecue maneuver was classified into three grades: 1) ineffective, in which positional vertigo and nystagmus were not alleviated, instead being worsened or converted to another type of nystagmus; 2) effective, where positional vertigo or nystagmus were alleviated but did not disappear; and 3) cure, where positional vertigo or nystagmus disappeared completely. The efficacy rate was defined as the combined percentage of cure and effective cases. All patients were followed up at 1 week and 1 month.

Statistical analysis

All quantitative data are presented as mean±standard-deviation values. For data that conformed to a normal distribution, the independent-samples *t*-test was used to compare the mean values of two groups. Enumeration data are expressed as percentages, and the chi-square test used to compare the differences between groups, with Yates continuity correction or Fisher's exact test applied if necessary. All tests were two-sided, and a p value of <0.05 was considered statistically significant. All data were analyzed using the SPSS software package (version 20.0, IBM Corp., Armonk, NY, USA).

RESULTS

Clinical baseline characteristics of patients with pH-DCPN

This study included 44 and 30 patients with pAG-DCPN and pG-DCPN, respectively, accounting for 21.0% and 14.3% of the 210 BPPV patients visiting our department during the study period. The 44 patients with pAG-DCPN comprised 19 (43.2%) males and 25 (56.8%) females, with a male-to-female ratio of 1:1.3, and they were aged 56.1±18.1 years. The 30 patients with pG-DCPN comprised 11 (36.7%) males and 19 (63.3%) females, with a male-to-female ratio of 1:1.7, and they were aged 50.7±14.9 years. There was no significant intergroup difference in age (p=0.180) or sex (p=0.575).

Clinical manifestations

The patients with pAG-DCPN included 14 (31.8%) with spontaneous vertigo and 30 (68.2%) with positional vertigo, while those with pG-DCPN included 9 (30.0%) with spontaneous vertigo and 21 (70.0%) with positional vertigo. These prevalence rates did not differ significantly between the two groups (p=0.999).

The durations from symptom onset to hospital admission were 3.2±2.0 and 3.8±2.3 days in the patients with pG-DCPN and pAG-DCPN, respectively (p=0.272). The disease durations were 0–7, 8–14, and 15–30 days in 30 (68.1%), 9 (20.5%), and 5 (11.4%), respectively, of the patients with pAG-DCPN, and in 6 (20.0%), 8 (26.7%), and 16 (53.3%) of the patients with pG-DCPN. There were significant differences in the disease duration between the two groups (p<0.0001) (Fig. 1).

Medical histories of patients

History of diseases associated with atherosclerosis

A previous history of diseases associated with atherosclero-

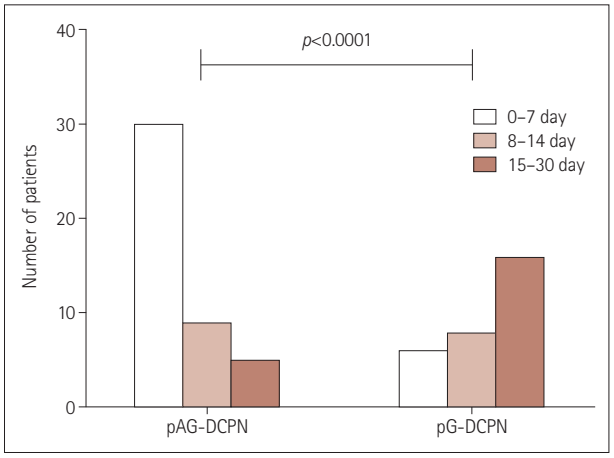

Fig. 1. Comparison of the disease duration between patients with pAG-DCPN and pG-DCPN (p<0.0001). DCPN: direction-changing positional nystagmus, pAG: persistent apogeotropic, pG: persistent geotropic.

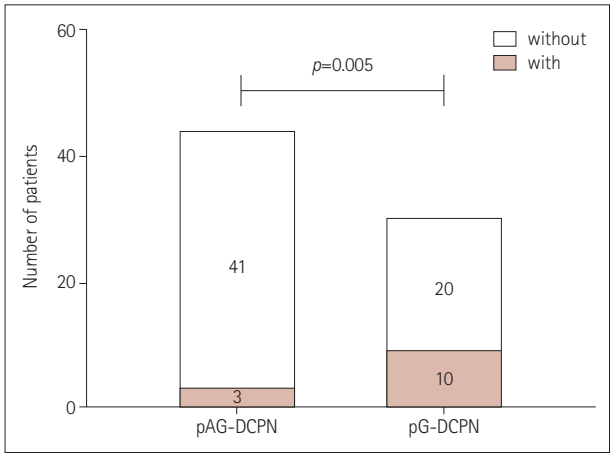

Fig. 2. Comparison of the history of migraine between patients with pAG-DCPN and pG-DCPN (p=0.005). DCPN: direction-changing positional nystagmus, pAG: persistent apogeotropic, pG: persistent geotropic.

sis was present in 17 (38.6%) patients with pAG-DCPN, including hypertension (n=14, 31.8%), coronary heart disease (n=5, 11.4%), diabetes (n=7, 15.9%), and hyperlipidemia (n=7, 15.9%), and in 4 (13.3%) patients with pG-DCPN, including hypertension (n=4, 13.3%) and hyperlipidemia (n=2, 6.7%). There were significant intergroup differences in the history of diseases associated with atherosclerosis (p=0.02) (Supplementary Fig. 1 in the online-only Data Supplement).

History of peripheral vestibular disorders and otological disease

A history of peripheral vestibular disorders and otologic disease was present in 18 (40.9%) patients with pAG-DCPN, including BPPV (n=15, 34.1%) and vestibular neuritis (n=3, 6.8%), and in 4 (13.3%) patients with pG-DCPN, including BPPV (n=2, 6.7%), vestibular neuritis (n=1, 3.3%), and sudden sensorineural hearing loss (SSNHL) (n=1, 3.3%). There were significant intergroup differences in the history of peripheral vestibular disorders and otological disease (p=0.019) (Supplementary Fig. 2 in the online-only Data Supplement).

History of migraine

A history of migraine was present in 3 (6.8%) patients with pAG-DCPN [1 (2.3%) and 2 (4.5%) patients had migraine with and without aura, respectively] and in 10 (33.3%) patients with pG-DCPN [4 (13.3%) and 6 (20.0%), respectively]. The history of migraine differed significantly between the two groups (p=0.005) (Fig. 2).

Nystagmus characteristics and the affected side in patients with pH-DCPN

Among the 74 patients with pH-DCPN, the SRT induced pAG-DCPN in 44 (59.5%) and pG-DCPN in 30 (40.5%), with both pAG-DCPN and pG-DCPN having no latency period or fatigue. During the SRT, the slow-phase velocity (SPV) of nystagmus on the affected side was significantly higher than that on the unaffect side in pG-DCPN patients (p=0.001), while it was significantly lower on the affected side in pAG-DCPN patients (p=0.003).

A second NP was found in 88.6% (39/44) of the patients with pAG-DCPN [on the left side in 15 (34.1%) and on the right side in 24 (54.5%)], and in 93.3% (28/30) of the patients with pG-DCPN [on the left side in 14 (46.7%) and on the right side in 14 (46.7%)]. The presence of the second NP did not differ significantly between groups (p=0.509). The angles of the second NP in patients with pAG-DCPN and pG-DCPN were 26.8±7.6° and 24.4±6.5°, respectively (p=0.143).

A third NP was found in 81.8% (36/44) of the patients with pAG-DCPN [on the left side in 14 (31.8%) and on the right side in 22 (50.0%)], and in 93.3% (28/30) of the patients with pG-DCPN [on the left side in 14 (46.7%) and on the right side in 14 (46.7%)]. The presence of the third NP did not differ significantly between groups (p=0.243). The angles of the third NP in patients with pAG-DCPN and pG-DCPN were 27.5±8.3° and 25.4±7.3°, respectively (p=0.584).

Three (6.9%) patients with pAG-DCPN showed pseudo-spontaneous nystagmus (PSN), with the fast phase directed toward the affected side. PSN was seen in nine (30.0%) patients with pG-DCPN, with the fast phase of nystagmus directed toward the unaffected side. The prevalence of PSN differed significantly between the two groups (p=0.011). The third NP was further identified in 12 of these patients, and its angles in patients with pAG-DCPN and pG-DCPN were 22.4±5.7° and 21.0±1.7°, respectively (p=0.245). During the SRT, the SPV of PSN was significantly lower in the upright sitting position than when lying down (p=0.002).

During the BLT, 31 (70.5%) patients with pAG-DCPN showed BN, with 28 (90.3%) and 3 (9.7%) showing BN with the fast phase directed toward the unaffected and affected sides, respectively. LN was found in 35 (79.5%) patients with pAG-DCPN [32 (91.4%) and 3 (8.6%)] exhibited nystagmus with the fast phase directed toward the affected and unaffected sides, respectively.

BN was found in 25 (83.3%) patients with pG-DCPN [23 (92.0%) and 2 (8.0%)] exhibited nystagmus with the fast phase directed toward the affected and unaffected side, respectively. LN was found in 25 (83.3%) patients with pG-DCPN [23 (92.0%) and 2 (8.0%)] exhibited LN with the fast phase directed toward the unaffected and affected sides, respectively. There were no significant intergroup differences in the BLT findings (p=0.102) or in the SPV of BN and LN (Fig. 3, Tables 1 and 2).

Results of vestibular and auditory evaluations in patients with pH-DCPN

Bithermal caloric tests were applied to 68 patients with pH-DCPN, which revealed that 20 (29.4%) patients (7 with pAG-DCPN and 13 with pG-DCPN) had abnormal canal paresis (CP) with a CP value of ≥25%. Among the seven patients with pAG-DCPN, the side of abnormal CP was consistent with the affected side in six patients with pG-DCPN. Among the 13 patients with pG-DCPN, the side of abnormal CP was consistent with the affected side in 8 patients with pAG-DCPN.

The vHIT was applied to 74 patients with pH-DCPN, of which 13 (17.6%) had abnormal results (4 with pAG-DCPN and 9 with pG-DCPN). Three of the four patients with pAG-DCPN experienced a decrease in function of the ipsilateral HC, and the fourth patient experienced decreases in function of the ipsilateral HC and the anterior semicircular canal. Six of the nine patients with pG-DCPN experienced a decrease in function of the ipsilateral HC, and the other three experienced decrease in functions of the contralateral HC and the posterior semicircular canal.

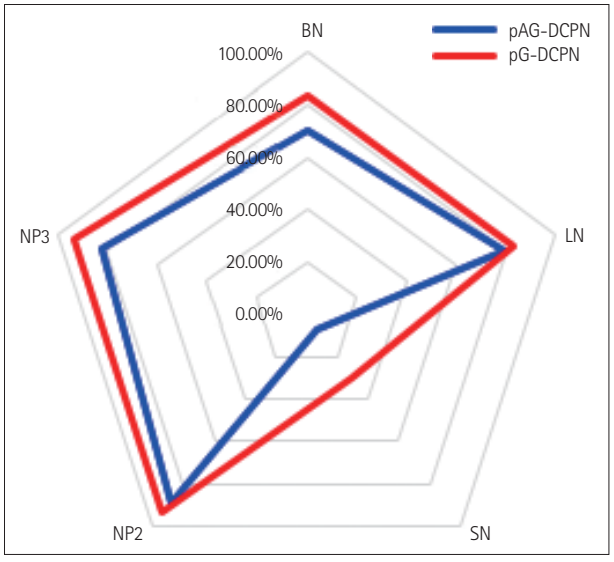

Fig. 3. Comparison of the results for different positional tests, the null point, bow-and-lean test, and pseudo-spontaneous nystagmus. BN: bowing nystagmus, DCPN: direction-changing positional nystagmus, LN: leaning nystagmus, NP2: second null point, NP3: third null point, pAG: persistent apogeotropic, pG: persistent geotropic, SN: spontaneous nystagmus.

Cervical VEMP (cVEMP) was measured in 74 patients with pH-DCPN, of which 12 (16.2%) showed an abnormal cVEMP (6 with pG-DCPN and 6 with pAG-DCPN). Five of the six patients with pAG-DCPN had a reduced cVEMP amplitude on the ipsilateral side, and an ipsilateral cVEMP was not elicited in the other patient. Three of the six patients with pAG-DCPN had a reduced cVEMP amplitude on the ipsilateral side, an ipsilateral cVEMP was not elicited in one patient, and two patients had a reduced cVEMP amplitude on the contralateral side.

A pure-tone test was applied to 72 patients with pH-DCPN, which revealed hearing loss in 14 (19.4%) patients (11 with pAG-DCPN and 3 with pG-DCPN). Five of the 11 patients with pAG-DCPN showed bilateral hearing loss, and the side of the hearing loss was consistent with the side affected by pAG-DCPN in 5 of the 6 patients with unilateral hearing loss. Three patients with pG-DCPN showed unilateral hearing loss, and the side of the hearing loss was consistent with the side affected by pAG-DCPN.

Immunological evaluations of patients with pH-DCPN

Immunological evaluations were performed in 74 patients with pH-DCPN, which revealed abnormalities in 12 (16.2%) patients [3 (6.8%) with pAG-DCPN and 9 (30.0%)] with pG-DCPN. Three patients with pAG-DCPN were positive for thyroid antibodies (TGAb and TPOAb), and one patient with pAG-DCPN was positive for RF. One of the nine patients with pG-DCPN was diagnosed with systemic lupus erythematosus, and the remaining eight patients were positive for both thyroid antibodies (TGAb and TPOAb). Four patients were positive for RF, and three patients were positive for ANA. The rate of positivity for autoimmune antibodies differed significantly between the two groups (p=0.011) (Fig. 4).

Treatments outcomes and follow-up

Immediately after treatment with the barbecue maneuver, the efficacy rates were 59.1% (26/44) and 6.7% (2/30) in patients with pAG-DCPN and pG-DCPN, respectively. Six (13.6%) patients with pAG-DCPN and no patients with pG-DCPN were cured. This maneuver was effective in 20 (45.5%) patients with pAG-DCPN and 2 (6.7%) patients with pG-DCPN.

Table 1. Nystagmus characteristics in patients with persistent geotropic direction-changing positional nystagmus

ID/sex/age	SRT_L		SRT_C		SRT_R		PSN		Bow		Lean		NP1	NP2	NP3
(years)	SPV	D	SPV	D	SPV	D	SPV	D	SPV	D	SPV	D			
1/F/58	10	LB	8	LB	17	RB	5	LB	8	RB	9	LB	-	R	R
2/F/57	22	LB	16	LB	51	RB	6	LB	9	RB	13	LB	+	R	R
3/M/38	19	LB	13	LB	33	RB	8	LB	15	RB	11	LB	+	R	R
4/M/37	8	LB	6	LB	16	RB	-	-	5	RB	6	LB	-	R	R
5/F/64	13	LB	8	LB	23	RB	-	-	9	RB	6	LB	-	R	R
6/F/62	17	LB	-	-	33	RB	-	-	9	RB	-	-	-	R	R
7/F/41	14	LB	8	RB	19	RB	-	-	-	-	7	RB	-	L	L
8/F/24	20	LB	9	RB	16	RB	6	RB	10	LB	9	RB	+	L	L
9/F/35	27	LB	6	LB	8	RB	-	-	13	LB	10	RB	-	L	L
10/M/24	35	LB	10	LB	17	RB	-	-	8	LB	9	RB	-	L	L
11/F/66	28	LB	16	LB	20	RB	5	LB	8	RB	8	LB	+	R	R
12/M/80	9	LB	-	-	23	RB	-	-	7	RB	9	LB	+	R	R
13/F/27	30	LB	22	LB	70	RB	8	LB	12	RB	11	LB	-	R	R
14/M/33	12	LB	7	LB	12	RB	-	-	8	RB	10	LB	-	R	R
15/F/60	9	LB	-	-	6	RB	-	-	-	-	-	-	-	-	-
16/F/30	25	LB	7	LB	15	RB	-	-	-	-	7	LB	-	L	L
17/F/72	10	LB	-	-	7	RB	-	-	8	LB	6	RB	-	L	L
18/F/53	36	LB	18	RB	25	RB	8	RB	6	LB	10	RB	+	L	L
19/F/47	15	LB	11	LB	23	RB	8	LB	7	RB	7	LB	+	R	R
20/M/61	17	LB	8	LB	20	RB	-	-	8	LB	7	RB	-	L	L
21/F/63	6	LB	-	-	7	RB	-	-	-	-	-	-	-	-	-
22/M/57	43	LB	12	RB	27	RB	-	-	-	-	10	RB	-	L	L
23/M/65	60	LB	18	RB	30	RB	-	-	9	LB	12	RB	-	L	L
24/M/61	34	LB	34	RB	18	RB	-	-	10	LB	14	RB	-	L	L
25/F/55	29	LB	12	RB	20	RB	-	-	6	LB	8	RB	-	L	L
26/F/38	6	LB	6	LB	14	RB	-	-	10	RB	12	LB	-	R	R
27/F/51	33	LB	10	RB	28	RB	8	RB	6	LB	8	RB	+	L	L
28/M/65	12	LB	10	LB	17	RB	-	-	5	LB	9	RB	-	R	R
29/F/51	7	LB	-	-	9	RB	-	-	8	RB	-	-	-	R	R
30/M/46	30	LB	3	RB	23	RB	-	-	6	LB	-	-	-	L	L

C: center, D: direction, F: female, L: left side, LB: left-beating nystagmus, M: male, NP: null point, NP1: first NP, NP2: second NP, NP3: third NP, PSN: pseudo-spontaneous nystagmus, R: right side, RB: right-beating nystagmus, SPV: slow-phase velocity (°/s), SRT: supine roll test, -: no nystagmus observed/no NP found, +: nystagmus observed/NP found.

The treatment efficacy differed significantly between the two groups (p<0.001).

The barbecue maneuver was performed again if necessary at the 1-week follow-up. The efficacy rates were 75.0% (33/44) and 13.3% (4/30) in patients with pAG-DCPN and pG-DCPN, respectively. Twelve (27.3%) patients with pAG-DCPN and 2 (6.7%) patients with pG-DCPN were cured. This maneuver was effective in 21 (47.7%) patients with pAG-DCPN and 2 (6.7%) patients with pG-DCPN. The treatment efficacy at the 1-week follow-up differed significantly between the two groups (p<0.001).

At the 1-month follow-up, nystagmus disappeared in 38 (86.3%) patients with pAG-DCPN and in all 30 (100%) patients with pG-DCPN, and the SPV of nystagmus was significantly decreased in the remaining 6 (13.7%) patients with pAG-DCPN (Supplementary Fig. 3 in the online-only Data Supplement).

DISCUSSION

Population characteristics and risk factors in patients with pH-DCPN

The male-to-female ratios in the present pAG-DCPN and pG-DCPN groups (1:1.3 and 1:1.7, respectively) are similar to those in previous studies.[8,10-12,22,23] pH-DCPN is more common in females than males. The prevalence rates of a history of diseases associated with atherosclerosis (e.g., hypertension, diabetes, and hyperlipidemia) and recurrent peripheral

Table 2. Nystagmus characteristics in patients with persistent apogeotropic direction-changing positional nystagmus

ID/sex/age (years)	SRT_L		SRT_C		SRT_R		PSN		Bow		Lean		NP1	NP2	NP3
	SPV	D	SPV	D	SPV	D	SPV	D	SPV	D	SPV	D			
1/F/38	24	RB	7	RB	10	LB	5	RB	6	LB	8	RB	+	R	R
2/M/35	16	RB	5	RB	17	LB	-	-	6	LB	7	RB	-	R	R
3/F/73	9	RB	-	-	5	LB	-	-	-	-	-	-	-	R	-
4/M/64	13	RB	-	-	6	LB	-	-	-	-	5	RB	-	R	-
5/M/71	23	RB	11	RB	15	LB	-	-	5	LB	9	RB	-	R	R
6/M/80	8	RB	5	LB	17	LB	-	-	6	RB	5	LB	-	L	L
7/F/62	69	RB	12	RB	41	LB	-	-	8	LB	12	RB	-	R	R
8/F/29	10	RB	7	LB	8	LB	-	-	6	LB	8	RB	-	R	R
9/F/54	55	RB	6	RB	24	LB	7	RB	6	LB	10	RB	+	R	R
10/F/56	19	RB	10	RB	14	LB	-	-	12	RB	9	LB	-	R	R
11/M/77	12	RB	-	-	11	LB	-	-	-	-	-	-	-	L	-
12/F/79	39	RB	9	LB	82	LB	6	LB	12	RB	9	LB	+	L	L
13/F/63	13	RB	8	RB	33	LB	-	-	8	LB	8	RB	-	L	L
14/F/49	33	RB	10	RB	18	LB	-	-	9	LB	8	RB	-	R	R
15/F/56	44	RB	12	LB	30	LB	-	-	10	LB	8	RB	-	R	R
16/F/24	23	RB	6	RB	12	LB	-	-	7	LB	6	RB	-	R	R
17/F/53	11	RB	-	-	5	LB	-	-	-	-	-	-	-	R	R
18/M/31	14	RB	6	LB	7	LB	-	-	-	-	6	LB	-	L	L
19/F/52	10	RB	-	-	18	LB	-	-	-	-	-	-	-	L	L
20/F/69	51	RB	15	RB	38	LB	-	-	8	LB	12	RB	-	R	R
21/M/75	19	RB	5	RB	8	LB	-	-	9	LB	7	RB	-	R	R
22/F/74	12	RB	5	RB	5	LB	-	-	11	LB	9	RB	-	R	R
23/M/67	8	RB	6	RB	12	LB	-	-	8	LB	7	RB	-	R	R
24/M/76	12	RB	5	RB	33	LB	-	-	8	LB	6	RB	-	R	R
25/M/56	6	RB	6	RB	16	LB	-	-	6	RB	6	LB	-	L	L
26/F/40	14	RB	5	RB	8	LB	-	-	-	-	6	RB	-	R	R
27/F/63	17	RB	-	-	10	LB	-	-	9	LB	7	RB	-	R	R
28/M/66	15	RB	-	-	38	LB	-	-	9	RB	5	LB	-	L	L
29/F/37	8	RB	7	LB	14	LB	-	-	-	-	7	LB	-	L	L
30/M/82	25	RB	8	LB	34	LB	-	-	10	RB	10	LB	-	L	L
31/M/80	7	RB	6	LB	11	LB	-	-	8	RB	6	LB	-	L	L
32/F/15	28	RB	10	LB	39	LB	-	-	8	RB	9	LB	-	L	L
33/F/66	17	RB	8	LB	25	LB	-	-	8	RB	8	LB	-	L	L
34/M/74	7	RB	-	-	5	LB	-	-	-	-	-	-	-	-	-
35/F/67	19	RB	8	RB	10	LB	-	-	6	LB	8	RB	-	R	R
36/F/52	11	RB	-	-	10	LB	-	-	-	-	-	-	-	-	-
37/M/31	7	RB	-	-	8	LB	-	-	-	-	-	-	-	-	-
38/M/82	8	RB	-	-	9	LB	-	-	-	-	-	-	-	-	-
39/M/40	17	RB	7	RB	26	LB			8	LB	10	RB	-	L	L
40/F/36	9	RB	-	-	9	LB	-	-	-	-	-	-	-	-	-
41/M/44	16	RB	11	LB	24	LB	-	-	10	RB	11	LB	-	L	L
42/F/60	18	RB	8	RB	11	LB	-	-	12	LB	8	RB	-	R	R
43/M/34	33	RB	11	RB	17	LB	-	-	9	LB	11	RB	-	R	R
44/F/37	46	RB	14	RB	23	LB	-	-	10	LB	12	RB	-	R	R

C: center, D: direction, F: female, L: left side, LB: left-beating nystagmus, M: male, NP: null point, NP1: first NP, NP2: second NP, NP3: third NP, PSN: pseudospontaneous nystagmus, R: right side, RB: right-beating nystagmus, SPV: slow-phase velocity (°/s), SRT: supine roll test, -: no nystagmus observed/no NP found, +: nystagmus observed/NP found.

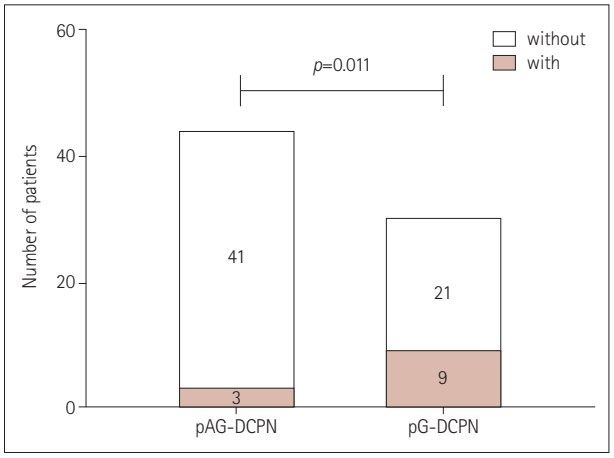

Fig. 4. Results of immunological evaluations of autoimmune antibodies (p=0.011). DCPN: direction-changing positional nystagmus, pAG: persistent apogeotropic, pG: persistent geotropic.

vestibular disorders (especially BPPV) are higher in pAG-DCPN patients than in pG-DCPN patients. We speculated that ischemia of the inner ear can affect the membranous labyrinth in patients with pAG-DCPN, with the degenerated otoliths being deposited on the cupula of the semicircular canal and damage occurring to the balance between the cupula and the endolymph, which in turn increases sensitivity of the semicircular canal to gravity.[6-8] In the present study, one patient with pG-DCPN was admitted to the hospital via an emergency department due to SSNHL, and contrast-enhanced MRI of the inner ear showed inner ear hemorrhage. Previous studies have observed irreversible morphological changes in the cupula in patients with SSNHL,[24] and degeneration of strial marginal cells was observed in animal models of inner ear ischemia.[25] Labyrinthine hemorrhage and inflammatory responses can cause acute damage to the inner ear that increases the specific gravity of the endolymph. Acute inner ear damage can destroy the blood–labyrinth barrier, allowing plasma proteins to enter the endolymph to increase the specific gravity of the endolymph.[26-28]

Previous studies have found autoimmune thyroiditis to be associated with BPPV.[29-32] ANA and RF are known to be markers of numerous autoimmune diseases, and TGAb and TPOAb are related to thyroid autoimmune diseases. This study also evaluated these immune-related indicators in patients with pH-DCPN. It is particularly interesting that our study found patients with pG-DCPN to be more likely to have positive test results for autoimmune antibodies (e.g., TGAb, TPOA, RF, and ANA) than patients with pAG-DCPN. We speculated that pAG-DCPN and pG-DCPN are mediated by different pathological mechanisms, the inner ear is one of the target organs in various non-organ-specific autoimmune diseases, and autoimmune damage to inner ear results from systemic autoimmune diseases. Changes in endolymphatic structures might be associated with autoimmune vasculitis or antibody cross-reactivity.[33,34] Other studies have observed inflammatory cells in the endolymph in animal models of endolymphatic hydrops.[35-37] We speculate that if inflammation occurs in the inner ear, changes in the concentrations of water-soluble macromolecular substances (e.g., proteoglycans in endolymph) can also change the specific gravity of the endolymph.

In this study, 36.4% of the patients with pG-DCPN had a history of migraine, which is consistent with previous findings. Tomanovic and Bergenius[38] found that about 40% of patients with a light cupula had a history of migraine, and all patients met the diagnostic criteria for vestibular migraine (VM). Radtke et al.[39] found that 28% of VM patients showed positional nystagmus, and considered that vasospasm in the inner ear and/or brain stem may cause endolymphatic hydrops in VM patients.

This study also found that disease duration was longer (by more than 2 weeks) in patients with pG-DCPN than in those with pAG-DCPN, which might be related to the different pathological mechanisms of pG-DCPN and pAG-DCPN. Most of the patients with pAG-DCPN had cupulolithiasis, and these patients can recover through treatment with the canalith-repositioning maneuver (CRM) and improving blood flow in the inner ear. However, pG-DCPN is most often mediated by inflammatory mechanisms or acute hemorrhage, which destroys the blood–labyrinth barrier, thereby changing the specific gravity and viscosity of the endolymph, and slowing the recovery process.

Nystagmus characteristics and the incidence of PSN in patients with pH-DCPN

In the present study, 30.0% of the patients with pG-DCPN had PSN with the fast phase directed toward the unaffected side in the sitting position, whereas only 6.9% of the patients with pAG-DCPN had PSN with the fast phase directed toward the affected side. Kim et al.[40] reported that PSN was present in 100% of patients with a light cupula, while another study did not find PSN in some patients with a light cupula when they were sitting with the head upright. Hong et al.[41] observed PSN more often in patients with pG-DCPN than in patients with transient DCPN, and the direction of PSN was toward the unaffected side. When the head is erect, an angle of 30° between the lateral semicircular canal and horizontal plane can place the ampulla in a higher position than the other semicircular canals, which causes the light cupula to deviate toward the utricle, leading to PSN. The present study found that in the SRT, the SPV of PSN in the sitting position was lower than that in lying-down nystagmus. It is speculated that the gravity force acting on the cupula varies in different positions,[34] which further indicates that the pathogenesis of pG-DCPN

may be different from that of transient DCPN.

During the SRT in the present study, nystagmus with equal intensity on both sides was observed in four patients with pAG-DCPN and two patients with pG-DCPN, and the affected side could not be determined according to Ewald's second law. The NP at which pG-DCPN or pAG-DCPN disappears can be identified when the position of the patient's head changes.[7,9,10] Ichijo[8] included 31 patients with a light cupula and 33 patients with a heavy cupula, and found the NP when turning the patient's head to affected side while the patient was in a midline neutral supine position. Kim et al.[14] investigated 26 patients with a light cupula, and found 3 NP at which nystagmus disappeared.

If a patient had PSN, the first NP was found when the nystagmus disappeared when the head was bowed in the pitch plane; the second NP was found with the patient in the supine position with the head tilted forward by 30°, when the nystagmus disappeared when the patient's head was rotated to the affected side; and the third NP was found with the patient bowed their head at 90°, when the nystagmus disappeared when the head was turned to the affected side. Previous morphological studies of squirrel monkeys and computed tomography of human inner ear revealed that the top of the cupula of the HC faces outward, and it is speculated that the cupula of the HC is at an angle of approximately 20° to the median sagittal plane.[41] Turning the patient's head toward the affected side at a certain angle will result in the long axis of the affected cupula being parallel to the axis of gravity, which does not cause deflection of the cupula, and produces no nystagmus; this is when the null plane is observed, and the side of the null plane is consistent with the affected side.[14] In our study, 88.6% of the patients with pAG-DCPN and 93.3% of the patients with pG-DCPN had the second NP. Moreover, this study found that the three NPs did not coexist. The presence of the first NP mainly depends on the presence or absence of PSN in patients with pH-DCPN, and the third NP is difficult to find due to the relatively complex positioning required, which can make patient cooperation difficult, whereas the second NP is relatively stable.

The angle of the second NP has varied markedly between different studies, with the angle relative to the sagittal plane reportedly ranging from 15° to 45°. Ichijo[8] found significant differences between patients with pAG-DCPN (5−89°) and pG-DCPN (5−85°) in the angle of the NP. In contrast, the present study found no significant differences in the angles of the second and third NPs between patients with pAG-DCPN (26.8±7.6° and 27.5±8.3°, respectively) and patients with pG-DCPN (24.4±6.5° and 25.4±7.3°, respectively). This may be due to anatomical and physiological differences between individuals, and differences in the degree of deformation of the cupula caused by the adhesion of otolith particles.

The BLT was proposed by Choung et al.[18] and is used to determine the affected ear in HC-BPPV. Previous studies found that the rate of positive responses on the BLT ranged from 60% to 80%, with BN and LN not being present simultaneously in any patients. BN and LN usually appear in the opposite directions, but they can also appear in the same direction in some patients.[7,18,19,42-44] Kim et al.[44] showed that the rate of positive BLT findings was as high as 100% in patients with light and heavy cupulae. However, we observed BN in 70.5% of the patients with pAG-DCPN, with most of those patients showing nystagmus with the fast phase directed toward the unaffected side, and LN in 75.0% of the patients with pAG-DCPN, with most of those patients showing nystagmus with the fast phase directed toward the affected side. Most (83.3%) of the patients with pG-DCPN showed BN with the fast phase directed toward the affected side, and 83.3% of the patients with pG-DCPN showed LN, with most of these patients showing nystagmus with the fast phase directed toward the unaffected side. The difference between the results of our study and those of Kim et al.[44] may be due to individual differences in the angle between the cupula and the sagittal plane, as well as differences in the size of the otolith particles, the displacement of the cupula, and the specific gravity of the endolymph. The BLT can assist in identifying the affected side, but it should be used in combination with the SRT, the second NP, and even evaluations of vestibular and audiology function to further determine the affected side.

Examinations of vestibular and auditory function in patients with pH-DCPN

In our study, 27.0% of the patients with pH-DCPN showed abnormal CP, 17.6% had vHIT abnormalities, 16.2% had unilateral cVEMP abnormalities, and 19.4% had hearing loss. The sides of abnormal CP, abnormal cVEMP, and hearing loss were consistent with the affected side of pH-DCPN in most of the patients. Tomanovic and Bergenius[38] investigated vestibular function using bithermal caloric tests, VEMPs, and subjective visual horizontal assessments in 20 patients with a light cupula. Those authors found that approximately 60% of the patients had vestibular dysfunction, and considered that pG-DCPN was a sign of inner ear dysfunction. Ichijo[45] performed bithermal caloric tests in 21 patients with a light cupula, and found that 21% of these patients had unilateral vestibular dysfunction. It is speculated that the mechanism of pH-DCPN reduces blood flow and induces inflammation in the inner ear, which can affect the density or viscosity of the endolymph in the inner ear and vestibular organ, thereby causing acute or chronic dysfunction of both organs. Wada et al.[46] found a high incidence of abnormal CP on the affected

side in patients with BPPV (p<0.01), that the recovery time in BPPV patients with an abnormal CP was long after performing the CRM, and that hearing loss was more common on the affected side of BPPV (p<0.01). Bi et al.[47] found that the prevalence of CP in BPPV patients was 57%, and that the recurrence rate in BPPV patients was significantly higher in those with abnormal CP than in those with normal CP. Vestibular and auditory examinations can be useful for determining the affected side of pH-DCPN, especially in patients with pAG-DCPN, since accurately identifying the affected side is essential for successfully treating this disease.

Treatment options, follow-up, and prognosis in patients with pH-DCPN

Currently there are no effective treatment options available for pG-DCPN, with a previous study[20] that used the barbecue maneuver to treat pG-DCPN not finding obvious effects. The barbecue maneuver,[45,48] the Gufoni maneuver,[18] and a combination of a mastoid-oscillation/head-shaking maneuver and the barbecue maneuver[49] have been reported to be effective in treating pAG-DCPN. The present study did not compare the efficacy of the CRM in the treatment of DCPN, and so we selected a common maneuver and conducted the same CRM (the barbecue maneuver) in both types of DCPN.

All of the patients included in this study were treated using the barbecue maneuver. Immediately after treatment, this maneuver was effective in 59.1% of the patients with pAG-DCPN but only 6.7% of the patients with pG-DCPN. At the 1-month follow-up, positional nystagmus disappeared in 86.3% of the patients with pAG-DCPN, and the remaining 13.7% of them showed weak nystagmus and did not complain of vertigo symptoms. The positional nystagmus disappeared in all patients with pG-DCPN. Our results are similar to those of previous studies. Kim and Hong[50] investigated 65 patients with pG-DCPN, and treated 35 of them with the CRM. Those authors found that the CRM was not effective in patients with pG-DCPN, which further suggests that the pathological mechanism responsible for pG-DCPN is not related to the attachment of light otoconial debris. Ichijo[8] found that 33 patients with a light cupula had a good prognosis, with dizziness and nystagmus disappearing within 2 weeks, and some patients recovering within 2 months. However, that author also did not report whether the patients were treated with the CRM or medication. Zhang et al.[51] used the barbecue maneuver to treat 18 patients with a light cupula, and at 1 week after treatment they found that no patients were cured, and that the symptoms improved in only 18.8% of the patients. None of the patients received further treatment, and at the 1-month follow-up 75% of the patients were cured and the symptoms were improved in 12.5% of the patients.

Based on all of the findings of the previous studies as described above, we consider that the CRM is not effective in most patients with a light cupula, and that light cupulae have a tendency for self-healing. However, we found that the barbecue maneuver was still effective in two patients immediately after treatment and in two patients at the 1-week follow-up; these patients had a history of recurrent BPPV, and so it is speculated that pG-DCPN can be caused by a light cupula. Previous studies[11,12,15] have found that when light debris such as decalcified and light otoconia particles adhere to the ampulla, the cupula is deflected by a buoyancy force and the light-cupula phenomenon occurs. This phenomenon can be used to explain the good prognosis in most patients with a light cupula. Therefore, whether a light cupula is a special type of HC-BPPV or only a pathological sign requires further investigation.

In conclusion, pAG-DCPN appears to be more compatible with the characteristics of cupulolithiasis, while pG-DCPN is more likely to be associated with a light cupula rather than canalolithiasis. pAG-DCPN is more likely to be accompanied by a disease associated with atherosclerosis, while pG-DCPN is often accompanied by autoimmune-related diseases and a history of migraine; however, these relationships need to be clarified further. The combination of the SRT, BLT, and NP (especially the second NP) contributes to the determination of the affected side of pH-DCPN. The CRM was effective in patients with pAG-DCPN and ineffective in patients with pG-DCPN, but most cases of pG-DCPN were self-limiting.

Study limitations

The retrospective design of this study might have resulted in selection bias, and the smallness of the sample may have restricted the ability to identify significant effects. Further prospective studies with larger samples are needed to confirm the present results.

Supplementary Materials

The online-only Data Supplement is available with this article at https://doi.org/10.3988/jcn.2021.17.3.443.

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Conflicts of Interest

The authors have no potential conflicts of interest to disclose.

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