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The effective clinical outcomes of the Gufoni maneuver used to treat 91 vertigo patients with apogeotropic direction-changing positional nystagmus (apo-DCPN)

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Abstract

This study aimed to observe and analyze the effects and outcomes of patients with apogeotropic direction-changing positional nystagmus (apo-DCPN) who received Gufoni maneuver.

A total of 91 patients with positional vertigo admitted to the specialized dizziness clinic in Zhejiang Provincial People's Hospital from February 2014 to August 2017 were included. The immediate treatment responses to the Gufoni maneuver were observed and recorded. The patients in whom the treatment was ineffective were followed up for 4 weeks to observe the outcome of apo-DCPN.

In 21 patients, the apo-DCPN was transformed after Gufoni maneuver, and 7 patients developed transformation within 4 weeks of follow-up. Spontaneous remission of apo-DCPN within the follow-up period was observed in 55 patients who were unresponsive to the Gufoni maneuver. The prevalence of migraine was significantly higher in the early remission group ($P < .05$) and the period between the initial visit and nystagmus remission was significantly shorter in the group of patients with migraine history ($P < .05$).

This study demonstrates that the immediate treatment efficacy of the Gufoni maneuver is poor in positional vertigo patients with apo-DCPN. We believe that the reason for the low efficacy is that the Gufoni maneuver is only effective for some patients with apo-DCPN type HSC-BPPV. In patients with early spontaneous remission and a history of migraine, central positional nystagmus of probable vestibular migraine (VM) or benign recurrent vertigo should be considered for the mechanisms of apo-DCPN generation.

Abbreviations: apo-DCPN = apogeotropic direction-changing positional nystagmus, BPPV = benign paroxysmal positional vertigo, CRP = canalith repositioning procedure, Cup-C = canal-sided of the cupula, Cup-U = utricular-sided of cupula, HSC Cup = horizontal semicircular canal cupulolithiasis, HSC-BPPV = horizontal semicircular canal benign paroxysmal positional vertigo, MV = migrainous vertigo, SPV = slow-phase velocity, SRT = supine roll test, VM = vestibular migraine.

Keywords: apogeotropic direction-changing positional nystagmus (apo-DCPN), Gufoni maneuver, migraine, pathophysiology, positional vertigo

1. Introduction

Apogeotropic direction-changing positional nystagmus (Apo-DCPN) was first described by Baloh et al[1] in 1995 as an upbeat horizontal nystagmus provoked by lying on the left or right side. Currently, the pathophysiological mechanisms of apo-DCPN are controversial. Horizontal semicircular canal cupulolithiasis (HSC Cup) is considered to be the most common peripheral cause of apo-DCPN. Central structural lesions manifested as apo-DCPN, such as nodular infaction or tissue masses, can be confirmed by imaging.[2,3] However, patients with central functional disorders such as VM combined with apo-DCPN are difficult to identify with HSC-BPPV by bedside assessment.[4,5] Compared with other types of benign paroxysmal positional vertigo (BPPV), the immediate treatment efficacy of the canalith repositioning procedure (CRP) is poorer in apo-DCPN.[6–8] The variation of pathophysiological mechanisms may be important factors that influence the curative effects and outcome of apo-DCPN treatment.[6,8]

In this study, the curative effects of CRP in 91 patients with positional vertigo manifested as apo-DCPN were evaluated. The prognosis and clinical outcomes of patients in this group were observed and analyzed. The pathophysiological mechanisms that contributed to the differences in curative effects and outcomes were also explored.

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The author(s) of this work have nothing to disclose and declare that they have no conflict of interest.

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2. Subjects and methods

2.1. Subjects

A total of 91 positional vertigo patients with apo-DCPN admitted to the specialized dizziness clinic in Zhejiang Provincial People's Hospital from February 2014 to August 2017 were enrolled. All patients signed informed consent before inclusion and this study was approved by the ethics committee of Zhejiang Provincial People's Hospital. The inclusion criteria were as follows: the chief complaint of positional vertigo according to the International Classification of Vestibular Disorders (Bárány Society, 2009)[9]; and observation of an apo-DCPN provoked by the supine roll test (SRT) performed according to the guidelines provided by the American Academy of Otolaryngology-Head and Neck Surgery.[7] The exclusion criteria were as follows: patients who had a possible cause of secondary BPPV, such as Ménière disease, or recent trauma; with one or more migraine features of VM[2]; asymptomatic apo-DCPN provoked by the SRT; comorbidity of other BPPV subtypes (mixed BPPV [7]) confirmed by the Dix–Hallpike test; the presence of identifiable central nervous system disorders that could explain the positional vertigo and nystagmus in neurologic examinations, including direction-changing gaze-evoked nystagmus, smooth pursuit, saccades abnormalities, and limb ataxia; a lesion responsible for positional nystagmus identified in a cranial magnetic resonance imaging (MRI) scan; and patients who had received any form of CRP before enrollment.

2.2. Procedures

The affected side was determined on the basis of weaker intensity of the nystagmus provoked by SRT when the head is rotated. If the intensity of nystagmus was symmetrical, the affected side was determined on the basis of the direction of "lying-down" nystagmus being predominantly toward the affected ear.[7] The procedures used in SRT are shown in Fig. 1.

All patients underwent the Gufoni maneuver [6,10] after determination of the affected side. The Gufoni maneuver was performed by a senior neurologist with a 10 years of experience within a specialized dizziness clinic. The procedures used in the Gufoni maneuver are shown in Fig. 2.

After each maneuver, patients were instructed to maintain an upright position without bending the head down until the evaluation to determine the immediate efficacy of the maneuver. The treatment response was determined 30 minutes after the initial maneuver. Successful treatment was defined as an absence of the positional nystagmus or a conversion to other forms of positional nystagmus (BPPV-type transformation). Patients were re-examined 30 minutes later and the Gufoni maneuver was repeated if apo-DCPN was still present. A Gufoni or an Epley maneuver was performed for the patients who exhibited transformation in geotropic forms or posterior canal BPPVs. If patients failed to respond successfully following the second administration of the Gufoni maneuver, they were advised to revisit the specialized dizziness clinic within 3 days of the initial maneuver and the outcome of apo-DCPN was observed and recorded. The follow-up was conducted at least once a week for 4 weeks.

The following clinical data were recorded: sex, age, history of previous positional vertigo, history of migraine or VM (according to the diagnostic criteria for migraine and VM in the International Classification of Headache Disorders, 3rd edition [2]), history of hypertension and diabetes, duration of period from symptom onset to initial visit, "affected side," apo-DCPN outcome (nystagmus transformation, direct remission, ineffective), and duration of period from initial visit to apo-DCPN transformation or remission. We grouped the patients who did not undergo nystagmus transformation before remission of apo-DCPN according to the duration of the nystagmus remission. "Early remission" was defined as a duration of the period from the initial visit to nystagmus remission not exceeding 3 days and "Late remission" was defined as a duration of the period from initial visit to nystagmus remission exceeding 3 days.

2.3. Statistical analysis

Statistical analysis was performed using SPSS Statistics 19.0 (SPSS/PC, Chicago, IL). Normality of the data distribution was evaluated using the Kolmogorov–Smirnov test. Variables with a normal distribution were compared using the Student t test, and values were presented as means ± standard deviation. For variables with an abnormal distribution, the Mann–Whitney U test was used for comparisons, and values were presented as medians (interquartile range). Categorical variables were presented as frequencies and were analyzed using the Chi-squared or Fisher exact test, as appropriate. The Kaplan–Meier method was applied to calculate the residual rate of apo-DCPN during the follow-up. Log-rank tests were used to analyze differences in the duration of the period from diagnosis to apo-DCPN remission between different groups. Two-sided P values $< .05$ were considered to indicate statistical significance.

3. Results

A total of 91 patients were continuously enrolled in this study, including 57 females and a female-male ratio of 1.68:1. The mean

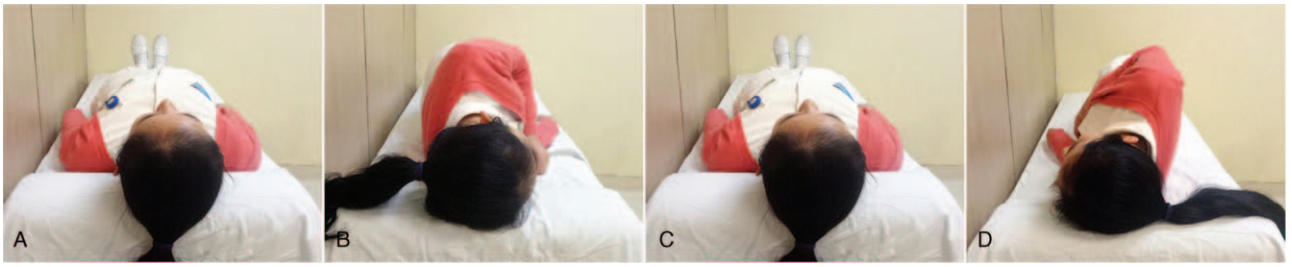

Figure 1. The procedures used in supine roll test. (A) The patient in the starting neutral position. The patient's head is turned rapidly to the right side (B) to examine for characteristic nystagmus. The head is then returned to the upward position (C), allowing the nystagmus to subside, and then turned rapidly to the left side (D) to repeat the examination for characteristic nystagmus.

Figure 2. The procedures used in the Gufoni maneuver. (A, B) The patient is taken from the sitting position to the lateral recumbent position on the affected side for approximately 30 s. (C) Then, the patient's head is quickly turned 45° upward and held in position for 1–2 min. (D) The patient is slowly returned to the sitting position.

age of the included patients was (58.73 ± 14.12) years (range 24–90 years), with no significant difference in age between the male and female patients (60.44 ± 13.55 vs 55.85 ± 14.78, t=-1.509, P=.375). Among the included patients, 53 had a history of previous positional vertigo; 15 had a confirmed history of migraine and no patients met the diagnostic criteria for VM; 28 had a history of hypertension, and 10 had a history of diabetes. The median duration from disease onset to the initial visit was 1 day (range 1–30 days). Among the cases, 42 were left-ear affected and 49 were right-ear affected. In 73 cases (80.22%), the affected side was determined as that with the weaker nystagmus by observing the difference in the intensity in the SRT. Symmetric SRT-induced nystagmus intensity was observed in 18 patients and the affected side was determined according to the direction of lying-down nystagmus. The clinical features of patients are summarized in Table 1.

With the exception of 8 patients lost to follow-up, all 83 patients experienced apo-DCPN remission during the 4-week follow-up period. Of these patients, the Gufoni maneuver was successful in 21 cases. After 1 week of follow-up, the apo-DCPN remission occurred in 72.73% of the patients, of whom 57.81% experience spontaneous remission. After the second and third weeks of follow-up, apo-DCPN remission occurred in 91.86% and 97.62% of the patients, respectively. Spontaneous remission of apo-DCPN was confirmed in the remaining patient at the fourth week of follow-up. The outcome of the apo-DCPN and the number of lost follow-up cases are summarized in Table 2.

A total of 28 patients underwent nystagmus transformation during the 4-week follow-up period, of which 21 cases were immediately converted to geo-DCPN by the Gufoni maneuver. The nystagmus in other 7 cases was spontaneously converted during the follow-up period (6 cases were converted to geo-DCPN, 1 case was converted to PSC-BPPV). Fifty-five cases of apo-DCPN were spontaneously remitted without conversion.

Table 1

Clinical and demographic characteristics.

Characteristics	AH-BPPV (n = 91)
Age, y	
Range	24–90
Mean ± SD	58.73 ± 14.12
Sex (n)	
Male	34
Female	57
Positional vertigo* (n)	53
Migraine (n)	13
Hypertension (n)	35
Diabetes mellitus (n)	10
Onset†, d	
M (P25, P75)	1 (1, 4)
Symmetric nystagmus‡ (n)	17
Lying-down nystagmus (n)	28
Affected side (n)	
Right	49
Left	42

* Positional vertigo: a history of previous positional vertigo.
† Onset: duration of the period from symptom onset until the first clinic visit.
‡ Symmetric nystagmus: similar intensity of nystagmus on both sides in the supine roll test.

Table 2

Remission of apo-DCPN after Gufoni maneuver and spontaneous remission.

Follow-up	Nystagmus transition (n = 28)	Spontaneous nystagmus remission (n = 55)	Lost to follow-up (n = 8)	Remission rate (n, %)
1st day	21	0	0	21 (23.07)
1st week	6	37	3	64 (72.73)
2nd week	0	15	2	79 (91.86)
3rd week	1	2	2	82 (97.62)
4th week	0	1	1	83 (100)

Table 3

Comparison of clinical characteristics between groups (n, %).

Characteristics	Transformable apo-DCPN (n = 28)	Nontransformable apo-DCPN (n = 55)	*P*	Total (n = 83)
Age, y Mean ± SD	60.11 ± 12.73	57.11 ± 15.06	.439	58.73 ± 14.12
Male	13 (46.43%)	18 (32.73%)	.222	31 (37.35%)
Migraine	3 (10.71%)	11 (20.00%)	.259	14 (16.87%)
Positional vertigo*	16 (57.14%)	35 (63.64%)	.566	51 (61.45%)
Hypertension	10 (35.71%)	15 (27.27%)	.428	25 (30.12%)
Diabetes mellitus	3 (10.71%)	4 (7.27%)	.594	7 (8.43%)
Onset† (<7 d)	24 (85.71%)	50 (90.91%)	.472	74 (89.16%)
Symmetric nystagmus‡	4 (14.27%)	13 (23.64%)	.672	17 (20.48%)
Lying-down nystagmus	7 (8.43%)	21 (38.18%)	.583	28 (33.73%)
Affected left side	12 (42.86%)	30 (54.54%)	.591	42 (50.60%)

* Positional vertigo: a history of previous positional vertigo.

† Onset: duration of the period from symptom onset until the first clinic visit.

‡ Symmetric nystagmus: similar intensity of nystagmus on both sides in the supine roll test.

There were no significant differences in the clinical characteristics of the patients in the transformable apo-DCPN group and those in the nontransformable apo-DCPN group (Table 3).

Fifty-five patients did not undergo nystagmus transformation before remission of apo-DCPN. Although there were no significant differences between the groups in terms of age, sex, duration of the period from symptom onset to the initial visit, prior history of positional vertigo attacks, affected side, and features of positional nystagmus, the occurrence of migraine was higher in the "early remission" group than that in the "late remission" group ($P = .015$) (Table 4).

We analyzed the related factors that may affect the duration of the period from the initial visit to apo-DCPN remission in 63 patients who were unresponsive to the Gufoni maneuver (55 patients with apo-DCPN who experienced remission without canal conversion and 8 patients lost to follow-up). The patients were grouped according to "the duration of the period from onset to treatment" (groups: ≤2 days and >2 days groups), "symmetry apo-DCPN" (groups: symmetric and asymmetric apo-DCPN induced by SRT) and "migraine" (groups: patients with and without a history of migraine). The Kaplan–Meier curve with a log-rank test showed that there were no significant differences in the duration from the period of the initial visit to apo-DCPN remission between the "duration of the period from the onset to treatment" and the "symmetric apo-DCPN" groups ($P > .05$). However, the duration of the period from the initial visit to apo-DCPN remission was significantly shorter in the group of patients with a history of migraine than that in the group of patients without a history of migraine ($P = .031$) (Figs. 3–5).

4. Discussion

There is no current consensus on the pathophysiological mechanisms underlying the generation of apo-DCPN, which is

Table 4

Comparison of clinical and demographic characteristics between groups (N, %).

	Early remission group (n = 27)	Late remission group (n = 28)	*P*	Total (n = 55)
Age (mean ± SD), y	55.19 ± 13.74	58.96 ± 16.26	.380	57.11 ± 15.06
Male	12 (44.44%)	6 (21.43%)	.069	18 (32.73%)
Migraine	9 (33.33%)	2 (7.14%)	.015	11 (20.00%)
Positional vertigo*	14 (51.85%)	17 (60.71%)	.508	31 (56.36%)
Hypertension	7 (25.93%)	9 (32.14%)	.612	16 (29.09%)
Diabetes mellitus	2 (7.40%)	1 (3.60%)	.531	3 (5.45%)
Onset† (<7 d)	23 (85.19%)	26 (92.86%)	.362	49 (89.09%)
Symmetric nystagmus‡	7 (25.93%)	5 (17.86%)	.469	12 (21.82%)
Lying-down nystagmus	8 (29.63%)	12 (42.86%)	.308	20 (36.36%)
Affected left side	12 (44.44%)	15 (53.57%)	.498	27 (49.09%)

* Positional vertigo: a history of previous positional vertigo.

† Onset: duration of the period from symptom onset until the first clinic visit.

‡ Symmetric nystagmus: similar intensity of nystagmus on both sides in the supine roll test.

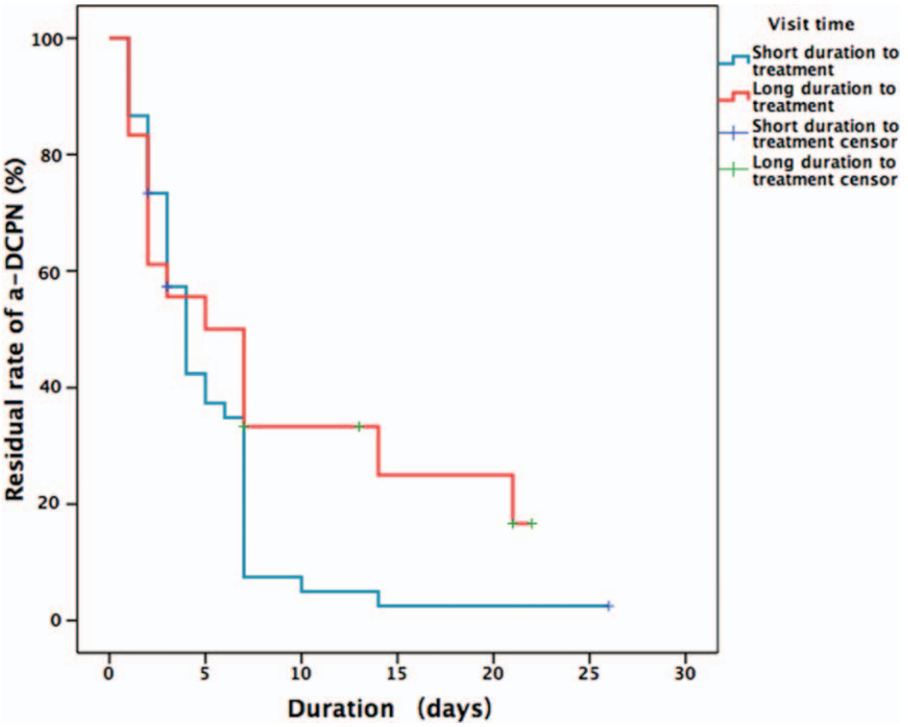

Figure 3. Comparison between the groups of patients with a short (≤2 days) and long duration (>2 days) of the period from the initial visit to the remission of apo-DCPN without canal conversion. The Kaplan–Meier curve with a log-rank test shows no difference between the 2 groups ($P = .284$).

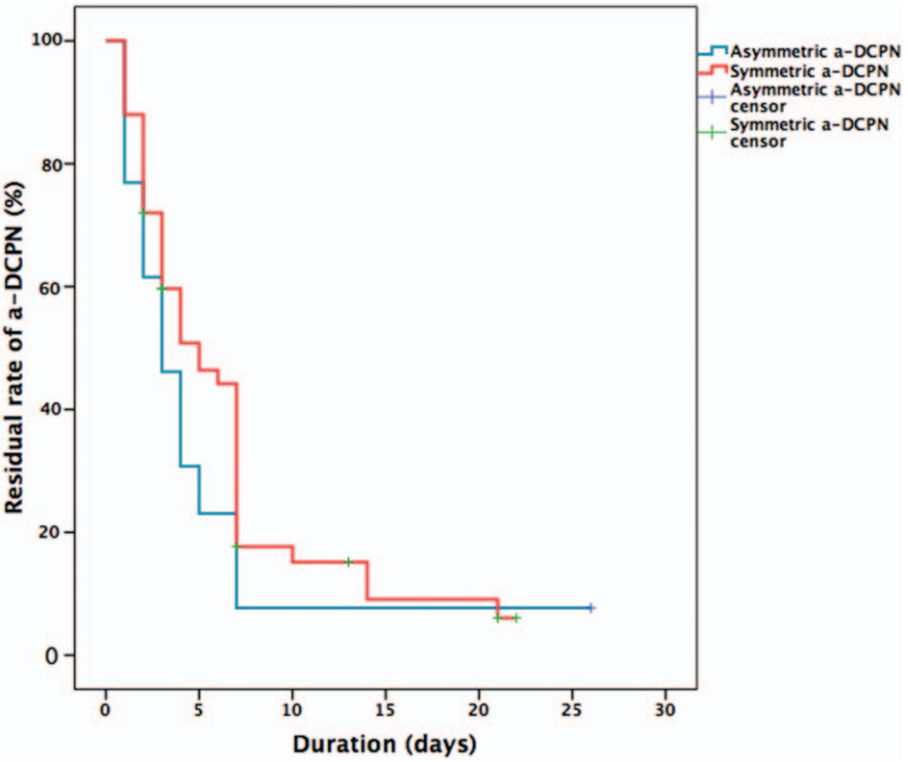

Figure 4. Comparison of the duration of the period from the initial visit to the remission of apo-DCPN without canal conversion between the groups of patients with asymmetric and symmetric apo-DCPN. Kaplan–Meier curve with a log-rank test shows no difference between the 2 groups ($P = .096$).

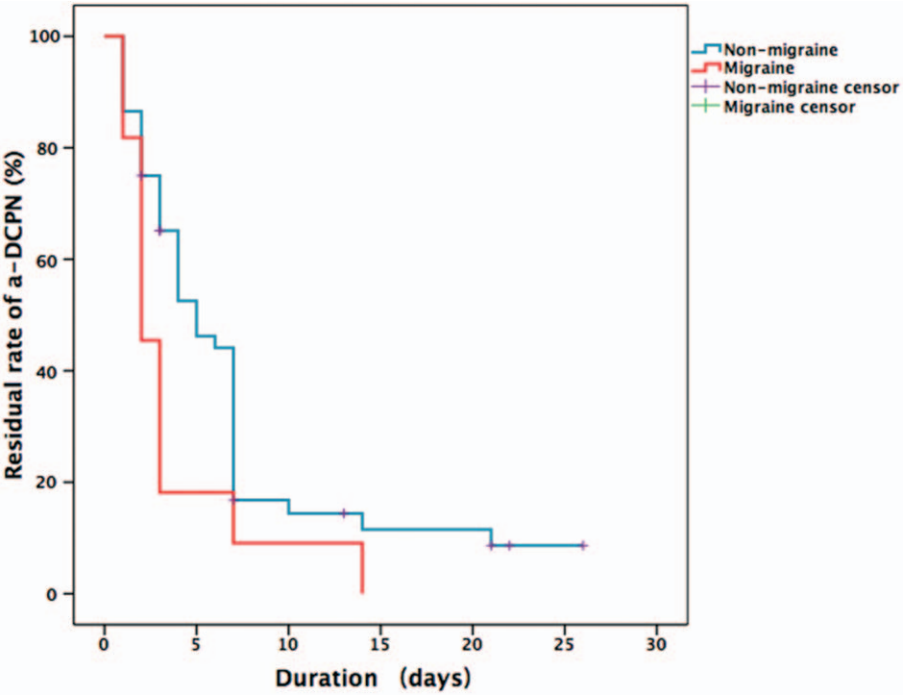

Figure 5. Comparison of the duration of the period from the initial visit to the remission of apo-DCPN without canal conversion between the groups of patients with and without a history of migraine. The Kaplan–Meier curve with a log-rank test shows a significant difference in the duration of the period from the initial visit to the remission of apo-DCPN between the 2 groups ($P = .031$).

thought to originate from central or peripheral lesions. HSC-BPPV is considered to be the most common peripheral cause of apo-DCPN. A theory for apo-DCPN of HSC-BPPV proposes that otoconial debris attached to the cupula or free otoliths located in the anterior part of the HSC cause abnormal stimulation of the vestibular apparatus.[1,7,11]

Disappearance of positional nystagmus after CRPs is as a sign of successful treatment. According to the existing studies, "immediate successful treatment" of the apogeotropic variant of horizontal canal semicircular BPPV is generally defined by the following 2 results: First, Apo-DCPN immediately converted to geo-DCPN after the CRP, with a possible mechanism that might be attributed to the displacement of free otoliths located in the anterior part of the HSC, or the detachment of otoliths adhering to HSC Cup-C into the posterior of HSC; however, these mechanisms are difficult to distinguish clinically. Second, immediate remission of the apo-DCPN after the CRP via a mechanism that is attributed to the detachment of otoliths adhering to the utricular-sided of cupula (Cup-U) into the utricle. The Gufoni maneuver is one of the available CRPs for apo-DCPN type HSC-BPPV. Two large-sample, multicenter randomized controlled trial (RCT) studies have demonstrated that the Gufoni maneuver showed better responses than the sham maneuver, and reports of the success rate of the CRP in the literature range from 17.3% to 73.1%. Differences in the number of repetitions of the maneuver and the duration of the period after treatment before efficacy assessment used by different investigators lead to differences in the proportion of the 2 outcomes classified as "immediate successful treatment."

Kim et al[12] evaluated the immediate response of 137 cases of the apogeotropic variant of HSC-BPPV that were randomly treated with the Gufoni maneuver and mastoid vibration. Among these patients, the success rate of the Gufoni maneuver is 47.1% (33/70), and 30% (21/70) of the apo-DCPN patients immediately converted to geo-DCPN after treatment, while immediate remission was observed in 17.1% (12/70) of the apo-DCPN patients. In this study, a total of 21 patients underwent nystagmus transformation immediately after Gufoni maneuver treatment, with an immediate transformation rate of 23.1%, while immediate resolution of nystagmus was not observed after treatment in any of the patients.

To further analyze the mechanisms for the failure of Gufoni maneuver, we performed a 4-week natural course follow-up of 70 patients who showed no response to the CRPs. A total of 7 patients underwent spontaneous nystagmus transformation during follow-up, of which 6 cases transformed to geo-DCPN in the first week and 1 case transformed to posterior semicircular canal BPPV. The incidence of spontaneous nystagmus conversion and the time of transition after treatment failure is similar to the literature.[12] We hypothesize that the pathophysiology for failure of the CRPs in these patients should be considered, as the debris attached on the Cup-C is more difficult to be detached by the Gufoni maneuver.

However, spontaneous remission of apo-DCPN was a more common outcome with rates of 64.3% and 74.6% reported in 2 separate studies.[13,14] Among the 63 patients without apo-DCPN transition in this study, all (55 patients) except 8 patients who missed a visit, had spontaneous remission of apo-DCPN within 4 weeks, and the proportion of patients with spontaneous nystagmus remission was 66.3%.

It should be noted that the spontaneous remission in most patients is short-lived. The results of this study showed that the period from initial visit to apo-DCPN remission did not exceed 7 days in 92.7% (51/55) of patients who had failed physiotherapy,

with the period not exceeding 3 days in 49.1% (27/55) in these patients. Shim et al[13] reported that the average course of spontaneous remission of apo-DCPN was only 4.4 ± 5.0 days. Imai et al[14] reported that average course and median duration of the spontaneous remission from the symptoms of apogeotropic variant of BPPV were 13 and 7 days, respectively, while the average course of the spontaneous remission from the symptoms of posterior semicircular canal and geotropic variant of BPPV were 39 and 16 days, respectively. Some investigators speculated that short natural course of the disorder and the low conversion rate support the higher incidence of Cup-U in the apogeotropic variant of HSC-BPPV.[12,15] On the basis of this theory, it is suggested that the otoliths adhering to the Cup-U may be induced to detach into the utricle by the head movements of daily life (e.g., walking, lateral lying) without the requirement for specific therapeutic maneuvers. However, the results of previous RCT studies all confirmed that most apo-DCPN did not remit directly with adequate physiotherapy.[6,8,12,15] The contradiction between the high early spontaneous remission rate and low efficacy of repositioning maneuvers suggested that the Cup-U theory does not perfectly explain the mechanism of apo-DCPN.

It has been hypothesized that the spontaneous dissolution of otoconia and a change in the density of the cupula-endolymph system could explain the spontaneous remission in some BPPV patients, especially in those patients with a long period from the onset to natural remission.[16–18] Zucca et al [16] reported that the spontaneous dissolution of otoconia usually took 2 to 6 weeks, while the positional nystagmus caused by "light cupula" could last longer than 6 months.[17] Therefore, the theory of spontaneous dissolution of otoconia or "heavy cupula" still does not explain the early spontaneous remission of apo-DCPN in some patients.

In a review of the inclusion criteria in several previous studies assessing the efficacy of the Gufoni maneuver and the natural course of apo-DCPN, we found that the use of imaging examinations as a major method to exclude central structural lesions does not allow exclusion of positional vertigo and nystagmus caused by central functional disorders for which normal structural images are generated. VM or migrainous vertigo (MV) are the most common central episodic vestibular syndrome. It has been reported in the literature that between 17% and 46% of MV patients had positional vertigo and central oculomotor disturbances, with 28% to 40% of the central oculomotor disturbances as positional nystagmus.[19–22] Using electronystagmography, Lechner et al[4] found striking similarities in the profiles of nystagmus slow-phase velocity (SPV) between VM and HSC cupulolithiasis. Therefore, it was difficult to distinguish VM and HSC cupulolithiasis only by using the naked eye to evaluate the features of apo-DCPN. It was necessary to combine details of the age of onset, duration of symptoms, recurrence frequency, and typical migraine attacks to distinguish from BPPV.[5,23] In our study, enrollment criteria excluded migraine features during the episode, and no patients met the diagnosis criteria of vestibular migraine. However, the results of this study suggested that migraine may be the factor that influenced the duration of spontaneous remission of apo-DCPN. In this study, the nystagmus in 27 patients who were unresponsive to physiotherapy remitted spontaneously within a period of no more than 72 hours. The duration of VM usually did not exceed 72 hours. Therefore, we speculated that these patients with apo-DCPN were suspected of VM who cannot meet the diagnosis criteria of VM due to less than 5 episodes or lack of migraine features during vestibular episodes.

Some limitations of this study should be noted. The end-point of evaluation of the curative effects was set as the remission (or transformation) of apo-DCPN; however, we found that mild residual positional nystagmus was still present in some patients with remission of vertigo symptoms, leading some researchers to postulate that central oculomotor disturbances should be considered in asymptomatic positional nystagmus.[24] Therefore, it was debatable whether the setting of end point would increase the value for evaluating the duration of vertigo symptom remission. Furthermore, this study was conducted in a single-center study with relatively few selected cases, no control group, and a short follow-up period. Further studies with larger sample sizes and a longer period of follow-up are required to confirm the results of this study.

The pathophysiological mechanisms of apo-DCPN have not yet been fully clarified. Although HSC-BPPV is considered to be the most common peripheral cause of apo-DCPN, it was difficult to distinguish this clinically from apo-DCPN, which is caused by central functional disorders manifested as positional vertigo and nystagmus. The results of this study suggest that the immediate success rate of the Gufoni maneuver for apo-DCPN is related to the differences in the underlying pathogenesis. For patients with immediate nystagmus transformation after receiving the Gufoni maneuver, the possibility of canalolithiasis in the anterior part of the HSC or Cup-C should be considered in the pathogenesis of apo-DCPN. However, in patients who are unresponsive to treatment and with a short duration of apo-DCPN remission and a history of migraine, central positional nystagmus of probable vestibular migraine or benign recurrent vertigo should be considered. In the future, further study will focus on how to identify peripheral and central functional disorders with apo-DCPN.

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Writing – original draft: Tianming Shi.
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