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PATHOLOGY OF BENIGN PAROXYSMAL POSITIONAL VERTIGO REVISITED

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The pathophysiology of benign paroxysmal positional vertigo (BPPV) is not completely understood. Although the concept of degenerated otoconia transforming the posterior canal (PC) crista into a gravity-sensitive sense organ has gained popular support, several temporal bone (TB) series have revealed similar deposits in normal TBs, suggesting they are a normal change in the aging labyrinth. Furthermore, some TBs from patients with BPPV do not contain particles in the posterior canal. Five TBs from patients with BPPV were studied quantitatively and qualitatively. A small PC cupular deposit was found in 1 TB, while none was seen in the other 4 TBs. The major pathological changes were 1) a 50% loss of ganglion cells in the superior vestibular division of all 5 TBs and 2) a 50% loss of neurons in the inferior division of 3 TBs, and a 30% loss in 2 TBs that contained abnormal saccular ganglion cells. These observations support a concept in the pathophysiology of BPPV that includes loss of the inhibitory effect of otolith organs on canal sense organs.

KEY WORDS — otolith function, positional vertigo, vestibular neuronitis.

INTRODUCTION

Since its original description,[1,2] the recurrent vestibulopathy of benign paroxysmal positional vertigo (BPPV) has represented a balance disorder unlike all others. It consists of a brief episode of vertigo that follows the assumption of a hyperextended head position wherein one ear faces toward the ground (geotropic) and the other faces away from the ground (ageotropic). Since a tilted head position is provocative, it was first assumed to be an otolith disorder.[1,2] Dix and Hallpike[2] supported this interpretation with histopathologic evidence of utricular end organ degeneration in the temporal bone (TB) from a patient with BPPV. Citron and Hallpike[3] devised a special tilt platform that permitted the gradual positioning of the patient's body from an upright to a Trendelenberg position with the head turned to one side. This change of position provoked the rotatory nystagmus response seen in BPPV.

Largely because of experimental demonstrations[4,5] that a nystagmus response is elicited by semicircular canal receptor activation and not by otolith stimulation, the otolith concept for BPPV was not generally embraced. In addition, Lindsay and Hemenway[6] presented the TB of a patient who experienced BPPV after recovering from an acute vestibular neuronitis. The superior vestibular ganglion (SVG) was completely degenerated in this TB, leaving intact the inferior vestibular ganglion (IVG) and sense organs. This observation focused interest on the posterior semicircular canal as the responsible sense organ. Subsequent experimental observations[4,5,7] confirmed that the posterior canal sense organ activates the contralateral inferior rectus and ipsilateral superior oblique extraocular muscles. This vestibulo-ocular response to the positional stimulus supported the premise that the posterior semicircular canal is activated in the provocative test position.

When Schuknecht and Ruby[8] demonstrated basophilic deposits in the cupula of the downmost posterior canal crista of TBs from patients who experienced BPPV, these deposits were presumed to represent degenerated otoconia (specific gravity, 2.7) probably derived from the utricular macula. It was hypothesized that these cupular deposits converted the sense organ into a gravity receptor that was activated by the Hallpike maneuver. The complete relief of vertigo and nystagmus following selective denervation of the posterior canal sense organ of the downmost labyrinth[9,10] supported the concept that it was the sense organ responsible for BPPV. Parnes and McClure[11] added the observation that free-floating particles could be seen in the limb of the posterior canal in patients undergoing occlusion of this canal for BPPV. This modification of the mechanical view of pathophysiology in BPPV was felt to account for the intermittent form of the syndrome. The fixed and free-floating types of deposits in the posterior semicircular canal were referred to by the terms cupulolithiasis and canalolithiasis.

Based on these clinical and histopathologic observations, a series of head maneuvers[12-14] were devel-

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TABLE 1. VESTIBULAR GANGLION CELL ESTIMATES IN TEMPORAL BONES FROM PATIENTS WITH BPPV

Case No.	*Age (y)*	*Sex*	*Cell Count*	*Vestibular Ganglion*	
				Superior	*Inferior*
1	48	F	1	6,688	4,074
			2	6,380	3,810
			3	6,732	4,136
			Average	6,600	4,007
2	65	M	1	5,658	5,650
			2	5,711	6,089
			3	5,843	5,904
			Average	5,797	5,881
3	75	F	1	6,248	4,602
			2	5,896	5,095
			3	5,720	4,532
			Average	5,955	4,743
4	80	F	1	4,620	3,766
			2	4,787	3,731
			3	4,594	4,145
			Average	4,667	3,880
5	91	F	1	4,734	3,872
			2	4,488	2,798
			3	4,505	2,798
			Average	4,576	3,156

BPPV — benign paroxysmal positional vertigo.

oped to reposition free-floating deposits from the posterior canal ampulla and/or membranous canal through the common crus and into the utricle, in which they could no longer activate the canal receptor. Although the short-term relief of BPPV by such particle repositioning maneuvers (PRMs) was promising,[12-15] subsequent reports with longer (>6 months) follow-up,[16] and compared to no treatment,[17] revealed equivalent rates of positional vertigo relief.

The concept of a mechanical alteration in labyrinthine physiology as being responsible for BPPV does not account for several features. These are 1) the latency, limited duration, and fatigability of the rotatory nystagmus despite sustained provocation; 2) the long (sometimes years) periods of remission between episodes of BPPV activity; 3) the absence of nystagmus in the presence of subjective symptoms with provocation in some patients; and 4) the absence of basophilic deposits in the cupula and membranous canal of the posterior canal sense organ in many of the donor TBs with a history of BPPV.

Citron and Hallpike[3] and Brandt[18] suggested that a neural component might be responsible for BPPV and could account for the features not explained by the mechanical concept. Gacek and Gacek[19] presented the TBs from 3 patients with BPPV in which degenerative changes were found in the IVG with sparing of the SVG. No basophilic deposits were seen in the posterior semicircular canal or cupula of the 3 TBs, but focal axonal degeneration and inflammatory changes were found in the IVG and nerve similar to those reported in neurotropic virus infection of sensory ganglion cells.[20-22] These observations indicated that the IVG is affected by an inflammatory process in BPPV, and may explain the concurrence of BPPV with other ear disorders caused by vestibular ganglionitis[23-25] (vestibular neuronitis and Meniere's disease).

In order to reexamine the histopathology in BPPV, a qualitative and quantitative examination was performed on TBs from 5 donors with antemortem diagnoses of BPPV. These observations support a neural concept of BPPV rather than one based on a purely mechanical hypothesis.

MATERIALS AND METHODS

The TBs had been acquired from 5 individuals with a clinical history of BPPV before death. Only the ear that was downmost in provocation was available from 4 donors, and both ears were available from 1 donor (No. 4 in Tables 1 and 2[26]). The TBs were processed in standard fashion after formalin fixation, decalcification with ethylenediamine-tetraacetate, and embedment in celloidin. Twenty-micron-thick sections were cut in a horizontal plane, and every 10th section was stained with hematoxylin and eosin, mounted, and placed on a coverslip for examination under a light microscope. The structures examined included the sense organs of the vestibular and auditory labyrinth, the cochlear and vestibular neuronal populations, the cupula and membranous limb of the posterior semicircular canal, and the meatal ganglion of the facial nerve. It is possible that subjecting every 10th section to analysis carries a risk of failure to detect small quantities of otoconial debris in the membranous posterior canal or its cupula. However, proponents of the lithiasis hypothesis have indicated that the presence of BPPV is dependent on the size of the deposits.[8] Therefore, small deposits may not have clinical significance.

Cell counts of the vestibular ganglion were recorded according to the technique used by Richter[27] and Velázquez-Villaseñor et al.[26] Ganglion cells with a visible nucleolus were counted in every stained section at a magnification of 400×. A square reticle subdivided into 4 equal smaller square fields was used in 1 eyepiece of a Nikon Labophot microscope to move by sequential fields across the ganglion. This minimized the chance for duplication or omission of ganglion cells in the count. The section with the smallest number of ganglion cells was considered the interface between the SVG and the IVG.

The number of counted ganglion cells was corrected for double counting of split nucleoli by the formula of Abercrombie.[28] Because of the increased

TABLE 2. TEMPORAL BONE PATHOLOGICAL FINDINGS FROM PATIENTS WITH BPPV

Case No.	Age (y)	Sex	Cause of Death	Otologic Diagnosis	Caloric Response	SVG*		IVG*		Normal for Age[26]		Sense Organs				PC Deposits
						No.	%	No.	%	SVG*	IVG*	LC	UM	SM	PC	
1	48	F	Arteriosclerotic heart disease	Sudden deafness, BPPV	Decreased	6,600	53	4,007	52	12,399	7,722	N	N	N	N	Small cupular
2	65	M	Pulmonary tuberculosis	BPPV	N	5,797	56	5,881	76	10,201	7,661	N	N	N	N	0
3	75	F	Respiratory and congestive heart failure	BPPV, idiopathic vestibulopathy	N	5,955	58	4,743	70	10,167	6,762	N	N	N	N	0
4	80	F	Gastrointestinal hemorrhage	Neural presbycusis, BPPV	N	4,667	46	3,880	57	10,167	6,762	N	N	N	N	Amorphous cupular
				Contralateral ear	N	5,570	55	5,535	82			N	N	N	N	0
5	91	F	Cerebrovascular accident	BPPV	Not available	4,576	45	3,156	49	10,136	6,468	N	N	N	N	0

SVG — superior vestibular ganglion, IVG — inferior vestibular ganglion, LC — lateral canal crista, UM — utricular macula, SM — saccular macula, PC — posterior canal crista, N — normal.

*Number of ganglion cells.

variability of nucleolar diameter in ganglion cells shrunken by pathological changes, the figure of 0.88 used by Velázquez-Villaseñor et al[26] was employed to compute the total ganglion cell count. A total of 3 counts separated in time by at least 7 days was completed for each of the 5 TBs (Table 1). The average of the 3 counts was then used to compute the total number of neurons in the vestibular ganglion.

RESULTS

The demographics (age, sex) were consistent with previous reports of this vestibulopathy. In 4 of the donors, the BPPV persisted for 4 years or longer, and likely until their demise. The duration of the BPPV was less than 1 year in 1 donor. The onset of positional vertigo followed head trauma in 1 patient and was idiopathic in the other 4 patients. In 1 of these 4 cases, the BPPV followed the sudden onset of sensorineural hearing loss and vertigo, while the onset was not associated with a specific illness in the other 3 patients.

The major abnormality in these TBs was a loss of vestibular ganglion cells. This loss was anticipated in the IVG of all TBs because of increased satellite cells and inflammatory cells surrounding ganglion cells, as well as fascicles of degenerated axons in the inferior part of the vestibular nerve and the ganglion. However, a significant loss in the SVG was not expected because of an absence of focal axonal degeneration in the ganglion or nerve trunk and increased satellite cells in portions of the SVG. The individual ganglion cell estimates were sufficiently close to compute a representative average number for the SVG and IVG in each TB (Table 1). The loss of SVG cells in all 5 TBs ranged from 42% to 55%, with a similar loss (43% to 51%) in the IVG of 3 TBs (Table 2). In 2 TBs, the IVG count was decreased by only 24% and 30%, but evidence of ganglion cell degeneration was found in the saccular nerve. Figure 1C illustrates degenerating ganglion cells in the saccular nerve of case 3, while the ganglion cells that innervate the posterior canal crista are surrounded by a heavy density of satellite cells (Fig 1D). The SVG cells were normal (Fig 1B), and no deposits were found in the cupula or ampulla of the posterior canal (Fig 1A). In case 2, the saccular part of the IVG contained a large number of shrunken neurons with few normal ganglion cells (Fig 2C), while most of the posterior canal ganglion cells were normal (Fig 2D). No shrunken ganglion cells were seen in the SVG (Fig 2B). The cupula and membranous limb of the posterior canal did not contain basophilic deposits (Fig 2A).

All vestibular sense organ neuroepithelium appeared normal by light microscopy. The response to caloric stimulation of the involved ear was normal in 3 of the cases, and was decreased in 1 case; caloric stimulation was not performed in 1 case.

There was severe degeneration of the organ of Corti and cochlear nerve throughout the cochlea of case 1, but all other TBs revealed basal turn end organ and cochlear nerve degeneration consistent with age.

DISCUSSION

The observations in this study indicate that the major pathological change in BPPV is degeneration of vestibular neurons, rather than an alteration in recep-

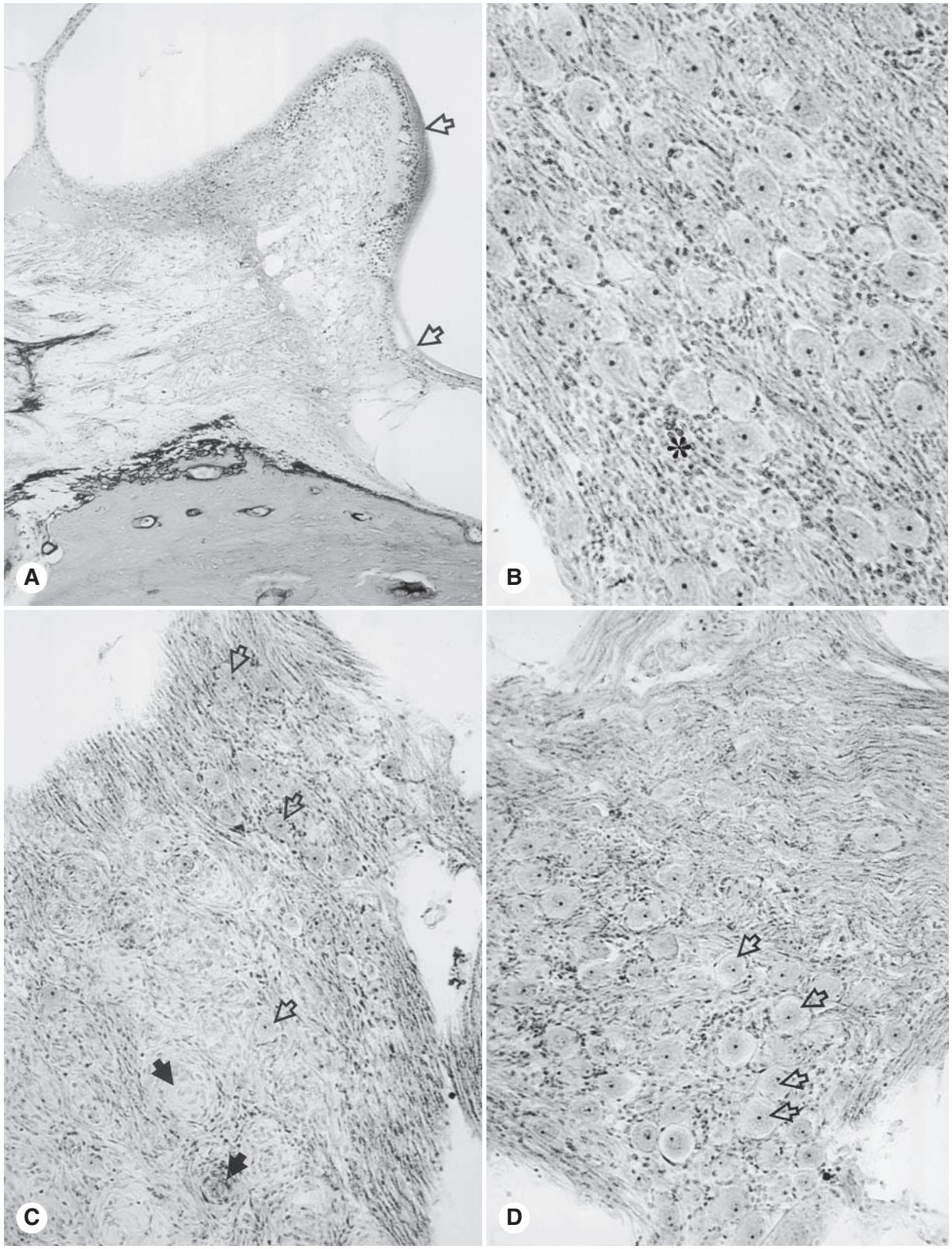

Fig 1. (Case 3) **A)** Shrunken cupula without basophilic deposits (arrows) was attached to normal posterior canal crista (original ×63). **B)** Superior vestibular ganglion cells appeared normal, but were surrounded by increased number of satellite cells (asterisk; original ×160). **C)** Saccular nerve(s) and its ganglion contained some intact neurons (open arrows) but many ganglion cells undergoing degeneration (solid arrows; original ×100). **D)** Ganglion cells (arrows) innervating posterior canal sense organ appeared normal, but were surrounded by many satellite and inflammatory cells (original ×100).

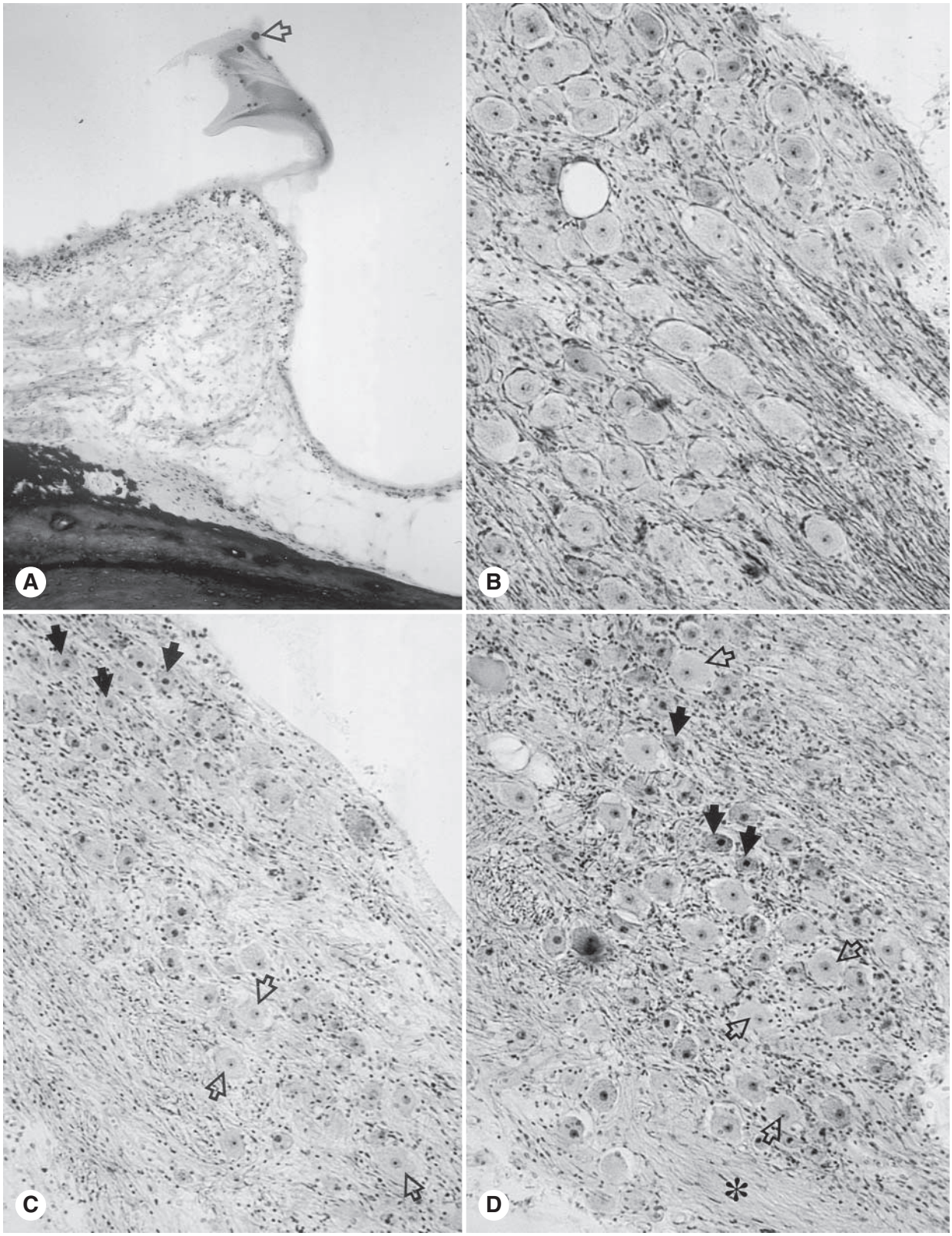

Fig 2. (Case 2) **A)** Posterior canal crista and its cupula were normal (original ×100). Arrow indicates stain artifact. **B)** Superior vestibular ganglion cells were normal and surrounded by normal number of satellite cells (original ×160). **C)** Saccular portion of inferior vestibular ganglion contained many dark, shrunken cell bodies (solid arrows) and some normal ganglion cells (open arrows; original ×160). **D)** Portion of inferior vestibular ganglion that supplies posterior canal crista held many normal-sized cell bodies (open arrows) and smaller number of dark, shrunken neurons (solid arrows; original ×160). Asterisk indicates fascicle of degenerated axons passing through ganglion.

tor sensitivity. Significant loss of SVG and IVG cells was found in all TBs, whereas vestibular sense organs were normal. The assessment of vestibular ganglion cell loss revealed an approximately 50% loss in the SVG of all 5 TBs and in the IVG of 3 TBs with BPPV. The IVG of the remaining 2 TBs revealed a 30% loss of neurons, but showed degenerative changes in saccular ganglion cells.

The cause of this ganglionic degeneration is probably the reactivation of latent neurotropic viral infection. Members of the alpha herpes virinae group (herpes simplex I and II, herpes zoster) are the most likely causative agents because of their ubiquity, their affinity for sensory ganglia,[22,29] and the presence of viral DNA products in patients with vestibular ganglionitis.[30,31] The common concurrence of BPPV in ears with Meniere's disease, vestibular neuronitis, and idiopathic facial paralysis, as well as other cranial neuropathies (zoster, labialis simplex), represents clinical support for this viral form of vestibular ganglionitis in BPPV.[25] Magnetic resonance imaging has demonstrated enhancement of both the SVG and IVG in patients with vestibular neuronitis and BPPV.[25] The histologic features of neurotropic viral ganglionitis include an increase in satellite and inflammatory cells surrounding ganglionic cells in tightly arranged clusters that may result in focal axonal degeneration in the vestibular nerve trunk when ganglion cells degenerate. This pattern of neural inflammation and degeneration has been observed in the TBs of patients with Meniere's disease, vestibular neuronitis, BPPV, and idiopathic facial paralysis.[25]

Gravity-sensitive deposits with a high specific gravity embedded in the cupula or free-floating in the membranous limb of the posterior canal have been implicated in the pathophysiology of BPPV.[8,11] This mechanism would appear to explain that the provocative stimulus is a positional rather than a positioning one. However, such basophilic deposits, probably derived from degenerated otoconia, have not been observed consistently in TBs of patients with BPPV. Parnes[14] reported particles in the posterior canal limb in only 8 of 22 patients who underwent canal occlusion for severe BPPV that did not respond to PRMs. In addition, cupular deposits have been found in a significant number of TBs without a history of positional vertigo.[32] Two studies describing the incidence of cupular deposits in normal pediatric[33] and adult[34] TBs indicate that the frequency of deposits increases with age. Cupular deposits, therefore, may be a morphological change associated with the aging labyrinth. A small deposit was embedded in the posterior canal cupula of 1 TB in the present series, but no deposits were seen in the membranous limb or ampullae of any of the 5 TBs.

Several additional observations are not explained on the basis of a change in the motion mechanics of cupular displacement in the positional test. The limited duration of nystagmus while provocation is maintained and the fatigability of this response cannot be explained by a change in the gravity sensitivity of the cupula. These features are more consistent with a refractory state of first-order vestibular neurons. The absence of nystagmus in patients with subjective symptoms when provoked by the positional stimulus is also difficult to explain on the basis of gravity-sensitive deposits in the endolymph. Therefore, the concept of a gravity-sensitive change in semicircular canal physiology in BPPV is inadequate to explain most of the ocular response features of this disorder.

The observation of neural pathological findings rather than deposits in the ampullary or canal segments of the posterior canal is therefore not surprising. The loss of the ionic gradient across cytoplasmic and nuclear membranes disrupted by virus reactivation may be responsible for degeneration of these primary neurons. Such neural degeneration should be reflected in decreased vestibular function. However, in BPPV, the burst of nystagmus and vertigo represents posterior canal receptor activation. This fact is based on anatomic[35] and physiological[4,5,7] demonstration of vestibulo-ocular response pathways activated by the posterior canal receptor, as well as the elimination of the response when the nerve to the posterior canal receptor has been transected in patients with BPPV.[9,10] Therefore, the mechanism responsible for BPPV must include degeneration of neural elements other than those supplying the posterior canal receptor.

The loss of vestibular neurons appeared to be evenly distributed in the SVG of this series of TBs. Despite a 50% decrease in innervation, 3 of the 5 patients with BPPV gave a normal response to caloric stimulation in the responsible ear (Table 2). This apparent mismatch of neuronal number and response suggests significant redundancy in vestibular nerve innervation of receptor neuroepithelium. However, a greater loss in the neuronal input from an individual end organ (ie, lateral canal crista) could result in a functional deficit. The nerve branch with the smallest neuronal complement[36] would be most at risk of being reduced to a critical level incapable of effective neural transmission. The significance of neuronal number is suggested by ganglion cell estimates in the contralateral ear of patient 4 (Table 2), in which the absence of BPPV was associated with a minimal decrease (18%) in the IVG estimate.

The present TB series suggests that degeneration

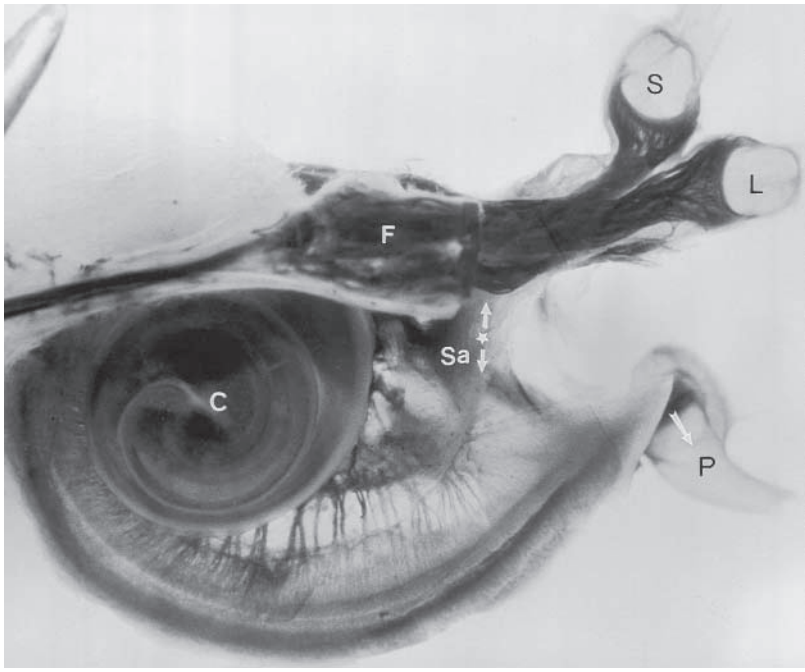

Fig 3. Dissected human labyrinth and its nerve supply (Sudan black) viewed from its lateral (middle ear) aspect. Arrows indicate hair cell polarity in saccular macula (Sa) and posterior canal crista (P). Star marks location of striola line. S — superior canal ampulla, L — lateral canal ampulla, F — tympanic portion of facial nerve, C — apex of cochlea.

of the saccular ganglion may play a key role in this disorder. The interaction between otolith and canal receptors is pertinent to the pathophysiology of BPPV. There is considerable experimental evidence to support an interactive relationship between otolith and canal sense organs. Convergence of canal and otolith input on neurons in the medial vestibular nucleus has been demonstrated by several investigators.[37,38] This interaction has usually taken the form of an inhibitory modulation of canal input by otolith activation. Otolith-canal interaction has been explored extensively in cats by Fluur et al.[39-42] In a large series of experimental conditions involving selective denervation of otolith and canal end organs in the cat, they observed that after denervation of the utricle, a horizontal nystagmus appeared when the lateral canal remained innervated. If lateral canal denervation preceded utricular denervation, nystagmus was absent. When the saccule was denervated in the presence of intact posterior canal innervation, a vertical nystagmus (upbeat-rotatory) appeared. If posterior canal denervation preceded saccular denervation, no nystagmus was observed. These observations indicate that an otolith organ exerts an inhibitory effect on the canal receptors. Without this inhibitory modulation, the response of the canal receptor is released.

This concept of vestibular receptor interaction is reflected in the morphological organization of hair cell polarization in vestibular sense organs. The directional sensitivity of vestibular hair cells is dependent on the arrangement of a single kinocilium adjacent to the tallest of many (>100) stereocilia in each hair cell. Deflection of the ciliary bundles toward the kinocilium leads to depolarization and an increase in the resting neural discharge, while deflection away from the kinocilium results in hyperpolarization and a decrease in resting neural activity.[43] Figure 3 illustrates the organization of hair cell polarization in the receptors supplied by the IVG. The hair cells in each half of the utricular macula are opposed to the polarization of hair cells in the lateral and anterior canal cristae; in the inferior vestibular division, the hair cells in the superior part of the saccular macula are polarized opposite to those in the posterior canal crista. Although a canal sense organ polarized in opposition to the inferior half of the saccular macula does not exist at the present stage of evolution in the primate labyrinth, the occasional appearance of a "crista quarta" or crista neglecta in other mammalian forms may signal a future phylogenetic stage.

The relationship between the two receptors innervated by the IVG is also reflected in their vestibulo-ocular response pathways (Fig 4). These neural projections have been demonstrated by anatomic and physiologic experimental studies in cats and monkeys.[4,5,35] The extraocular eye muscles activated by these two sense organs are antagonistic. When the posterior canal is stimulated, resulting in contraction of the inferior rectus and superior oblique extraocular muscles, the superior rectus and inferior oblique muscles activated by the superior part of the saccule impart an antagonistic muscle contraction to stabilize the globe.

When the head is placed in the so-called Hallpike position, the hair cells in the superior part of the saccule and those in the posterior canal crista are depo-

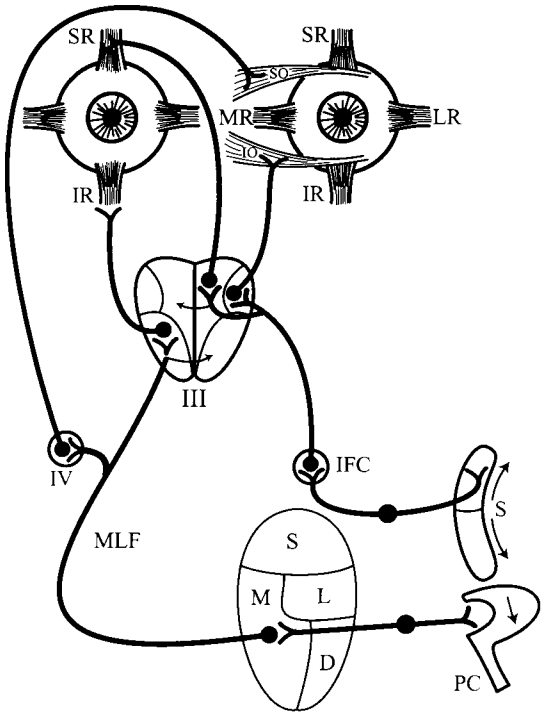

Fig 4. Line drawing summarizes vestibulo-ocular reflex pathways from posterior canal crista (PC) and superior portion of saccular macula (S with arrows). Arrows in sense organs indicate hair cell directionality. S, M, L, and D signify superior, medial, lateral, and descending vestibular nuclei. IFC — infracerebellar nucleus, MLF — medial longitudinal fasciculus, SR — superior rectus muscle, IR — inferior rectus muscle, MR — medial rectus muscle, LR — lateral rectus muscle, SO — superior oblique muscle, IO — inferior oblique muscle, III — oculomotor nucleus, IV — trochlear nucleus.

larized, activating antagonistic extraocular muscles. However, if the saccular macula or its neural input is degenerated, the antagonistic effect on posterior canal input is lost, and the rotatory upbeat nystagmus associated with posterior canal receptor activation is released. If the posterior canal neural input were also degenerated, nystagmus would not appear in the ear with a degenerated saccular nerve. A degenerated or atrophic singular nerve was never encountered in more than 250 surgical exposures of this nerve in patients with chronic BPPV.[10] The nystagmus of posterior canal BPPV, therefore, may result from inadequate inhibition from the saccular macula, especially its superior part. In a similar way, lateral canal BPPV[44] may represent decreased utricular inhibition of lateral canal activation.

The severity (nystagmus and nausea) of the provoked response may depend on the degree to which the saccular input is impaired. It is possible that some patients may have only nausea and imbalance without nystagmus,[45] if the saccular deficit is minimal. If the saccular loss is almost total, the vertigo and nausea may be disabling. Most BPPV patients fall somewhere between these two extremes. Alleviation of the response in these patients by PRMs may result from stimulation of remaining functional units in the saccule, which inhibits activation of the posterior canal crista. This form of treatment would succeed in cases in which there is sufficient residual saccular input.

Although this neural concept of BPPV differs radically from the currently held "lithiasis" theory, the treatment of the disorder remains unchanged. Use of the PRM or waiting for spontaneous resolution is still recommended for the initial presentation of BPPV. The PRM may also be effective for symptomatic control of the recurrent form of BPPV. Those patients with a history of chronic (>1 year) disabling BPPV who do not respond to conservative measures may be candidates for surgical ablation of posterior canal function.

CONCLUSIONS

Observations in 5 TBs from patients with posterior canal BPPV suggest that the pathophysiological mechanism responsible for a position-induced vestibulo-ocular response in this disorder is neural, rather than mechanical stimulation of the sense organ. Loss of the inhibitory action of otolith organs on canal activation caused by degeneration of otolith neurons (saccular, utricular) is a possible explanation of the brief canal response induced by the positional stimulus.

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