Title:

Cochlin-tomoprotein test and hearing outcomes in surgically treated true idiopathic perilymph fistula

Short title:

Surgical outcomes in perilymph fistula positive for CTP

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Abstract

Objectives/Hypothesis: Idiopathic spontaneous perilymph fistula (sPLF) cannot be diagnosed reliably. We speculated that this condition occurs in patients with vertigo-accompanied acute sensorineural hearing loss that progresses rapidly in spite of steroid therapy. We herein evaluated cochlin-tomoprotein (CTP) test results in patients with sPLF who underwent exploratory tympanotomy and considered surgical outcomes with true sPLF.

Study Design: Retrospective study.

Methods: Twenty-three patients diagnosed with sPLF based on the clinical diagnosis criteria who underwent exploratory tympanotomy were included.

Results: CTP test results were positive in 11 cases. In CTP-positive cases, the mean hearing level was 66.5 dB preoperatively and 42.3 dB postoperatively. The hearing level postoperatively completely recovered in 4 cases, markedly recovered in 3 cases, slightly recovered in 1 case, and showed no response in 3 cases. Hearing level improvements were significantly better in CTP-positive patients who underwent surgery within 7 days of the disease onset than in those treated 8 or more days after the disease onset.

Conclusion: Approximately 50% of patients with sPLF based on the clinical diagnosis criteria were definitively diagnosed with CTP-positive sPLF. These results suggest that early surgery within 7 days of the disease onset contributes to improvements in the therapeutic response of hearing loss.

1. Introduction

The etiology of sudden sensorineural hearing loss (SSNHL) is unknown. Hearing loss associated with SSNHL, which is a clinical symptom of this disease, typically does not undergo rapid changes or progression [1]. Perilymph fistula is characterized by acoustic and equilibrium disturbances due to leakage of the perilymph through a fistula that forms in the oval and round window following sudden changes in middle ear pressure. Idiopathic spontaneous perilymph fistula (sPLF), a type of perilymph fistula known to develop without any evident precipitating event, cannot be diagnosed reliably. Thus, an indicator needs to be developed in order to objectively diagnose sPLF. In 2001, Ikezono identified cochlin-tomoprotein (CTP), a specific protein found in the perilymph [2]. As a result, it is now possible to definitively diagnose sPLF through the measurement of CTP.

The present study was based on the assumption that sPLF is a causative factor for SSNHL. We surmised that sPLF occurs in patients with SSNHL who exhibit rapid changes in their hearing levels or progressive hearing loss in spite of systemic steroid therapy. We also attempted to clarify the positive rate of CTP with clinically sPLF and considered the surgical outcomes of true sPLF.

2. Materials and Methods

Twenty-three patients who were diagnosed with sPLF based on a clinical diagnosis and underwent exploratory tympanotomy between September 2012 and August 2014 were included. We diagnosed sPLF based on the following clinical criteria (Table 1). Patients with SSNHL who developed vertigo or nystagmus during medical treatments. Patients with progressive

hearing loss despite systemic steroid therapy. Patients without typical episodes, nystagmus, or a hearing profile associated with Meniere's disease. Patients without significant trauma, atmospheric pressure-related changes, or other events associated with perilymph fistula formation. We defined progressive hearing loss when all three frequencies adjacent to each other deteriorated by more than 10dB.

Sixteen men and seven women were included, with a mean age of 45 years (11-74 years). The right ear was affected in 11 patients and the left in 12. Temporal bone CT was performed preoperatively, but did not reveal any evidence of a soft-density opacity within the tympanic cavity, pneumolabyrinth, or other lesions.

Clinical data were analyzed from the disease onset to surgery, and included the surgical duration, CTP test results, pre- and postoperative hearing levels, pre- and postoperative vertigo, and postoperative complications. Data were statistically analyzed using R software. The significance level was set at $P < 0.05$ (two-tailed).

All surgeries were performed as approved by our institutional Ethics Committee. All patients provided written informed consent prior to all procedures.

CTP test

CTP was measured using the following standard method. The tympanic cavity was washed 3-4 times with 0.3 ml of normal saline, and at least 0.1 ml of the lavage fluid was collected. A CTP level $\geq$ 0.4 ng/mg was considered positive for sPLF, while $<$ 0.4 ng/mg was negative. The specificity of CTP as a means of diagnosing perilymph fistula was previously reported to be 98% [3].

Surgical Procedure (Figure. 1)

Surgery was performed endoscopically on all patients via the external auditory meatus under general anesthesia. A tympanomeatal flap was created, and the tympanic membrane was everted to enable visualization of the tympanic cavity. After the CTP test was conducted (Figure. 1A), the oval and round window was closed by applying an absorbable gelatin sponge (Gelfoam®) (Figure. 1B). All surgeries were performed by the same surgeon.

Parameters Investigated

Hearing levels were measured immediately before surgery and at least 1 month postoperatively once hearing stabilized. Hearing levels were measured at five frequencies (0.25, 0.5, 1.0, 2.0, and 4.0 kHz), and the average was defined as the hearing level. Therapeutic responses were evaluated based on the clinical criteria shown in Table 2 [4].

3. Results

The mean surgical duration in these cases was 39 min (21-69 min). The chorda tympani nerve was preserved in all patients, and none of the patients had tympanic perforation postoperatively. No adverse events occurred. The CTP test was positive in 11 cases (0.46 - 1.31 ng/mg) and negative in 12 cases (<0.2 ng/mg - 0.39 ng/mg). No significant differences were observed, such as in gender or age, between the CTP-positive group and -negative group.

CTP-Positive Patient Results (Table 3)

Six men and five women were positive for CTP. The median period from the disease onset to surgery was 13 days (3-37 days). Three patients (27%) had a history of SSNHL on the affected side and the opposite side. The mean preoperative hearing level was 66.5 dB (31.0-104.0 dB). Preoperative hearing loss deteriorated in the following patterns: deterioration in the low frequency range followed by the high frequency range (n = 4); high frequency range alone (n = 3); and low frequency range alone (n = 3).

The mean postoperative hearing level was 42.3 dB (15.0-74.0 dB). Hearing levels completely recovered after surgery in 4 cases (36%), markedly in 3 cases (27%), and slightly in 1 case (9%). No improvement was observed in 3 cases (27%).

The hearing improvement observed in patients who underwent surgery within 7 days of the disease onset was 42dB, while that of patients treated 8 or more days after the disease onset was 9dB **(Figure. 3)**, and this difference was significant (evaluated with the *t*-test).

Postoperative observation periods ranged from 18 to 36 months. No recurrence of the disease was observed during the follow up periods.

All patients developed vertigo preoperatively, but not nystagmus. Postoperatively, stimulus-induced nystagmus was observed in two cases (18%), but disappeared after 1 day in both. In all cases, subjective vertigo and nystagmus disappeared by 1 month postoperatively.

4. Discussion

We herein report the clinical outcomes of 11 CTP-positive patients with sPLF based on

the clinical diagnosis in the present study. According to our clinical criteria, 48% of these patients were positive for CTP, suggesting that sPLF occurs in approximately 50% of all SSNHL cases showing progressive hearing loss, even in the absence of clear factors causing the formation of sPLF. Since CTP may be falsely diagnosed as negative in patients with perilymph leakage at the time of testing, the true prevalence of positivity for CTP may be even higher.

In the present study, three patients had a previous history of SSNHL in the affected ear and in the opposite ear. This result suggests that sPLF occurs in some patients diagnosed with Meniere's disease, idiopathic hearing loss, or unexplained progressive hearing loss. There was no significant trend in hearing level changes or deterioration patterns, whereas the low-frequency tonal range appeared to be the most frequently affected. We consider these symptoms to be due to relative endolymphatic hydrops caused by the loss of the perilymph [5].

Postoperative hearing improvements were better in patients who underwent surgery within 7 days of the disease onset than in those treated 8 or more days after the disease onset. A previous study reported that early surgery improved hearing prognoses in patients with perilymph fistula due to barotrauma [6]. These findings and the results of the present study suggest that early surgery may contribute to improvements in hearing levels. In one patient, the hearing level was worse postoperatively than that preoperatively (a -7dB elevation in the mean threshold); however, the subjective hearing level did not deteriorate.

Vertigo was alleviated in all cases. The response rate of vertigo in these sPLF cases

appears to be high when alleviation through compensatory changes is also considered. Endoscopic surgery was possible in all cases. An external incision was not required in any case, which contributed to a shorter surgical duration, more esthetically favorable outcome, and improved postoperative analgesia [7]. The surgical duration was short in all cases. Thus, surgery was less invasive overall. Since we consider it important to refrain from excessive surgery, the surgical criteria for sPLF need to be clarified in future studies.

5. Conclusion

Among patients with vertigo-associated SSNHIL showing progressive hearing loss, approximately 50% were definitely diagnosed with CTP-positive sPLF. The results of examining true sPLF revealed that early surgery in these patients may contribute to alleviating hearing loss in a less invasive manner. Thus, new therapeutic approaches to SSNHL may be available.

Conflict of Interest: The authors declare that there is no conflict of interest regarding the publication of this manuscript.

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Table 1. Clinical criteria for idiopathic sponteneous perilymph fistula

1. Patients with SSNHL who present with vertigo or nystagmus during medical treatments.
2. Patients with progressive hearing loss despite systemic steroid therapy.
3. Patients without typical episodes, nystagmus, or a hearing profile associated with Meniere's disease.
4. Patients without significant trauma, atmospheric pressure-related changes, or other events associated with perilymph fistula formation.

We defined progressive hearing loss when all three frequencies adjacent to each other deteriorated by more than 10dB.

Table 2. Criteria for evaluating hearing recovery in sudden deafness by the Ministry of Health, Labor and Welfare Acute Severe Hearing Loss Study Group

Complete Recovery	1) Recovery to a hearing level within 20 dB at all five frequencies tested: 0.25Hz, 0.5Hz, 1.0kHz, 2.0kHz, 4.0kHz 2) Recovery to the same hearing level as the “good” side
Marked Recovery	More than a 30 dB recovery in the mean hearing level at the five frequencies tested
Slight Recovery	Recovery of 10-29 dB recovery in the mean hearing level at the five frequencies tested
No response	Recovery < 10 dB recovery in the mean hearing level at the five frequencies tested

Hearing levels were measured at five frequencies (0.25, 0.5, 1.0, 2.0, and 4.0 kHz), and the average was defined as the hearing level.

Table 3. Results obtained for CTP-positive patients

No.	Age	Gender	Days from onset to surgery	Average hearing level (dB) pre operative / post operative	Magnitude of improvement	Nystagmus	CTP (ng/mg)	past SSNHL same side /opposite side
1	54	M	3	43 / 20	Complete Recovery	− → +	0.52	
2	46	M	4	83 / 15	Complete Recovery	−	0.58	
3	74	F	5	51 / 33	Complete Recovery	− → +	0.46	
4	51	F	12	31 / 21	Complete Recovery	−	0.66	
5	60	F	5	82 / 44	Marked Recovery	−	0.54	
6	43	M	7	104 / 41	Marked Recovery	−	0.56	
7	68	M	12	82 / 47	Marked Recovery	−	1.30	
8	71	F	8	77 / 67	Slight Recovery	−	0.72	y / y
9	56	M	14	61 / 57	No Response	−	1.31	y / y
10	63	M	36	39 / 46	No Response	−	0.65	
11	19	F	37	79 / 74	No Response	−	0.50	y / y

Abbreviations: (+), positive; (−), negative; (− → +), negative preoperatively and positive postoperatively; y, yes; n, no

fig 1

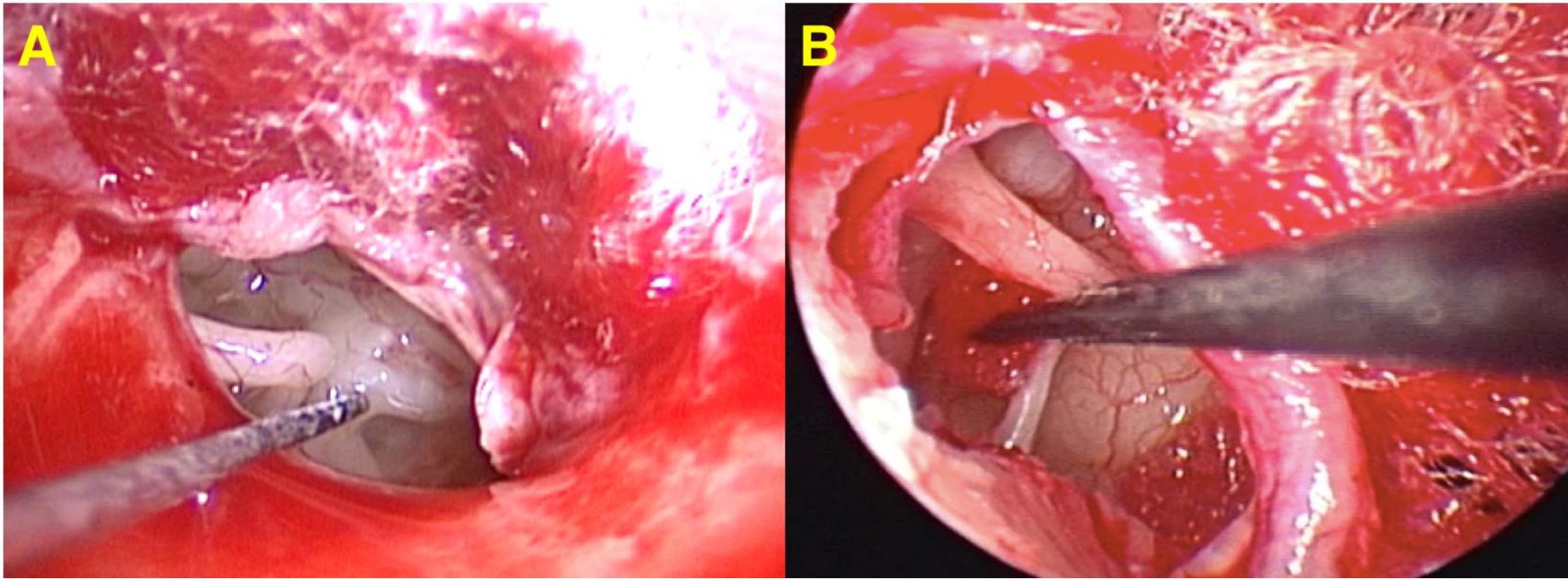
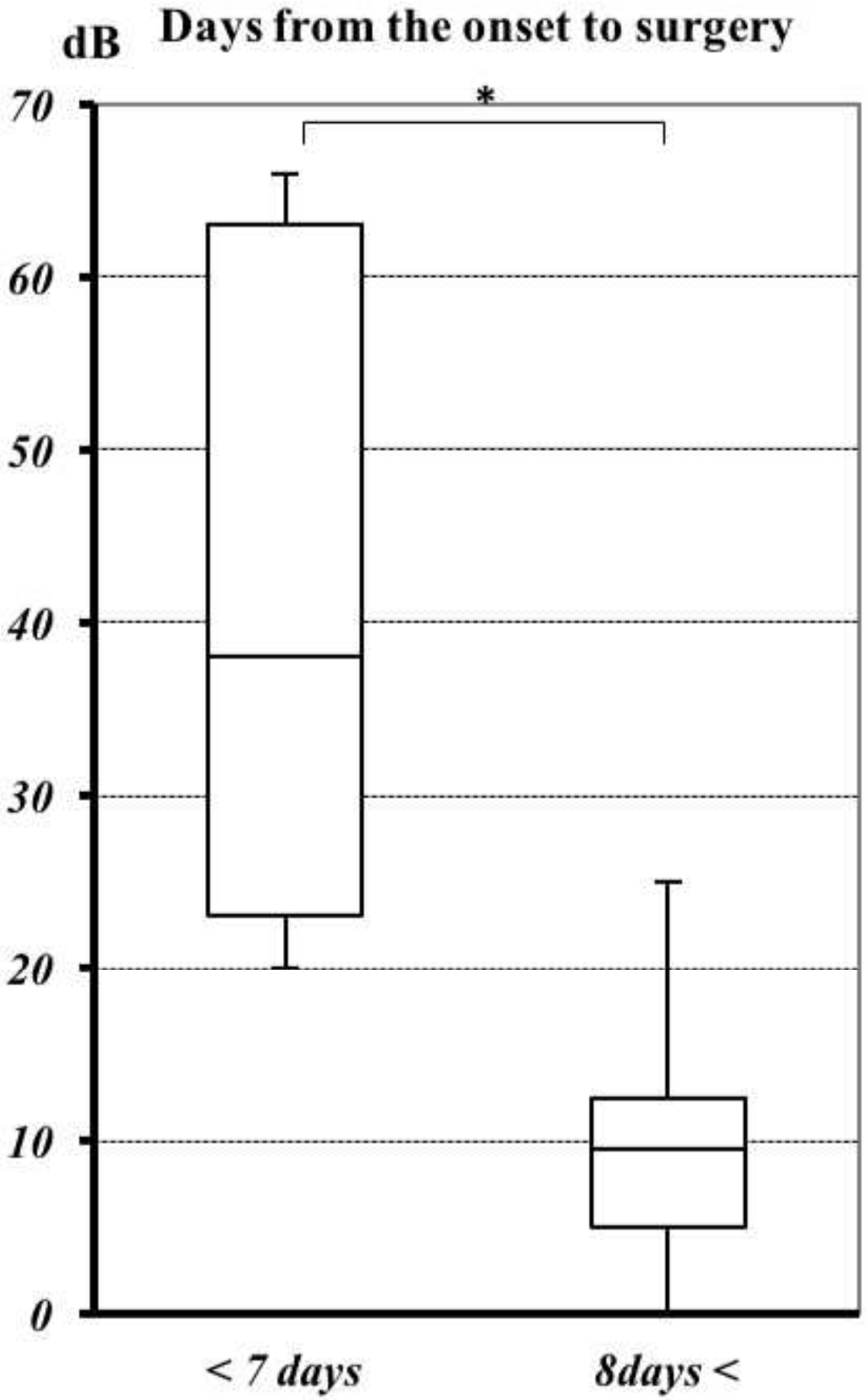


fig 3


dB
Days from the onset to surgery
*
70
60
50
40
30
20
10
0
< 7 days
8days <