Does Endolymphatic Sac Decompression Surgery With Local Steroids Prevent Bilateral Development of Meniere's Disease?

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ABSTRACT

Objectives: The aim in the study was to elucidate whether endolymphatic sac decompression surgery (ESDS) has the potential to prevent unilateral Meniere's disease (MD) from becoming bilateral.

Methods: Between 1996 and 2008, we performed a glycerol test (G-test) and electrocochleography (ECoG) on 237 patients with intractable unilateral MD. We performed ESDS on 179 patients (144 with no endolymphatic hydrops and 35 with silent endolymphatic hydrops in the contralateral ear). The other 58 patients (40 without endolymphatic hydrops and 18 with silent endolymphatic hydrops in the contralateral ear) were given available medical treatments. All underwent regular follow-up for at least 5 years.

Results: Altogether,22.4% (53/237) of patients with clinically diagnosed unilateral intractable MD had silent endolymphatic hydrops in the contralateral ear using G-test and ECoG. In the nonsurgical group, 6 of 40 patients with unilateral MD with no endolymphatic hydrops in the contralateral ear developed bilateral disease, whereas in the surgical group 12 of 144 patients did so (p=0.231, Fisher's test). In the nonsurgical group, 9 of 18 patients with unilateral MD and silent endolymphatic hydrops developed the disease in the contralateral ear, whereas in the surgical group 6 of 35 patients developed bilateral disease (p=0.022, Fisher's test).

Conclusions: The present findings suggest that ESDS may decrease the incidence of developing MD in silent endolymphatic hydronic contralateral ears diagnosed with G-test and ECoG within the first five postoperative years.

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INTRODUCTION

Meniere's disease, characterized by recurrent vertigo, fluctuating hearing loss and persistent tinnitus, is a common disease with an incidence of 15–50 per 100,000[1]. If Meniere's disease (MD) was a unilateral vertigo disease, even intractable cases could be cured simply by vestibular ablative surgery. In fact, 10–40% of MD gradually develops from unilateral to bilateral disease[2-4]. The bilateral disease is associated with the development of bilateral sensorineural hearing loss that gradually becomes the focus of the patient's problems instead of vertigo[3]. It is for this reason that MD was designated a specific disease by Japan's Ministry of Health, Labour and Welfare in 1957[5]. Despite its importance, there have been few well-designed clinical studies concerned with preventing bilateral MD that have included control groups or long-term observation.

The aim of the present study was to determine if endolymphatic sac decompression surgery (ESDS)6-8 has the potential to prevent unilateral MD from becoming bilateral.

METHODS AND MATERIALS

The Ethics Committee of Osaka University Hospital approved the present study (certificate number 0421). It was registered by ClinicalTrials.gov of the US Food and Drug Administration (certificate number NCT00500474). All the patients included in the present study received informed consents and signed permission to join in this study.

Patients and treatments

Between April, 1996 and March, 2008,5838successive patients with MD-like symptoms aged at least 20 years were sent by home doctors and prescreened for eligibility in the vertigo and dizziness department of Osaka University Hospitals to determine whether they had received a clinical diagnosis of unilateral (n=1492) and bilateral (n=398) definite MD according to the 1995 American Academy of Otolaryngology–Head and Neck Surgery (AAO-HNS) criteria9. 3948 patients with diseases other than MD that cause vertigo and dizziness were excluded. 373 intractable MD(unilateral: 272; bilateral: 101) were clinically diagnosed in patients who had undergone various forms of medical and psychological management for at least 3-6 months for their symptoms but it had failed according to the Lancet Seminar10. Patients with either bilateral MD or MD not intractable were also excluded from the study.

Our study protocol for prevention from MD bilateralization in the present study is shown in **Figure-1**. This protocol was originally demonstrated as surgical results of ESDS in the previous paper7. There were some points modified from original one as follows: Because of strict long-term follow-up systems in Osaka, Japan, we excluded cases in Kyoto, Japan and treated additional unilateral intractable ones in our hospitals in Osaka, Japan. We were allowed to perform a glycerol test (G-test) and electrocochleography (ECoG) on 237 out of 272 patients with unilateral intractable MD and evaluated endolymphatic hydrops in the contralateral ear before treatment11. We then offered ESDS for all the patients and actually performed ESDS on 179 of these patients6-8: 144 without endolymphatic hydrops and 35 with silent endolymphatic hydrops in the contralateral ear. These patients formed the OP group. We treated the remaining 58 patients, who declined ESDS, with the best available medicines12.Among them,40 had no endolymphatic hydrops, and 18 had silent endolymphatic hydrops in the contralateral ear. These patients formed the non-OP group. All the patients were followed up regularly until March, 2013for at least 5 years. ESDS is a very common strategy for patients with intractable MD as seen in the Lancet Seminar10. It would thus be difficult to not apply this surgery to some patients for a perfect randomized controlled trial. The patients' backgrounds in both groups are shown in **Table-I**. The best available medicines used for 179 cases in the OP group and 58 cases in the non-OP group during the study period are listed in **Table-II**.

Examinations for inner ear hydrops

To detect endolymphatic hydrops not only in the ipsilateral ear but also in the contralateral ear, we carried out a G-test and ECoG before treatment11. The G-test is considered positive in pure tone audiometry (PTA) if there is a 10-dB or more improvement at two or more frequencies between 0.25 and 2.0 kHz. ECoG is considered positive if the negative summating potential/active potential ratio is ≥0.40. We diagnosed endolymphatic hydrops if there was at least one positive result for the two examinations (G-test and ECoG).

Surgical procedures

The technical details of ESDS are follows6-8. Simple mastoidectomy was performed, clearly exposing the endolymphatic sac in the area between the sigmoid sinus and the inferior margin of the posterior semicircular canal. It was opened with an L-shaped incision made along the posterior and distal margins of the lateral wall. It was then filled with 20 mg of prednisolone. While it was dissolving, we prepared a bundle of absorbable gelatin film with fan- and stick-shaped ends. These films were tied to each other with biochemical adhesive at the stick-shaped end. The fan-shaped end was then inserted into the sac. Small pieces of absorbable gelatin sponge soaked in a high concentration of dexamethasone (32 mg/4 ml) were placed inside and outside the sac lumen, which expanded with the bundle. The dexamethasone-containing sponges placed outside the sac were coated with the adhesive so dexamethasone was slowly delivered into the sac over a long period of time. The stick-shaped end extending out of the sac was fixed to the front edge of the mastoid cavity with the same adhesive so the incision into the sac remained expanded for as long as possible. The mastoid cavity was filled with relatively large pieces of absorbable gelatin sponge dipped in a steroid–antibiotic solution(ofloxacinetc., harmless to the inner ear), after which the wound was closed with skin sutures.

Diagnosis of bilateralization

Contralateral MD is clinically diagnosed based on recurrent vertigo attacks originating from the contralateral ear or if hearing fluctuates in the contralateral ear. A definitive spell of vertigo (lasting >20 minutes) accompanied by contralateral ear cochlear symptoms (tinnitus, hearing loss, ear fullness) is regarded as having its origin in the contralateral ear. Hearing fluctuation is evaluated by PTA based on the four-tone average formulated by (a+b+c+d)/4 (a, b, c, and d are hearing levels at 0.5, 1.0,2.0, and 4.0 kHz, respectively). Changes in hearing levels of >10 dB in the contralateral ear were regarded as hearing fluctuation. Finally, at the 5th postoperative year, we calculated the ratio of the number of patients becoming from unilateral to bilateral in both groups.

Statistical analysis

The data were shown as the ratio of the total number of cases and those treated. They were analyzed statistically using SPSS version 14.0 software (SPSS, Chicago, IL, USA). These data were analyzed with a 2 × 2 contingency table method. Each correlation was assessed using the $\chi 2$ test or Fisher's test. All reported p values were two-sided, with $p< 0.05$ as the accepted level of significance.

All the statistical analyses in the present study were conducted by Dr. Michiko Shuto, a registered statistician independent from our organization.

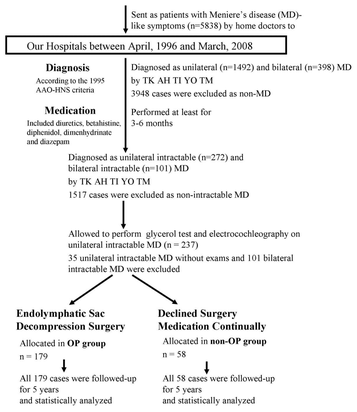

Figure-1:A flowchart of subjects in the present study
Patients were eligible for enrollment if they had received a clinical diagnosis of unilateral and bilateral definite Meniere's disease(MD) according to the 1995AAO-HNS criteria. Between April, 1996 and March, 2008, we offered endolymphatic sac decompression surgery (ESDS) for 237 patients with unilateral intractable MD and performed ESDS on 179 of these patients (OP group). We treated the remaining 58 patients, who declined ESDS, with the best available medicines (non-OP group). All the patients were followed up regularly until March, 2013for at least 5 years.

Table-I: Patients' backgrounds in four groups.

	contraEH (+/-)	Age (yo)	Sex (m/f)	Dur (mo)	Vf (a/mo)	wHL (dB)	pAVP (pg/ml)	
OP n=144	(-)	47.2±4.5	71/73	45.5±16.8	3.0±1.2	52.2±18.0	3.0±1.8	N.S.
OP n=35	(+)	49.6±6.6	15/20	47.2±24.5	3.2±2.1	60.8±12.6	3.8±3.0	
non-OP n=40	(-)	50.3±7.2	21/19	50.2±18.2	2.8±2.0	47.5±20.2	3.2±2.2	
non-OP n=18	(+)	54.8±6.3	9/9	51.0±28.6	2.6±1.7	56.3±15.8	3.5±3.2	N.S.

In surgical group (OP), non-endolymphatic hydrops were found in 144 cases (contraEH(-)) and silent endolymphatic hydrops in 35 cases (contraEH(+)) in the contralateral ear. In non-surgical group (non-OP), non-endolymphatic hydrops were found in 40 cases (contraEH(-)) and silent endolymphatic hydrops in 18 cases (contraEH(+)) in the contralateral ear. There were no significant differences in patients' backgrounds between OP and non-OP groups.

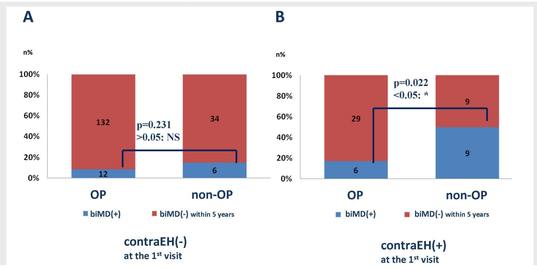

Figure-2: The ratio of bilaterality after surgical and non-surgical treatments
(A) During 5-year-post-therapeutic observation, there were 6 bilaterally developed cases (biMD(+)) out of 40 with unilateral Meniere's disease with non-endolymphatic hydrops in the contralateral ear in the non-surgical group (contraEH(-) in non-OP), whereas 12 bilaterally developed cases (biMD(+)) out of 144 in the surgical group (contraEH(-) in OP).
(B) There were 9 bilaterally developed cases (biMD(+)) out of 18 with unilateral Meniere's disease with silent endolymphatic hydrops in the contralateral ear in the non-surgical group (contraEH(+) in non-OP), whereas 6 bilaterally developed cases (biMD(+)) out of 35 in the surgical group (contraEH(+) in OP).

Table-II: The best available medicines for 237 cases during the study period.

The Best Available Medicines for 237 Cases During the Study Period.

Group	contraEH, +/−	Adenosine Triphosphate/ Betahistine/Chinese Diuretics /Diazepam/Dimenhydrinate/ Osmotic Diuretics*
OP, n = 144	−	88/85/16/76/57/88
OP, n = 35	+	28/30/4/25/20/24
non-OP, n = 40	−	34/35/5/25/24/34
non-OP, n = 18	+	15/16/4/12/12/16

The best available medicines used for 179 cases in the OP group and 58 cases in the non-OP group during the study period are listed here. There were no significant differences in these medicines between OP and non-OP groups.

RESULTS

A total of 237 patients were clinically diagnosed as having unilateral intractable definite MD. Among them, 161 patients had positive signs in the ipsilateral ear (161/237, 67.9%) and 53 patients had also positive signs in the contralateral ear (53/237, 22.4%)using G-test and ECoG. There were no significant differences in patients' backgrounds between OP and non-OP groups **(Table-I)**.

Among 40 patients treated medically (non-OP group) who had unilateral MD without endolymphatic hydrops in the contralateral ear, 6 developed bilateral MD during the 5-year follow-up. During the same time period, 12 of 144 patients in the OP group developed bilateral MD (p=0.231, Fisher's test) **(Figure-2A)**. Among 18 patients in the non-OP group who had unilateral MD with silent endolymphatic hydrops in the contralateral ear, 9 developed bilateral disease. In the OP group, 6 of 35 patients developed bilateral disease (p=0.022, Fisher's test) **(Figure-2B)**.

DISCUSSION

Yamakawa in Osaka, Japan13and Hallpike in London, UK14almost simultaneously revealed that the otopathology of MD was endolymphatic hydrops. Their conclusions were based on the results of temporal bone studies they had conducted. Several similar studies thereafter indicated that approximately 30% of patients with MD had endolymphatic hydrops in bilateral ears15. Based on clinical observations alone, the ratio of bilateral cases approximated 30%2-4. Also, neuro-otologic examinations showed that the ratio of unilateral MD with silent endolymphatic hydrops in the contralateral ear was 10–35%16,17, similar to the 22.4% reported in the present study.

We neuro-otologists cannot ignore these ratios because bilateralization is one of the most important pivotal factors in changing simple MD into an intractable form. We earlier proposed a modified ESDS technique with the application of steroids to the intra-endolymphatic sac in patients with intractable MD6-8. The aim of the present study was to determine if ESDS has the potential to prevent unilateral MD from becoming bilateral. Our 5-year findings suggest that ESDS can prevent the onset of MD in patients with silent endolymphatic hydrops in the contralateral ear. It did not prevent it, however, in patients who did not have endolymphatic hydrops in the contralateral ear.

The mechanisms by which bilateralization of MD was prevented by ESDS in the present study deserve discussion. Although it has not been established that Reissner's membrane rupture theory is true18, ESDS significantly suppressed progression of endolymphatic hydrops to the onset of Meniere's symptoms in patients with silent endolymphatic hydrops in the contralateral ear. Previous clinical studies19,20 and basic studies21,22demonstrated that a high level of plasma vasopressin was a possible cause of endolymphatic hydrops in MD patients. ESDS was shown to decrease the plasma vasopressin level in MD patients in advance of good surgical results23. These findings led to the possibility that ESDS—in addition to its decompression effects in the ipsilateral ear—could lessen the severity of endolymphatic hydropsin the contralateral ear by reducing the systemic plasma vasopressin level. In another recent study, we showed that abundant water intake, tympanic ventilation tubes, and sleeping in darkness could manage vasopressin secretion in Meniere's patients with good results [Kitahara T et al., unpublished data]. Therefore, regardless of the treatment strategy, reducing the plasma vasopressin level might ameliorate the severity of endolymphatic hydrops and suppress bilateralization of MD.

On the other hand, ESDS did not significantly suppress hydrops generation or the onset of MD in the contralateral ear that did not have endolymphatic hydrops. One possibility for these results is that a follow-up of more than 5 years is needed to determine whether ESDS can suppress hydrops generation or MD onset in the contralateral ear in the absence of endolymphatic hydrops2-4. Another possibility is that the duration of MD before treatment in our study was around 4–5 years in both the OP and non-OP groups. The absence of endolymphatic hydrops in the contralateral ear at that time may indicate that the ear would be free of endolymphatic hydrops in future regardless of the treatment applied2-4.

It was previously reported that, compared with nonsurgical treatment, surgery prevented clinically diagnosed unilateral MD from becoming bilateral24. There were a few problems in that report, however. First, the surgeries included both conservative and ablative operations. Second, the patients excluded from the surgical arm of study were subjected to stricter criteria than those in the nonsurgical group. In the present study, ESDS was the only surgical treatment. Also, endolymphatic hydrops in the contralateral ear was detected by means of the G-test and ECoG in both the OP and non-OP groups. We are planning a randomized controlled study for the future.

In the present study, both unilateral and bilateral definite MD was diagnosed based on clinical symptoms according to the 1995 AAO-HNS criteria9. At that time, neuro-otologic examinations looking for signs of endolymphatic hydrops were not necessarily included in the criteria. This limitation may have caused the diagnosis of definite MD to be confused with non-endolymphatic hydrops. On the other hand, in the present study, both unilateral and bilateral endolymphatic hydrops were diagnosed by neuro-otologic examinations such as the G-test and ECoG. Each of these tests has approximately 60% sensitivity at most11,25. In recent reports, including those from our group, endolymphatic hydrops was demonstrated using gadolinium-enhanced inner ear magnetic resonance imaging (MRI)25-27. The sensitivity of this imaging analysis for endolymphatic hydrops was higher than 90%—better than that of neuro-otologic examinations. Further studies including gadolinium-enhanced inner ear MRI could evaluate the effects of treatment for MD on the suppression of bilateralization.

CONCLUSIONS

Among our patients, 22.4% with clinically diagnosed unilateral intractable definite MD had silent endolymphatic hydrops in the contralateral ear using G-test and ECoG. ESDS prevented MD onset in these patients but did not prevent it in those without endolymphatic hydrops in the contralateral ea rusing G-test and ECoG within the first five postoperative years.

REFERENCES

1. Stahle J, Stahle C, Arenberg IK. Incidence of Meniere's disease. Arch Otolaryngol1978; 104: 99-102.
2. Paparella MM, Griebie MS.Bilaterality of Meniere's disease. ActaOtolaryngol1984; 97: 233-237.
3. Stahle J, Friberg U, Svedberg A. Long-term progression of Meniere's disease. ActaOtolaryngolSuppl1991; 485: 78-83.
4. Havia M, Kentala E.Progression of symptoms of dizziness in Meniere's disease. Arch Otolaryngol Head Neck Surg2004; 130: 431-435.
5. Watanabe I.Ménière's disease:with special emphasis on epidemiology, diagnosis and prognosis-Review-. ORL J Otorhinolaryngol Relat Spec 1980; 42: 20-45.
6. Kitahara T, Takeda N, Mishiro Y, Saika T, Fukushima M, et al.Effects of exposing the opened endolymphatic sac to large doses of steroids to treat intractable Meniere's disease. Ann OtolRhinolLaryngol2001; 110: 109-112.
7. Kitahara T, Kubo T, Okumura S, Kitahara M.Effects of endolymphatic sac drainage with steroids for intractable Meniere's disease: A long-term follow-up and randomized controlled study. Laryngoscope 2008; 118: 854-861.
8. KitaharaT, FukushimaM, UnoA, ImaiT, Ohta Y, et al.Long-term results of endolymphatic sac drainage with local steroids for intractable Meniere's disease. Auris Nasus Larynx 2013 ; 40: 425-430.
9. Committee on hearing and equilibrium.Committee on hearing and equilibrium guidelines for diagnosis and evaluation of therapy in Meniere's disease. Otolaryngol Head Neck Surg1995; 113: 181-185.
10. Sajjadi H, Paparella M. Meniere's disease. Lancet 2008; 372: 406-14.
11. Arts HA, Kileny PR, Telian SA.Diagnostic testing for endolymphatic hydrops. Otolaryngol Clin North Am 1997; 30: 987-1005.
12. Claes J, Van de Heyning PH. A review of medical treatment for Meniere's disease. Acta Otolaryngol Suppl2000; 544: 34-39.
13. Yamakawa K.Uber die pathologische Veranderung beieinem Meniere-Kranken. J Otolaryngol Jpn1938; 44: 2310-2312.
14. Hallpike CS, Cairns H.Observations on the pathology of Meniere's syndrome. J LaryngolOto1938; 53: 625-655.
15. Yazawa Y, Kitahara M. Bilateral endolymphatic hydrops in Ménière's disease: review of temporal bone autopsies-Review-. Ann Otol Rhinol Laryngol 1990; 99: 524-528.
16. Moffat DA, Baguley DA, Harries ML. Bilateral electrocochleographic findings in unilateral Meniere's disease. Otolaryngol Head Neck Surg 1992; 107: 370-373.
17. Conlon BJ, Gibson WPR. Meniere's disease: the incidence of hydrops in the contralateral asymptomatic ear. Laryngoscope 1999; 109: 1800-1802.
18. SchuknechtHF. Pathophysiology of endolymphatic hydrops. Arch Otorhinolaryngol 1976; 212: 253-262.
19. Takeda T, Kakigi A, Saito H. Antidiuretic hormone (ADH) and endolymphatic hydrops. ActaOtolaryngolSuppl 1995; 519: 219-222.
20. KitaharaT, DoiK, MaekawaC, KizawaK, HoriiA, et al. Meniere's attacks occur in the inner ear with excessive vasopressin type-2 receptors. J Neuroendocrinol 2008; 20: 1295-1300.
21. Kumagami H, Loewenheim H, Beitz E, Wild K, Schwartz H, et al. The effect of anti-diuretic hormone on the endolymphatic sac of the inner ear. Pflugers Arch 1998; 436: 970-975.
22. Takeda T, Takeda S, Kitano H. Endolymphatic hydrops induced by chronic administration of vasopressin. Hear Res 2000; 140: 1-6.
23. Horii A, KitaharaT, UnoA, KondohK, MorihanaT, et al. Vestibular function and vasopressin. Acta Otolaryngol Suppl 2005; 553: 50-53.
24. Rosenberg S, Silverstein H, Flanzer J.Bilateral Meniere's disease in surgical versus non-surgical patients. Am J Otol 1991; 12: 336-340.
25. Fukuoka H, Takumi Y, Tsukada K, Miyagawa M, Oguchi T, et al. Comparison of the diagnostic value of 3T MRI after intratympanic injection of GBCA, and the glycerol test in patients with Meniere's disease. Acta Otolaryngol 2012; 132: 141-145.
26. Nakashima T, Naganawa S, Sugiura M, Teranishi M, Sone M, et al. Visualization of endolymphatic hydrops in patients with Meniere's disease. Laryngoscope 2007; 117:415-420.
27. Uno A, ImaiT, WatanabeY, TanakaH, KitaharaT, et al. Changes in endolymphatic hydrops after sac surgery examined by Gd enhanced MRI.ActaOtolaryngol 2013; 133: in press.