Effects of Endolymphatic Sac Drainage With Steroids for Intractable Ménière’s Disease: A Long-Term Follow-Up and Randomized Controlled Study

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Objective: Ménière’s disease is a common inner ear disease with an incidence of 15 to 50 per 100,000 population. Since Ménière’s disease is thought to be triggered by an immune insult to the inner ear, we examined intraendolymphatic sac application of steroids as a new therapeutic strategy for intractable Ménière’s disease.

Study Design: Prospective randomized controlled study.

Methods: Between 1996 and 2005, we enrolled and assigned 197 intractable Ménière’s patients to three groups in a randomized controlled trial: Group I (G-I)—patients who underwent endolymphatic sac drainage and steroid-instillation; Group II (G-II)—those who underwent endolymphatic sac drainage without steroid-instillation; and Group III (G-III)—those who declined endolymphatic sac drainage. Definitive spells and hearing in all three groups were determined for 2 to 7 years after treatment.

Results: According to the 1995 American Academy of Otolaryngology–Head and Neck Surgery (AAO-HNS) criteria, 2-year results demonstrated that vertigo was completely controlled in 88.0% of patients in G-I (n = 100), 85.1% of patients in G-II (n = 47), and 8.0% in G-III (n = 50). Statistically, G-I = G-II > G-III. Hearing was improved in 49.0% of patients in G-I, 31.9% in G-II, and 6.0% in G-III (G-I > G-II > G-III). Results after 7 years showed that vertigo was completely controlled in 78.8% of patients in G-I, 79.2% in G-II, and 28.0% in G-III (G-I = G-II > G-III). Hearing improved in 36.5% of patients in G-I, 8.3% in G-II, and 0.0% in G-III (G-I > G-II = G-III).

Conclusions: From non-surgical observation in G-III for at least 7 years after treatment, steroids instilled into endolymphatic sac in G-I patients significantly improved hearing in intractable Ménière’s patients, more so than endolymphatic sac drainage without steroids in G-II patients.

Key Words: Ménière’s disease, intractable, endolymphatic sac drainage, steroids.


INTRODUCTION

Ménière’s disease, characterized by recurrent attacks of vertigo, fluctuating hearing loss (HL), and tinnitus, is a common disease with an incidence of 15–50 per 100,000 population. Some patients with Ménière’s disease are strongly prevented from participating in activities of daily life and interaction with their social environment, such as work and schooling, due to frequent attacks of vertigo, especially with progressive sensorineural HL, despite various kinds of medication. This type of Ménière’s disease is called intractable Ménière’s disease. Although the otopathology in Ménière’s temporal bones was revealed in 1938 to be inner ear endolymphatic hydrops, the definite pathogenesis of Ménière’s disease is still unknown and there is no radical treatment for the original pathogenesis of this disease.

It has, however, been reported that Ménière’s disease is usually triggered by immune, metabolic, infectious, traumatic, or other insults to the inner ear associated with a small misplaced malfunctioning endolymphatic sac. Among these insults, immune-mediated responses in the inner ear endo-organs such as the endolymphatic sac, stria vascularis, and spiral ligament, are thought to be the main reason for the development of symptoms in Ménière’s disease. Thus, systemic administration and/or local perfusion of corticosteroids into the middle ear have been adopted as an antimimmune or antiinflammatory therapy for patients with intractable Ménière’s disease.
disease.\textsuperscript{10,11} These treatments were reported to result in good relief from vertigo and improvement of hearing in some cases. However, these results, especially for hearing, did not last long enough to discontinue additional repetitive applications of steroids.\textsuperscript{12} Since Ménière’s disease is characterized by repeated attacks of vertigo with fluctuating and/or progressive HL, unlike other inner ear diseases without recurrence such as sudden deafness and vestibular neuritis, it is necessary to refrain from repetitive applications of steroids for long-term follow-up with Ménière’s patients because of side effects.

For inner ear drug delivery, we noted another hopeful but unevaluated route, the longitudinal route from the endolymphatic sac to the cochlea and vestibule, suggested by several lines of evidence in animal studies. Morgenstern et al.\textsuperscript{13} and Lee et al.\textsuperscript{14} demonstrated that the intraendolymphatic sac materials could reach the cochlear endolymphatic site through the vestibular aqueduct using a test marker and an ototoxic drug, respectively. Recently, Yamasoba et al.\textsuperscript{15} suggested the possibility of gene therapy through the vestibular aqueduct route. We also revealed that intraendolymphatic sac steroids could upregulate a water channel molecule, aquaporin-3 mRNA, in the cochlea.\textsuperscript{16} In this study, we examined the intraendolymphatic sac application of steroids as a new therapeutic strategy for intractable Ménière’s disease.

**MATERIALS AND METHODS**

**Patients**

Patients were eligible for enrollment if they had received a clinical diagnosis of intractable Ménière’s disease according to the 1995 American Academy of Otolaryngology–Head and Neck Surgery (AAO-HNS) criteria.\textsuperscript{17} These criteria can be briefly described as follows: 1) repeated attacks of vertigo—a definitive spell is spontaneous vertigo lasting at least 20 minutes and a mixed type of spontaneous nystagmus is observed during attacks; 2) fluctuating cochlear symptoms—the hearing test usually reveals a marked fluctuation of the threshold in the low and middle tone range (if necessary, we carried out a glycerol test or electrocochleogram to...
detect endolymphatic hydrops;\textsuperscript{18} and 3) exclusion of other causes—
to exclude other disorders, a thorough history, neurologic, neu-
rotologic, and MRI examinations were carried out. Intractable
Ménière’s disease was designated in cases where various forms
of medical and psychological managements failed for at least 6
months. Medical managements included diuretics, betahistine,
diphenidol, dimenhydrinate, and diazepam, which were thought to
be effective for persistent symptoms in Ménière’s disease.\textsuperscript{19}

**Randomization and Treatment**

Between April 1996 and March 2005, a total of 197 patients
were enrolled and assigned to three study groups in a randomized

![Fig. 2. Schematic representation of endolymphatic sac drainage with steroid-instillation into the sac (right ear) in Group I patients (A–C) and
endolymphatic sac expanding surgery without steroid-instillation into the sac (right ear) in Group II patients (D–F). To elucidate the effects of
a high concentration of intraendolymphatic sac steroids on the treatment of intractable Ménière’s disease, we compared results in vertigo and
hearing between endolymphatic sac drainage with (A–C) and without steroid-instillation into the sac (D–F). B, C, and E, F are high
magnifications of areas around the endolymphatic sac in A and D, respectively. Abbreviations used: ext. = external; lat. = lateral; post. = posterior.

**TABLE I.**

Demographics of Patients With Intractable Ménière’s Disease.

<table>
<thead>
<tr>
<th>Group</th>
<th>Sex</th>
<th>Age (Years ± SD)</th>
<th>Duration (Years ± SD)</th>
<th>Vertigo (a/mo ± SD)</th>
<th>Stage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group I (n = 100)</td>
<td>Male = 44 Female = 56</td>
<td>50.3 ± 14.5</td>
<td>8.7 ± 7.5</td>
<td>3.8 ± 2.3</td>
<td>I = 4, II = 18, III = 60, IV = 18</td>
</tr>
<tr>
<td>Group II (n = 47)</td>
<td>Male = 21 Female = 26</td>
<td>55.6 ± 10.1</td>
<td>9.5 ± 8.9</td>
<td>3.9 ± 2.6</td>
<td>I = 3, II = 5, III = 32, IV = 7</td>
</tr>
<tr>
<td>Group III (n = 50)</td>
<td>Male = 24 Female = 26</td>
<td>53.7 ± 12.4</td>
<td>8.8 ± 6.2</td>
<td>3.6 ± 2.3</td>
<td>I = 3, II = 8, III = 27, IV = 12</td>
</tr>
</tbody>
</table>

Statistical Analysis

- \( P = .895 \) (NS) by \( \chi^2 \)
- \( P = .057 \) (NS) by one-way ANOVA
- \( P = .811 \) (NS) by one-way ANOVA
- \( P = .832 \) (NS) by one-way ANOVA
- \( P = .742 \) (NS) by \( \chi^2 \)

SD = standard deviation; a/mo = number of attacks per month; NS = not significant; ANOVA = analysis of variance.
TABLE II

<table>
<thead>
<tr>
<th>Group</th>
<th>Complete</th>
<th>Others</th>
<th>n</th>
<th>po2y</th>
<th>po3y</th>
<th>po4y</th>
<th>po5y</th>
<th>po6y</th>
<th>po7y</th>
</tr>
</thead>
<tbody>
<tr>
<td>G-I</td>
<td>100</td>
<td>41</td>
<td>52</td>
<td>100</td>
<td>88</td>
<td>12</td>
<td>89</td>
<td>80</td>
<td>90</td>
</tr>
<tr>
<td></td>
<td>(88%)</td>
<td></td>
<td></td>
<td>(100%)</td>
<td>(88%)</td>
<td></td>
<td>(100%)</td>
<td>(90%)</td>
<td>(90%)</td>
</tr>
<tr>
<td>G-II</td>
<td>47</td>
<td>28</td>
<td>52</td>
<td>47</td>
<td>42</td>
<td>7</td>
<td>47</td>
<td>42</td>
<td>47</td>
</tr>
<tr>
<td></td>
<td>(85%)</td>
<td>(89%)</td>
<td></td>
<td>(100%)</td>
<td>(89%)</td>
<td>(15%)</td>
<td>(100%)</td>
<td>(89%)</td>
<td>(89%)</td>
</tr>
<tr>
<td>G-III</td>
<td>50</td>
<td>4</td>
<td>52</td>
<td>50</td>
<td>46</td>
<td>92</td>
<td>50</td>
<td>46</td>
<td>50</td>
</tr>
<tr>
<td></td>
<td>(8%)</td>
<td>(8%)</td>
<td></td>
<td>(100%)</td>
<td>(92%)</td>
<td>(100%)</td>
<td>(100%)</td>
<td>(92%)</td>
<td>(92%)</td>
</tr>
</tbody>
</table>

Statistical analysis

<table>
<thead>
<tr>
<th>G-I vs. G-II</th>
<th>G-I vs. G-III</th>
<th>G-II vs. G-III</th>
</tr>
</thead>
<tbody>
<tr>
<td>p = 1.00 E-11</td>
<td>p = 7.34 E-6</td>
<td>p = 7.34 E-6</td>
</tr>
<tr>
<td>p = 0.001</td>
<td>p = 0.001</td>
<td>p = 0.001</td>
</tr>
</tbody>
</table>

Note: NS = not significant; po2y = 2 years postoperative; po3y = 3 years postoperative; po4y = 4 years postoperative; po5y = 5 years postoperative; po6y = 6 years postoperative; po7y = 7 years postoperative.

**Functional Examinations**

A definitive spell lasting more than 20 minutes was regarded as a Ménière’s vertigo attack according to the 1995 AAO-HNS criteria.**1** Frequency of vertigo was calculated based on the number of vertigo attacks during the 6 months before treatment. The number of attacks in G-III patients who refused endolymphatic sac drainage was also determined. Frequency of vertigo after treatment, for example, at the 3rd follow-up year was calculated based on the number of vertigo attacks during the 6 months between 30 and 36 months after treatment. Frequency of vertigo in G-III patients at this time point was also determined. “Complete” control of vertigo at the 3rd follow-up year meant no vertigo attacks during that period (0 < before/after < 0.8) was regarded as better, 1.2 ≤ before/after as worse, and the others as no change.

Hearing function was measured by a pure tone audiometer and was evaluated based on the particularly weighted three-tone average formula by $(a + 2b + c)/4$ (where a, b, and c are hearing levels at 0.5 kHz, 1 kHz, and 2 kHz, respectively) accord-
ing to the modified 1995 AAO-HNS criteria. The worst hearing level during the 6 months before treatment was adopted as the hearing level before treatment and, for example, the worst hearing level during the 6 months between 42 and 48 months after treatment was adopted as the hearing level at the 4th follow-up year. More than 10 dB differences in hearing levels before and after treatment were regarded as better, less than −10 dB differences as worse, and the others as no change.

Vestibular function was measured by a caloric test using an electronystagmogram (ENG). For the caloric test, the external auditory canal was irrigated in turn with 30°C cold water and 44°C hot water (20 mL, respectively) for 10 seconds. The induced nystagmus was recorded using ENG in a dark, open-eyes situation. Based on the averaged maximum slow-phase eye velocity (max-SPEV) in the treated side, max-SPEV after treatment/max-SPEV before treatment was calculated and values of more than 1.1 were recognized as an improvement in vestibular function at the 2nd follow-up year.

Statistical Analysis
All the data from treatment results were presented as the ratio of the number of cases and treated statistically with the use of SPSS, version 14.0 (SPSS Inc, Chicago, IL). In each postoperative year result, the Mann-Whitney U test was used to analyze the data between each of two groups out of all three groups, G-I, G-II and G-III. All reported P values were two sided, and those under .05 were considered significant.

RESULTS
Patients’ backgrounds in all three groups including sex, age, duration of disease, vertigo frequency before treatment, and stage of disease before treatment, are shown in Table I. Duration of disease indicates the period between the onset of symptoms and the date of treatment. Stage of disease is based on hearing. Stages I, II, III, and IV indicate that the particularly weighted three-tone average of the worst audiogram in the 6 months before treatment was <25, 25 to 40, 41 to 70 and >70, respectively. As shown in Table I, there were no significant differences in patients’ backgrounds among all three groups, G-I, G-II, and G-III.

According to the criteria in 1995 AAO-HNS, long-term results in vertigo control and hearing improvement during the 2- to 7-year follow-up period in all groups are shown in Tables II and III (raw data) and Figure 3 (graphs).

As shown in Figure 3A, vertigo attacks in G-I patients were completely suppressed (i.e., vertigo frequency = 0) from 88.0 to 78.8% of patients during the 2- to 7-year follow-up period after treatment. Vertigo attacks in G-II patients were completely suppressed from 85.1 to 79.2% during the 2- to 7-year follow-up period. Vertigo attacks in G-III patients were completely suppressed from 8.0 to 25.0% during the 2- to 7-year follow-up period.

As shown in Figure 3B, hearing in G-I patients improved (≥10 dB) from 49.0 to 36.5% of patients and worsened (≤−10 dB) from 7.0 to 13.5% during the 2- to 7-year follow-up period after treatment. Hearing in G-II patients improved from 31.9 to 8.3% and worsened from 12.8 to 37.5% during the 2- to 7-year follow-up period. Hearing in G-III patients improved from 6.0 to 0.0% and worsened from 42.0 to 75.0% during the 2- to 7-year follow-up period.

To compare the long-term results among all three groups, 2-year results demonstrated that definitive spells were completely controlled in 88.0% in G-I patients, 85.1% in G-II patients, and 8.0% in G-III patients (G-I = G-II > G-III: Mann-Whitney). Hearing was improved in 49.0% in G-I patients, 31.9% in G-II patients, and 6.0% in G-III patients (G-I > G-II > G-III: Mann-Whitney). Seven-year results showed that definitive spells were completely controlled in 78.8% in G-I patients, 79.2% in G-II patients, and 25.0% in G-III patients (G-I = G-II > G-III: Mann-Whitney). Hearing was improved in 36.5% in G-I patients, 8.3% in G-II patients, and 0.0% in G-III patients (G-I > G-II = G-III: Mann-Whitney). Exact P values are all shown in Table II.

Vestibular function was examined in 56 out of 100 cases in G-I just before and 2 years after treatment. Two years after treatment, recovery of vestibular function occurred in just 50% (28 of the 56). In 28 of the 56 with improved vestibular function (≥10%), vertigo was completely controlled in 26 (92.9%). In 28 of the 56 with non-improved vestibular function (<10%), vertigo was completely controlled in 25 (89.3%). There were no significant differences in vertigo control between cases with improved or non-improved vestibular function after treatment.

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**TABLE III.**

<table>
<thead>
<tr>
<th>Hearing Improvement</th>
<th>po2y n</th>
<th>G-I</th>
<th>G-II</th>
<th>G-III</th>
</tr>
</thead>
<tbody>
<tr>
<td>Better</td>
<td>49 (49%)</td>
<td>44 (44%)</td>
<td>26 (55%)</td>
<td>26 (42%)</td>
</tr>
<tr>
<td>No Change</td>
<td>7 (7%)</td>
<td>6 (13%)</td>
<td>6 (13%)</td>
<td>8 (12%)</td>
</tr>
<tr>
<td>Worse</td>
<td>89 (89%)</td>
<td>82 (82%)</td>
<td>45 (85%)</td>
<td>38 (61%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Hearing Improvement</th>
<th>po3y n</th>
<th>G-I</th>
<th>G-II</th>
<th>G-III</th>
</tr>
</thead>
<tbody>
<tr>
<td>Better</td>
<td>45 (51%)</td>
<td>38 (43%)</td>
<td>26 (55%)</td>
<td>20 (40%)</td>
</tr>
<tr>
<td>No Change</td>
<td>6 (7%)</td>
<td>8 (17%)</td>
<td>20 (40%)</td>
<td>20 (40%)</td>
</tr>
<tr>
<td>Worse</td>
<td>74 (74%)</td>
<td>72 (72%)</td>
<td>36 (48%)</td>
<td>32 (48%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Hearing Improvement</th>
<th>po4y n</th>
<th>G-I</th>
<th>G-II</th>
<th>G-III</th>
</tr>
</thead>
<tbody>
<tr>
<td>Better</td>
<td>36 (49%)</td>
<td>32 (48%)</td>
<td>12 (29%)</td>
<td>11 (29%)</td>
</tr>
<tr>
<td>No Change</td>
<td>42 (42%)</td>
<td>40 (40%)</td>
<td>21 (50%)</td>
<td>18 (50%)</td>
</tr>
<tr>
<td>Worse</td>
<td>74 (74%)</td>
<td>72 (72%)</td>
<td>32 (48%)</td>
<td>30 (48%)</td>
</tr>
</tbody>
</table>


d = number; NS = not significant; po2y = 2 years postoperative; po3y = 3 years postoperative; po4y = 4 years postoperative; po5y = 5 years postoperative; po6y = 6 years postoperative; po7y = 7 years postoperative.

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Kitahara et al.: Steroid-Treatment via Endolymphatic Sac.
DISCUSSION

Systemic administration and/or local perfusion of corticosteroids into the middle ear have sometimes been adopted as an anti-immune therapy for patients with intractable Ménière’s disease. In a number of studies concerned with steroid treatment, only Shea et al.14 and Sennarougлу et al.11 observed steroid-treated patients for longer than 2 years in accordance with the 1995 AAO-HNS criteria.17 Sennarougлу et al. reported that intratympanic perfusion of dexamethasone suppressed vertigo completely in 42.0% of patients and improved hearing significantly in 16.0% 2 years after treatment. Shea et al. demonstrated that systemic and intratympanic combined administration of dexamethasone suppressed vertigo completely in 63.4% and improved hearing significantly in 35.4% 2 years after treatment. On the other hand, Silverstein et al.12 suggested that intratympanic application of dexamethasone showed no significant benefit over placebo in their prospective, randomized, double-blind, crossover trial. In fact, these studies showed that steroid treatment appeared to result in good relief of vertigo and improvement of hearing in some cases. However, there were limitations in the long-term findings of systemic and/or intratympanic steroid application, and it often happened to consider additional repetitive applications of steroids for recurrences of symptoms, especially progressive HL, along with the risk of side effects.

Endolymphatic sac surgery, which was first performed by Portmann23 in 1927 is another option for patients with intractable Ménière’s disease. Thomsen et al.,24 Pillsbury et al.,25 and Bretlau et al.26 suggested that endolymphatic sac surgery was no more effective than a placebo. Despite this controversy, endolymphatic sac surgery is still a commonly performed procedure worldwide.27 This kind of conservative surgery is thought to be effective for inner ear decompression against endolymphatic hydrops and several modifications of these surgeries have been tried and reported. Moffat et al.,28 Huang et al.,29 Gibson et al.30 and Gianoli et al.31 reported 2-year results of their modified endolymphatic sac surgery as follows: complete control of vertigo in 43.0%, 84.4%, 56.8%, and 60.0% of patients, respectively, and significant hearing improvement in 19.0%, 12.8%, 4.7%, and 60.0% of patients, respectively. Ostrowski et al.,32 however, followed up Gianoli’s results for 4 to 5 years, which resulted in 47.0% having complete control of vertigo and 18.0% having significant hearing improvement. Goin et al.33 suggested that endolymphatic sac surgery did not modify the natural course of Ménière’s disease with respect to hearing. Stahle et al.34 suggested that Ménière’s patients were more annoyed with progressive HL rather than vertigo attacks during long-term follow-up because of spontaneous relief of vertigo over the years. With the poor long-term results in hearing with systemic and/or intratympanic application of steroids and endolymphatic surgery mentioned above, it is time to think of ways to improve and maintain the inner ear function, especially hearing, in patients with intractable Ménière’s disease.

In our study, it was demonstrated that long-term results of treatment in G-I patients were excellent, as seen in Figure 3. The intraendolymphatic sac application of large doses of steroids in G-I patients could have additional effects to those of endolymphatic sac-expanding surgery in G-II patients, especially on hearing, and was, of course, superior to non-surgical treatment of intractable Ménière’s disease in G-III patients, both for vertigo control and hearing improvement for at least 7 years.

Our study has limitations. From the long and controversial history of evaluations of surgical treatments for intractable Ménière’s disease,25–27 it is well understood that it is necessary to include a non-surgical control group when surgical effects are evaluated because of the spontaneous relief of symptoms. However, as mentioned above, endolymphatic sac drainage is a very common strategy for patients with intractable Ménière’s disease.28 It would thus be difficult to not apply drainage to some patients for a perfect randomized controlled trial. Therefore, in the G-III group, we included only 50 patients who declined to undergo endolymphatic sac drainage. As well, it was confirmed that there were no significant differences in patients’ backgrounds among all three groups, G-I, G-II, and G-III.

A high concentration of intraendolymphatic sac steroids in G-I patients could have almost the same effects on vertigo control and make additional effects on hearing.

<table>
<thead>
<tr>
<th>TABLE III. (Continued)</th>
</tr>
</thead>
<tbody>
<tr>
<td>po5y</td>
</tr>
<tr>
<td>n</td>
</tr>
<tr>
<td>---</td>
</tr>
<tr>
<td>74</td>
</tr>
<tr>
<td>40</td>
</tr>
<tr>
<td>30</td>
</tr>
</tbody>
</table>

P = .0028 <.01 P = .0026 <.01 P = 2.38 E–8 <.001
P = .00025 <.01 P = .0063 NS P = 7.92 E–6 <.001
Fig. 3. Graphic presentation of long-term results for 2 to 7 years for patients with intractable Ménière’s disease in Group I, Group II, and Group III. (A) Vertigo control: all of the bar graphs were made according to the raw data in Table II, A. Dotted columns (no vertigo) represent the percentage of patients with no vertigo attacks and black columns (recurrent [rec] vertigo) represent the percentage of patients with recurrent vertigo during each period. (B) Hearing improvement: all bar graphs were made according to the raw data in Table II, B. Dotted columns (better) represent the percentage of patients with more than 10 dB hearing improvement, black columns (worse) represent the percentage of patients with more than 10 dB hearing deterioration and gray columns (no change) represent the others.
improvement compared with endolymphatic sac drainage without steroids in G-II patients. Two years after treatment in G-I patients, definitive spells were completely controlled in 88.0%, although recovery of vestibular function appeared in just 50.0% of all cases, such as hearing improvement in 49.0%. This means that recovery of vestibular function is not always necessary for suppressing vertigo attacks, unlike recovery of cochlear function for hearing improvement. Functional recovery of cochleae is, of course, crucial for hearing improvement in treatment for Ménière’s disease. Intraendolymphatic sac application of steroids may have potential for that recovery for at least 7 years after treatment. The results from this study have encouraged us to continue our investigations to ascertain an ideal treatment for intractable Ménière’s disease.

CONCLUSIONS
From non-surgical observation in G-III patients for at least 7 years after treatment, steroids instilled into endolymphatic sac in G-I patients significantly improved hearing in intractable Ménière’s patients, more so than endolymphatic sac drainage without steroids in G-II patients.

Acknowledgments
This study was awarded a Politzer Prize at the 26th Politzer Society meeting in Cleveland, Ohio, U.S.A, 2007.

The authors wish to thank a registered statistician, Dr. Yamagiwa (certified number: 0540072) for his helpful advice about statistical analysis. This study was supported by the Foundation from Osaka University, School of Medicine.

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