



ORIGINAL ARTICLE

## Glucocorticoid influence on prognosis of idiopathic sudden sensorineural hearing loss<sup>☆</sup>

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Received 26 February 2013; accepted 1 February 2014

### KEYWORDS

Hearing loss, sudden;  
Prognosis;  
Audiometry;  
Primary treatment

### Abstract

**Introduction:** Idiopathic Sudden Sensorineural Hearing Loss (ISSHL) is defined when a loss of at least 30 dB occurs in over 3 continuous frequencies, in up to 72 hours, of which etiology is not established, despite adequate investigation. Different types of treatment regimens have been proposed, but only glucocorticoids have shown some evidence of benefit in the literature.

**Objective:** To analyze whether the type of treatment or time of treatment with glucocorticoids have any influence on hearing recovery in ISSHL.

**Methods:** Observational retrospective cohort study. One hundred twenty-seven patients with ISSHL, treated at outpatient clinics between the years 2000 and 2010, were studied. We evaluated the prognostic correlation of the type of treatment and time to treatment with glucocorticoids and ISSHL. **Results:** The absolute hearing gain and the relative hearing gain was as follows: 23.6 dB and 37.2%. Complete recovery was observed in 15.7% of patients, significant recovery in 27.6% and recovery in 57.5%.

**Conclusion:** In this study, there was no difference between the use and nonuse of glucocorticoids in hearing improvement. However, when started within seven days after onset, the use of glucocorticoids was a factor of better prognosis.

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### PALAVRAS-CHAVE

Perda auditiva súbita;  
Prognóstico;  
Audiometria;  
Tratamento primário

### Influência dos corticosteroides no prognóstico auditivo da perda auditiva neurossensorial súbita idiopática

### Resumo

**Introdução:** A perda auditiva neurossensorial súbita idiopática (PANSSI) é definida pela queda dos limiares auditivos tonais de, pelo menos, 30 dB em três frequências contíguas em até 72 horas e apesar de uma investigação apropriada, a etiologia da lesão não é encontrada. Diversos tipos de tratamentos já foram idealizados para a PANSSI, no entanto, os corticosteroides são os que encontram as melhores evidências de efetividade na literatura.

<sup>☆</sup>Please cite this article as: Bogaz EA, Suzuki FAB, Rossini BAA, Inoue DP, Penido NO. Glucocorticoid influence on prognosis of idiopathic sudden sensorineural hearing loss. Braz J Otorhinolaryngol. 2014;80:213-9.

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**Objetivo:** Avaliar se o tipo de tratamento e o tempo de demora em iniciar o tratamento com corticosteroides têm correlação com a melhora dos limiares auditivos na PANSSI.

**Métodos:** Estudo de coorte retrospectivo observacional. Foram avaliados 127 pacientes com PANSSI provenientes do ambulatório entre os anos de 2000 e 2010. Foi avaliada a correlação prognóstica do tipo de tratamento e tempo de demora para o início de tratamento e a PANSSI.

**Resultados:** As taxas de recuperação absoluta e relativa foram 23,6 dB e 37,2% respectivamente. Apresentaram melhora completa 15,7% dos pacientes, 27,6% apresentaram melhora significativa e 57,5% melhora.

**Conclusão:** Neste estudo, não houve diferença entre o uso ou não de corticosteroide na melhora auditiva. Contudo, quando iniciado até sete dias, o uso de corticosteroide foi fator de melhor prognóstico.

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## Introduction

Sudden sensorineural hearing loss (SSHL) is defined when a loss of sensorineural thresholds of at least 30 dB occurs in over 3 continuous frequencies, within a period ranging from minutes of up to 72 hours.<sup>1,2</sup> The incidence of SSHL ranges from 5 to 20 individuals per 100,000 people a year.<sup>2</sup>

When the investigation includes an etiological diagnosis, it is categorized as a case of SSHL with known cause and should receive special treatment, as in schwannomas, degenerative diseases of the central nervous system (multiple sclerosis), syphilis, Lyme borreliosis and others. One must always seek to establish an etiology and specific treatment. The cases of undetermined etiology are classified as idiopathic sudden sensorineural hearing loss (ISSHL), and in this situation, there are some theories concerning the etiopathology such as vascular injury, ruptured membranes of the inner ear, viral or bacterial infection, autoimmuneantibody lesion.<sup>3-6</sup>

Systemic corticosteroids have been used in clinical practice as a primary treatment of ISSHL; however, there is a lack of consistent data on its effectiveness.<sup>1,7,8</sup> Corticosteroid therapy is started as early as possible, with high doses of the drug by oral or parenteral route, maintained for up to two weeks, after which it is gradually withdrawn. Several other forms of treatment have been or are being used and studied, such as plasma expanders, carbogen, antiviral therapy, hyperbaric oxygen, antioxidants such as minerals and vitamins, but with less statistical evidence of efficacy than systemic corticosteroids.<sup>1,8-11</sup>

In addition to the doubt regarding the efficacy of corticosteroids in ISSHL, spontaneous recovery of hearing thresholds occurs in 32% to 65% of cases according to Mattox et al.<sup>12</sup> These patients would not likely benefit from the use of high doses of corticosteroids.

This study aims to evaluate the impact of time delay in initiating therapy with corticosteroids, and the type of treatment performed, on prognosis of hearing recovery in patients with ISSHL.

## Methods

Patients were evaluated based on an observational retrospective cohort study. Individuals from the Outpatient Clinic of ISSHL, treated between 2000 and 2010 who had idiopathic sudden sensorineural hearing loss were assessed.

This study was approved by the Ethics Committee, under the CEP protocol number 0715/11.

## Inclusion and exclusion criteria

Patients included in this study had unilateral ISSHL of at least 30 dB in at least three consecutive frequencies occurring within 72 hours. They were treated at the Outpatient Clinic of ISSHL for at least 2 months and by that time exhibited hearing recovery stabilization, or normalization of hearing. Patients treated with different types of therapeutic approaches were followed. The standard treatment, when used, was oral prednisone 1 mg/kg/day, with a maximum daily dose of 60 mg for at least 7 days, followed by gradual drug tapering.

Some patients received Pentoxifylline at a dose of 1,200 mg/day divided into 3 doses for 2 months, either combined with corticosteroids or as a single treatment. Patients who did not receive any drug therapy had known contraindication to medication or refused treatment. Treatment with Pentoxifylline was used in the first years of this study and subsequently abandoned for lack of evidence of effectiveness.<sup>10</sup>

The study excluded patients with a history of middle and inner ear diseases and those whose etiology was defined as trauma, infection, Meniere disease, retrocochlear diseases, exposure to ototoxic drugs, perilymphatic fistula, barotrauma, middle or inner ear malformations and history suggestive of mumps, among others.

Bilateral cases, patients with intermittent hearing loss were also excluded, as were those with hearing loss in the contralateral ear that prevented the calculation of recovery rates (contralateral loss higher than the current ISSHL), and those who started follow-up after 90 days of hearing loss onset.

## Patient assessment

Patients who met the inclusion criteria underwent a detailed history and otorhinolaryngological examination.

The following clinical data were analyzed: gender, date of hearing loss onset, concomitant symptoms such as tinnitus, vertigo, ear pain and ear fullness, presence of comorbidities, such as hypertension, diabetes mellitus, glaucoma, thyroid alterations and habits; drug use and audiometric parameters; previous episodes of hearing loss and family history.

Auditory assessment of patients was performed with an MA 41 audiometer, calibrated annually by a competent company, manufactured by DBA Maico Diagnostics, Minne-

sota, USA. Initial audiometric thresholds were obtained, which coincided with the start of treatment/follow-up, as well as the final ones, with the latter being obtained after at least two months of the initial audiometry and hearing improvement had stabilized, or earlier in case of threshold normalization.

The patients were also submitted to laboratory tests that included blood count, measurement of lipids, serum fasting glucose, renal and thyroid function, erythrocyte sedimentation rate. Serological tests for syphilis, AIDS, Lyme borreliosis were also performed, when deemed necessary.

In suspected cases, screening for autoimmune diseases was performed. A total of 87 patients underwent magnetic resonance imaging of peripheral and central auditory pathways.

### Calculating the means of affected frequencies

The arithmetic means of pure tone audiometry (PTA) were obtained at the beginning and end of follow-up in all patients, using the following method: arithmetic means of pure tones for each patient, according to the group of affected frequencies. When low and middle frequencies were affected, the arithmetic means of 0.25, 0.5, 1 and 2 kHz were obtained; when middle and high frequencies were affected, the arithmetic means of 1, 2, 3, 4, 6, 8 kHz were obtained; when only high frequencies were affected, the arithmetic means of 3, 4, 6 and 8 kHz were obtained; when low, middle and high frequencies were affected, the mean of all 8 frequencies was obtained. PTA was also calculated by averaging the frequencies affected in the contralateral ear of each patient, according to the frequency group of the affected ear. When severe hearing loss thresholds were not detected, the maximum audiometer threshold of 120 dB was considered as response.

### Calculating recovery rates

To obtain the absolute and relative rates of hearing recovery we took into account the non-affected side, according to the following formulas:

Absolute recovery rate of PTA (dB):

$$\frac{(\text{initial PTA in affected ear} - \text{initial PTA in non-affected ear}) - (\text{final PTA in affected ear} - \text{final PTA in non-affected ear})}{\text{initial PTA in affected ear} - \text{initial PTA in non-affected ear}}$$

Relative recovery rate of PTA (%):

$$\frac{(\text{initial PTA in affected ear} - \text{initial PTA in non-affected ear}) - (\text{final PTA in affected ear} - \text{final PTA in non-affected ear})}{\text{initial PTA in affected ear} - \text{initial PTA in non-affected ear}} \times 100$$

### Hearing improvement criteria by pure tone audiometry

For the analysis of hearing improvement, an increase in the arithmetic mean of pure tones (final PTA - initial PTA) was considered and the change in functional category, as follows: normal hearing and mild, moderate, severe and profound losses.

**Improvement:** Change of functional category and improvement  $\geq 15$  dB.

**Significant improvement:** When there was improvement and the final hearing loss was mild.

**Complete improvement:** When there was improvement and hearing thresholds returned to normal. ( $\leq 25$  dB).

### Treatment assessment

The following factors were evaluated in the treatment, based on the rates of hearing recovery and degree of improvement.

1. Type of treatment performed:

Regarding the type of treatment performed, patients were categorized according to the drug used in treatment: corticosteroids alone; corticosteroid + Pentoxifylline, Pentoxifylline only and no treatment.

2. Time in days until the start of treatment:

Regarding the time for start of treatment, days until corticosteroid therapy start were considered, categorized as: up to 2 days, 3 to 7 days, 8 to 10 days, > 10 days, no treatment. Patients who used Pentoxifylline only were allocated in the group without treatment.

There was no randomization for allocation of patients to the different treatment categories, which was decided based on clinical indication, as well contraindications, patient refusal, inability to treat and others. Patients were not matched by age, gender, presence of comorbidities, audiometric parameters, and other possible prognostic factors in group categorization.

Statistical methodology: the Chi-square tests were used, indicated to verify differences in the distribution of a categorized characteristic (2 or more categories) relative to another categorized characteristic, and ANOVA to compare 3 or more groups of data with numerical measurement, with a statistical significance level of  $p < 0.05$ .

## Results

A total of 277 patients with sudden sensorineural hearing loss treated at the ISSHL Outpatient Clinic were assessed between 2000 and 2010. Of these, 8 patients did not meet the criteria for ISSHL definition. Ten patients had bilateral hearing loss and in 33 (12%) the hearing loss etiology was established. Seventy-five patients were lost to follow-up and informed consent for treatment information use was not obtained in 24. Thus, 127 patients that met the inclusion criteria for unilateral ISSHL were included in the study.

The minimum age of the population was 12 and the maximum 82 years, with a mean of 48 years. Of the patients, 64 were females and 63 males. The right side was involved in 46.5% of cases and the left in 53.5%. Smoking was recorded in 11% of cases, hypertension in 34.6%, diabetes in 15% and dyslipidemia in 11%. The following were present in cases of personal history: disease in 9.4%, stroke in 2.4%, hypothyroidism in 6.3% and renal failure in 3.1%. Tinnitus was the most common associated symptom in 92.1% of cases.

Vertigo was observed in 52.8% of cases and 43.3% had ear fullness. A total of 87 patients underwent MRI assessment.

The mean initial and final PTA and rates of hearing recovery in the sample are shown in Tables 1 and 2.

According to the criteria adopted, there was improvement in 57.5%, a significant improvement in 27.6%, and full improvement in 15.7%.

**Table 1** Mean initial and final pure tone audiometry (PTA) values in ears (dB).

	Initial PTA affected side	Final PTA affected side	Initial PTA normal side	Final PTA normal side
Mean	84.68	59.29	17.63	15.89
Median	83.75	60.00	16.25	14.37
Minimum	37.50	1.66	1.87	0.00
Maximum	120.00	120.00	52.50	54.37
SD	22.38	31.54	9.78	10.52
n	127	127	127	127

SD, standard deviation.

**Table 2** Mean rates of hearing recovery in the population.

	Absolute PTA recovery in dB	Relative PTA recovery in (%)
Mean	23.64	37.21
Median	20.62	32.14
Minimum	-32.50 <sup>a</sup>	-73.23 <sup>a</sup>
Maximum	105.00	115.38
SD	24.04	36.23
n	127	127

SD, standard deviation.

<sup>a</sup>Negative values show poorer thresholds in relation to the initial one.

### 1. Type of treatment performed

PTA reduction and the rates of recovery were analyzed, taking into consideration the type of treatment (Tables 3 and 4).

There was no statistically significant difference in PTA reduction and recovery rates in the different groups. However, there is statistical evidence that the groups that used corticosteroids had lower final PTA and higher recovery rates.

### 2. Time in days until start of treatment

It was observed that the initial PTA was statistically similar in the different ranges of days until the start of treatment. As for the absolute reduction in PTA, there was no statistical difference in the 3 groups that started treatment in up to 10 days. There were smaller reductions in PTA for those who were treated after more than 10 days or had no treatment. For the absolute rate of hearing recovery, untreated cases showed less improvement than the ones that started treatment in up to 7 days.

For the relative rate of hearing recovery, patients who started treatment within 7 days had higher recovery than untreated ones or the ones that started treatment after seven days, with statistical significance. Patients that started treatment before 7 days showed PTA reduction with high significance ( $p < 0.0001$ ) (Tables 5 and 6).

**Table 3** Means of the initial and final PTA (dB) between the different types of treatment performed and ANOVA.

Type of treatment		PTA of affected side	
		Initial	Final
Corticosteroids only	Mean	82.39	52.33
	Standard deviation	23.10	31.43
	n	33	33
Corticosteroids+Pentoxifylline	Mean	85.60	58.10
	Standard deviation	22.26	31.46
	n	66	66
Pentoxifylline only	Mean	97.00	83.13
	Standard deviation	22.29	21.36
	n	10	10
Notreatment	Mean	78.72	63.19
	Standard deviation	20.30	32.26
	n	18	18

Effect p-value

Treatment	0.0817
PTA (initial × final)	< 0.0001
Treatment × PTA	0.0742

**Table 4** ANOVA tests between categories of treatment for recovery rates.

		Type of Treatment				ANOVA p	Outcome
		Corticosteroids only	Corticosteroids + Pentoxifylline	Pentoxifylline only	No treatment		
Absolute PTA recovery (dB)	Mean	28.79	25.66	12.00	13.30	0.052	Similar
	Standard deviation	27.64	23.34	12.45	20.52		
	n	33	66	10	18		
Relative PTA recovery (%)	Mean	43.79	40.16	14.76	26.82	0.075	Similar
	Standard deviation	39.08	35.09	13.96	38.94		
	n	33	66	10	18		

**Table 5** Means of the initial and final PTA (dB) for time (in days)until treatment start.

Time of treatment		Moment	
		Initial	Final
Notreatment	Mean	85.25	70.31
	Standard deviation	22.47	30.03
	n	28	28
Up to 2 days	Mean	87.83	51.73
	Standard deviation	23.94	29.19
	n	21	21
3 to 7 days	Mean	82.74	51.61
	Standard deviation	20.69	33.01
	n	38	38
8 to 10 days	Mean	76.59	50.81
	Standard deviation	23.20	26.89
	n	11	11
Morethan 10 days	Mean	87.50	67.41
	Standard deviation	23.54	30.99
	n	29	29

Effect	p-value
Time of treatment	0.2057
PTA (initial × final)	< 0.0001
Time of treat. × PTA	0.0111

**Table 6** ANOVA tests between the categories of time in days until treatment start and hearing recovery rates.

		Time of treatment					ANOVA p	Outcome
		No treat.	Up to 2 days	2 to 7 days	8 to 10 days	More than 10 days		
Absolute PTA recovery (dB)	Mean	12.83	33.98	29.85	24.02	18.35	0.008	(No treat.) < (up to 2) = (2 to 7)
	Standard deviation	17.81	23.08	24.57	15.17	27.51		
	n	28	21	38	11	29		
Relative PTA recovery (%)	Mean	22.51	50.07	48.51	44.60	24.49	0.004	(up to 2) = (2 to 7) > (> 10) = (no treat.)
	Standard deviation	32.47	31.33	39.27	27.55	34.35		
	n	28	21	38	11	29		

**Discussion**

The interpretation and comparison of studies on treatment and prognostic factors in ISSHL remains a challenge to date, as most of them use different methodologies and criteria for evaluation of hearing recovery. Some studies evaluate PTA through three frequencies (0.5, 1, 2 kHz),<sup>12</sup> 4 frequencies (0.5, 1, 2, 4 kHz),<sup>13</sup> 6 frequencies (0.25, 0.5, 1, 2, 4, 8 kHz),<sup>14</sup> and others use the mean of all frequencies. There are tests that assess only the mean of the frequencies affected by hearing loss.<sup>15</sup>

In a previously performed study, which analyzed the different methodologies used in the assessment of ISSHL, In-

oue et al. found that when using the mean of 6 frequencies (0.25, 0.5, 1, 2, 4, 8 kHz), 8 frequencies (0.25, 0.5, 1, 2, 3, 4, 6; 8 kHz) and affected frequencies, the same power of assessment is obtained, without statistical differences between these means.<sup>16</sup> However, this same analysis did not compare the means of 3 and 4 frequencies, used in several studies in the past, which targeted low and middle frequencies. The choice in this study was the use of PTA calculation through the affected frequencies, as we believe it is more representative individually, as it prevents disregarding the calculation of affected frequencies and also the inclusion of other non-affected frequencies, thus underestimating the extension of loss expressed by the mean.

In the same study, Inoue et al., evaluated the different *improvement criteria* used in the literature. It was observed that criteria that consider a *significant improvement* in which the patient's final result is a minimum mild hearing loss can measure more accurately a significant increase of the individual's hearing. This is due to the fact that, with a mild hearing loss, one can often attain a natural adaptation to this new condition, with less chance of needing individual sound amplifiers or other types of hearing aids. For these reasons, we chose to use the same *improvement criteria* that Inoue et al. in this study, which were described in the previous section.

We also chose to evaluate the time until the start of treatment with corticosteroids as a prognostic factor, and the use or not of corticosteroids in the treatment, since this is the main and most widespread form of therapy used today in ISSHL, even though doubts about its effectiveness remain.

The mean rates of absolute and relative recovery in this sample were respectively, 23.7 dB and 37.2%. A total of 57.5% of patients had some type of improvement and only 27.6% showed significant improvement, i.e., at the end of the follow-up, these patients had mild hearing loss or normal hearing (full improvement = 15.7%). Cvorovic et al. in 2008 studied 541 patients with ISSHL and found similar rates of recovery of 15.1 dB and 47%.<sup>17</sup> However, their rate of patients with significant improvement (final PTA < 40 dB) was 57%. Xenellis et al., in 2006, found complete recovery rates of 37.7% of cases.<sup>18</sup> In this study, the absolute rate of recovery of the studied population was 24.3 dB and the mean final PTA of the population was 47.7 dB, whereas in this sample, the mean final PTA was 59.2 dB.

When analyzing the recovery rates of studied patients and not considering the time until the start of treatment, it was observed that patients treated with corticosteroids did not show a statistically significant recovery that was better than no treatment, although the analysis shows a trend that treatment is better. Wei et al. performed a review of clinical trials and concluded that there is insufficient evidence to confirm or rule out the efficacy of corticosteroids in ISSHL.<sup>19</sup> Other studies, including prospective, randomized, double-blind clinical trials suggest the benefit of corticosteroid therapy for SSSL. 1.<sup>20-24</sup>

Corticosteroids are drugs with potent anti-inflammatory and even immunosuppressive action, acting at an early stage of the inflammatory cascade. ISSHL occurs due to damage to the auditory system, the cause of which is still unknown. There are several theories to explain this injury: viral infection, ruptured membranes of the inner ear, vascular aggression, autoimmune attack to the vestibule, and others,<sup>3-6</sup> and all have inflammatory aggression involved in their pathogenesis.

Several types of treatment have been devised, with the systemic use of corticosteroids being the most often employed, as it would treat the inflammatory process, which is the final pathway of aggression in all these physiopathological mechanisms. In 2007, in the meta-analysis by Collins et al., which included five randomized trials, no evidence was found that corticosteroids have better performance than placebo or other therapies in ISSHL. However, systemic or intratympanic, corticosteroid therapy is the only therapy that maintains the recommendation in the latest consensus of the American Academy of Otolaryngology in ISSHL.<sup>8</sup>

The analysis of this sample indicates that different types of treatment, not taking into account the time of its onset, showed no statistical difference in the degree of improvement. However, groups using corticosteroids were the only ones that showed a trend toward greater recovery when compared to the ones that effectively had no treatment. Patients who received Pentoxifylline were allocated to treatment groups, according to the use or nonuse of corticosteroids and were therefore assessed, but disregarding its use as an effective treatment.

Probst et al., in a prospective, randomized, double-blind study, evaluated 331 cases of ISSHL and acoustic trauma, treated in three groups with infusions of Pentoxifylline, dextran and saline solution, and found no statistical difference in improvement between these medication groups and the placebo group.

In this sample, as in other studies, there was a good correlation between the time until the start of treatment and prognosis, as shown by the statistical analysis.<sup>17,18,20,25-29</sup>

The time until the start of treatment took into account the days until the corticosteroid therapy was initiated, which in almost all cases, coincided with the day the patient was included in our protocol and the initial audiometry. It was observed that PTA at the beginning of the follow-up was similar in the different ranges of days before the start of treatment, indicating that the initial degree of hearing loss was similar in the different groups. There was no statistical difference in PTA reduction in the three groups that started treatment within 10 days.

However, there were lower reductions in PTA for those who started treatment after more than 10 days or had no treatment. Patients who started treatment before seven days showed reduced PTA with high significance ( $p < 0.0001$ ). In addition, it is clearly observed that patients who started treatment before 7 days showed better rates of absolute and relative recovery when compared to those who started treatment in the categories more than 7 and 10 days. This fact might have influenced the lack of statistical significance that occurred when both treatments were compared, as in this analysis, patients who used corticosteroids were allocated into a group that did not take into account the time until the start of treatment.

There was no statistical difference in recovery rates in patients who started treatment with corticosteroids before 48 hours or in up to 7 days, indicating that the drug has similar efficacy if started within 7 days. Huy et al. found no benefit with early treatment when compared to individuals that started corticosteroid therapy after 2 or even 3 to 7 days. The same study, however, did not evaluate any patient that started treatment with corticosteroids after 7 days. Few analyses found no correlation between time of start of treatment and prognosis.<sup>13,30</sup>

Although the statistical data indicate a significant influence of the time until the start of treatment with corticosteroids as an important prognostic factor in the analysis of these patients, there is a point that cannot be ignored.

According to Mattox et al., one to two thirds of patients with ISSHL show spontaneous improvement without treatment, a figure that is close to our improvement rate of 57.5%. When considering that patients who started treatment and, in this case, had the initial audiometry after 10 days of evolution, this can lead us to think that these patients have already undergone a significant period in which

there have been partial improvement in audiometric thresholds, and, thus, the potential for improvement in these patients becomes smaller, which impairs the analysis of the real influence of corticosteroids in this category.

This is confirmed by the study of Ito et al. that evaluated 90 patients with ISSHL and which group of patients showed improvement of more than 50% in hearing thresholds in the first 2 weeks of evolution and showed better final hearing recovery.<sup>31</sup> This shows that many patients have a significant recovery of thresholds in the first and second weeks, making those treated after 10 days, which have already shown some recovery, have a lower potential for hearing gain than those assessed at onset or, those who have not had significant recovery of thresholds fail to do so successfully. In addition, patients who start treatment and evaluation in early days of the picture may not be necessarily improving due to treatment itself, as the rates of spontaneous recovery, mentioned before, are close to the rates of improvement in treated patients.

As it is not possible to detect the specific etiology for each individual with ISSHL, these patients will possibly have distinct etiologies, and this factor will certainly compromise the analysis and final comparison of hearing recovery in these individuals. There are still many questions regarding the pathogenesis of ISSHL that need to be clarified scientifically.

## Conclusion

In this study there was no statistically significant improvement in hearing recovery rates among individuals with ISSHL treated or not with corticosteroids, in general. However, when this treatment was instituted within seven days of onset, the use of corticosteroids was significantly better in relation to recovery of hearing thresholds.

## Conflicts of interest

The authors declare no conflicts of interest.

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