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Prognostic Factors in Sudden Sensorineural Hearing Loss

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Background: Sudden sensorineural hearing loss (SSNHL) is still a complex and challenging process which requires clinical evidence regarding its etiology, treatment and prognostic factors. Therefore, determination of prognostic factors might aid in the selection of proper treatment modality.

Aims: The aim of this study is to analyze whether there is correlation between SSNHL outcomes and (1) systemic steroid therapy, (2) time gap between onset of symptoms and initiation of therapy and (3) audiological pattern of hearing loss.

Study Design: Retrospective chart review.

Methods: Patients diagnosed at our clinic with SSNHL between May 2005 and December 2011were reviewed. A detailed history of demographic features, side of hearing loss, previous SSNHL and/or ear surgery, recent upper respiratory tract infection, season of admission, duration of symptoms before admission and the presence of co-morbid diseases was obtained. Radiological and audiological evaluations were recorded and treatment protocol was assessed to determine whether systemic steroids were administered or not. Treatment started ≤5 days was regarded as "early" and >5 days as "delayed". Initial audiological configurations were grouped as "upward sloping", "downward sloping", "flat" and "profound" hearing loss. Significant recovery was defined as thresholds improved to the same level with the unaffected ear or improved ≥30 dB on average. Slight recovery was hearing improvement between 10-30dB on average. Hearing recovery less than 10 dB was accepted as unchanged.

Results: Among the 181 patients who met the inclusion criteria, systemic steroid was administered to 122 patients (67.4%), whereas 59 (32.6%) patients did not have steroids. It was found that steroid administration did not have any statistically significant effect in either recovered or unchanged hearing groups. Early treatment was achieved in 105 patients (58%) and 76 patients (42%) had delayed treatment. Recovery rates were no different in these two groups; however, when unchanged hearing rates were compared, it was statistically significantly lower in the early treatment group ($p<0.05$). When hearing outcomes were compared according to initial audiological pattern, significant recovery and unchanged hearing rates did not differ between groups; however, slight recovery rate was highest in the "flat" type audiological configuration ($p<0.05$).

Conclusion: According to this patient series, oral steroid therapy does not have any influence on the outcomes of SSNHL. However, mid-frequency hearing loss of flat type and initiation of treatment earlier than 5 days from the onset of symptoms, seem to have positive prognostic effects. Further randomized controlled subject groups might contribute to determine prognostic factors of SSNHL.

Keywords: Audiological configuration, delayed treatment, prognostic factors, sudden sensorineural hearing loss, systemic steroids

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Sudden sensorineural hearing loss (SSNHL) is defined as an acute onset, within a 72-hour period, with loss over 30 dB, in at least three consecutive frequencies in one or both ears (1-3). However, in clinical practice, the definition is expanded to cases with less than 30 dB loss or in 2 consecutive frequencies (1,4). SSNHL is usually unilateral in 98-99% of cases (5-7). The incidence of SSNHL is reported as 5-20/100,000 per year (7). Spontaneous recovery rates are reported to range from 32-70% by different authors (8-10).

Etiology of SSNHL is controversial (1,3,5,7,8,11). Perilymphatic fistula, vestibular schwannoma, multiple sclerosis are some of the well-known causes (3,5,8). Also, certain drugs such as phosphodiesterase-5 inhibitors, ribavirin and interferon-α are among the rare causes of SSNHL (11,12). Approximately 85-90% of SSNHL cases are considered idiopathic and possible etiologic factors including infections (especially viral), autoimmune diseases and alterations of microcirculation (1,3,6,8,11). As the majority of patients have idiopathic SSNHL, treatment options also depend on hypotheses. Steroids, rheological agents, vasodilators, antiviral agents, vitamin-electrolyte complexes, anticoagulants and hyperbaric oxygen therapy are being used for SSNHL in form of "gun-shot" therapy (3,10,13-16).

Sudden sensorineural hearing loss is a sophisticated process with multiple possible etiologies and treatment modalities. None of the treatment options have superiority on the others in randomized clinical trials (6,7,11,16). Certain prognostic factors have been defined for SSNHL. Increased age of the patient, presence of vestibular symptoms, accompanying systemic diseases, such as diabetes, hypertension, and hypercholesterolemia, severity of initial hearing loss, longer period between the onset of symptoms and initial therapy are known as poor prognostic factors (6,16).

The aim of this study is to analyze whether there is a correlation between SSNHL outcomes and (1) systemic steroid therapy, (2) time gap between onset of symptoms and initiation of therapy and (3) audiological pattern of hearing loss.

MATERIALS AND METHODS

A retrospective chart study was performed involving patients diagnosed with SSNHL between May 2005 and December 2011 in an otolaryngology clinic of a university hospital. Approval from the local ethical committee of the university was obtained before the study was conducted (GO 14/582).

All subjects with SSNHL who completed full course treatment and attended follow-up examinations were included in the study. The age of the patients was not an exclusion criteria; both adults and children were enrolled in the study group. Patients without radiological and follow-up audiological evaluations were not included. When these assessments were not available from the files, those patients were also excluded. Patients were reviewed in terms of demographic features, side of hearing loss, previous history of SSNHL and/ or ear surgery, recent history of upper respiratory tract infection, season at admission, duration of symptoms before admission, radiological evaluation and results, exploration surgery with suspicion of perilymphatic fistula and results, presence of co-morbid diseases (such as diabetes mellitus, hypertension and other systemic diseases), initial pattern of audiogram, and audiological evaluation at initiation and at the end of the treatment.

The standard radiological tool was magnetic resonance imaging (MRI); however, temporal computed tomograpy (CT) was also obtained from certain patients (e.g. suspicion of perilymphatic fistula or inner ear anomaly) if indicated.

Our department's routine treatment protocol consisted of intravenous 5mg/kg low molecular weight dextran (Rheomacrodex, Eczacıbaşı-Baxter; İstanbul, Turkey), 24 mg peroral betahistine (Betaserc, Abbott Healthcare SAS; Chalarone, France) and 20 mg trimethazidine (Vastarel, Servier Laboratories; Suresnes, France) twice daily, with 200 mg oral acyclovir (Zovirax, GlaxoSmithKline; Abbotsford, Victoria, Australia) 5 times daily. Also, if there were no contraindications, 1 mg/kg oral prednisolone (Deltacortril, Pfizer; New York, USA) which was tapered by 10 mg every three days was administered together with 30 mg lansoprozol (Lansoprol, Nobel; İstanbul, Turkey) twice daily. The patients who had uncontrolled diabetes mellitus, coronary heart disease, hypothyroidism, hyperlipidemia, chronic kidney disease and schizophrenia were regarded as contraindications to systemic steroid administration according to internal medicine consultation. The group of patients with uncontrolled diabetes were told that during systemic steroid administration, usually insulin treatment will be required instead of oral antidiabetics and in certain patients insulin might be used for prolonged periods after steroids were stopped. The patients who refused to tale systemic steroids were placed in the steroid-free group. One patient had a recent history of acute myocardial infarction; therefore, systemic steroid was contraindicated to not prevent cardiac remodeling and healing of the myocardial tissue. Another patient had refractory hypertension due to hypothyroidism which again contraindicated systemic steroid usage. The patient with hyperlipidemia had an accompanying heart failure in whom systemic steroids were considered to lead to hypervolemia, so the patient with chronic kidney failure was also therefore avoided. Lastly, the schizophrenic patient had a previous history of systemic steroid administration which aggravated psychotic symptoms, so the hearing loss treatment was steroid-free.

Time elapsed between onset and treatment initiation was also derived from the records. Treatment initiation ≤5 days was regarded as "early" and >5 days as "delayed", arbitrarily.

The audiograms were performed on initial admission and at the end of treatment on the 10th day. Pure tone audiogram (PTA) from 250 Hz to 4000 Hz was taken into consideration for the comparison of groups. The types of initial audiograms were classified as: upward-sloping type (hearing loss more severe in low frequencies), downward-sloping type (hearing loss more severe in high frequencies), flat type (no more than 10 dB deviation on PTA thresholds) and profound type (PTA thresholds worse than 70 dB on all frequencies).

The outcomes of hearing were categorized into 3 groups: significant recovery, slight recovery and unchanged. The significant recovery group was defined as thresholds improved to the same level as the unaffected ear or improved ≥30 dB on average. Slight recovery was hearing improvement between 10 - 30 dB on average. Hearing recovery less than 10 dB was accepted as unchanged.

For statistical analysis, Statistical Package for Social Sciences for Windows 18.0 version software (SPSS Inc.; Chicago, Illinois, USA) was used and $p<0.05$ was defined as the cut-off for statistical significance.

RESULTS

Between May 2005 and December 2011, there were 732 patients diagnosed with SSNHL and treated in our department. However, only 181 subjects met the criteria and were included in the study. In almost all patients who were excluded, either the audiological follow-up or other file data were missing. Eighty-two were female and 99 were male, with a mean age of 43.7±16.3, ranging between 2 and 90 years old. The underlying etiological factor was determined to be vestibular schwannoma in 1 patient, intracochlear hemorrhage in another adult and inner ear malformation in 5 patients; 3 patients with incomplete partition type II (IP II) together with large vestibular aquaduct (LVA) and 2 isolated LVAs. Eight subjects underwent exploration due to presumed perilymphatic fistula; in 3 of them, a round fistula was observed and repaired. Afterwards, a routine treatment protocol was also administered in these patients. In the whole group, 10 patients (5.5%) were diagnosed with an underlying etiology of SSHNL, while the remaining 171 patients (94.5%) were considered idiopathic.

The side of SSNHL was right in 83 patients (45.9%) and left in 98 patients (54.1%). Previous history of SSNHL was present in 30 patients (16.6%), while the remaining 151 patients (83.4%) were admitted at their first attack. Among those patients, 16 subjects previously experienced SSHNL on the same side, 6 subjects on the contralateral side and 8 subjects on both the same and contralateral ears.

Seventeen patients (9.4%) had a previous history of ear surgery; 4 had bilateral ventilation tube placement, 3 had stepedotomies on the contralateral side, one had undergone exploration for a presumed perilymphatic fistula on the opposite side, 2 patients had endolymphatic sac decompression and one patient had labryntectomy on the same ear due to endolymphatic hydrops, while 5 patients had a history of tympanoplasty and one patient had mastoidectomy.

The whole group was also investigated to determine whether there is a history of upper respiratory tract infection (URTI) before SSNHL; 48 patients (26.5%) claimed a recent history of URTI and 133 patients (73.5%) did not have such a history.

Seasonal distribution at the time of diagnosis was as follows: 39 patients (21.5%) were admitted in winter, 56 patients (31.5%) in spring, 39 patients (21.5%) in summer and 47 patients (26%) in autumn. It was found that there was no statistically significant difference regarding the season in which SSNHL was diagnosed (p=0.362).

Oral steroid therapy was administered to 122 (67.4%) subjects, as mentioned in our standard treatment protocol, but 59 (32.6%) patients could not be treated with oral steroid supplements due to their co-existing systemic diseases such as diabetes mellitus, coronary heart disease, hypothyroidism, hyperlipidemia, chronic kidney disease and schizophrenia. In the group given oral steroid therapy, significant recovery occurred in 20 patients (16.4%), slight recovery in 36 patients (29.5%) and unchanged hearing in 66 patients (54%); in the steroid free group, however, this was 8 patients (13.6%), 22 patients (37.3%) and 29 patients (49.2%), respectively (Table 1). For the reliability of statistics, significant and slight recovery were considered together in each group. It was found that steroid administration did not have any statistically significant effect, neither in recovery nor in the unchanged groups (p=0.653).

Time of initiation of treatment was considered to be another probable prognostic factor of SSNHL outcome in the study. Mean time elapsed between the onset of symptoms and start-

TABLE 1. Hearing outcomes in steroid received and steroid free groups. Steroid administration does not have statistically significant effect on hearing outcomes (p=0.653).

		Response to therapy			
Peroral steroid therapy		A	B	C	Total
Steroid positive	N	20	36	66	122
	percent	16.4	29.5	54.1	100.0
Steroid free	N	8	22	29	59
	percent	13.6	37.3	49.2	100.0
Total	N	28	58	95	181
	percent	15.6	31.7	52.8	100.0

A: significant recovery; B: slight recovery; C: unchanged hearing; N: number of patients

ing treatment was 6.8 days; this ranged from a few hours to 30 days. The cut-off value was determined to be 5 days. There were 105 subjects (58%) admitted to our center on day 5 or earlier. On the other hand, 76 patients (42%) started their therapy after 5 days. In the early treatment group, 21 patients (20%) achieved significant recovery, 36 patients (34.3%) showed slight recovery and 48 patients (45.7%) had unchanged hearing at the end of the therapy, whereas these rates were 7 patients (9.2%), 22 patients (28.9%) and 47 patients (61.8%), respectively, in the group experiencing delayed treatment (Table 2). Again, in order to gain reliable statistical results, significant and slight recovery were combined. The recovery rate difference between early and delayed treatment groups was not statistically significant. However, when patients with unchanged hearing were compared, starting SSNHL therapy in the first 5 days was found to have a statistically significant positive prognostic effect ($p<0.05$).

All patients underwent audiological assessment with PTA at the time of referral and on the 10th day, at the end of treatment. The initial audiograms were grouped as upward-sloping, downward-sloping, flat and profound types. Forty-one patients (22.7%) had upward-sloping, 47 patients (26%) had downward-sloping, 54 patients (29.8%) flat type and 39 patients (21.5%) had profound hearing loss. According to audiological configuration, the distribution of subjects did not show any statistically significant difference ($p=0.245$). Significant recovery rates were 9.8% in upward-sloping, 19.1% in downward-sloping, 16.7% in flat and 15.4% in profound type. Significant recovery rates of all four groups did not have any statistically significant difference ($p=0.463$). Slight recovery rates were 34.1% in upward-sloping, 27.7% in downward-sloping, 42.6% in flat and 20.5% in profound type. Slight recovery rate was highest in flat type audiogram and the difference was statistically significant ($p=0.045$). The unchanged hearing rates were 56.1% in upward-sloping, 53.2% in downward-sloping, 40.7% in flat and 64.1% in profound type of SSNHL. Unchanged hearing in these audiological configurations did not differ significantly ($p=0.963$) (Table 3).

TABLE 2. Hearing outcomes according to 4 different types of audiological configurations. Slight recovery rate was found to be statistically significantly better compared to other configurations ($p=0.045$). Significant correlation did not exist with the other types.

Type of hearing loss (initial audiogram)		Response to therapy A	B	C	Total
1 (Upward)	N	4	14	23	41
	Percent	9.8	34.1	56.1	100.0
2 (Downward)	N	9	13	25	47
	Percent	19.1	27.7	53.2	100.0
3 (Flat)	N	9	23	22	54
	Percent	16.7	42.6	40.7	100.0
4 (Profound)	N	6	8	25	39
	Percent	15.4	20.5	64.1	100.0
Total	N	28	58	95	181
	Percent	15.5	32.0	52.5	100.0%

A: significant recovery; B: slight recovery; C: unchanged hearing; N: number of patients

TABLE 3. Correlation of hearing outcomes and early and delayed treatment. The rate of unchanged hearing was statistically significantly lower in early treatment group ($p<0.05$).

Time to start therapy		Response to therapy A	B	C	Total
≤5 days	N	21	36	48	105
	Percent	20.0	34.3	45.7	100.0
>5 days	N	7	22	47	76
	Percent	9.2	28.9	61.8	100.0
Total	N	28	58	95	181
	Percent	15.5	32.0	52.5	100.0

A: significant recovery; B: slight recovery; C: unchanged hearing; N: number of patients

DISCUSSION

Sudden sensorineural hearing loss is a sophisticated process with multiple possible etiologies and treatment modalities. Approximately 85-90% are considered idiopathic. Similarly, in this study, 94.5% of the cases were found to be idiopathic (1,3). Perilymphatic fistulae and inner ear abnormalities were the two most common etiological factors in this series, which are also widely known. Thirty patients had a history of a previous SSNHL attack, which is usually suggestive of underlying endolymphatic hydrops pathophsyiology. Surprisingly, patients with LVAs did not have a previous history of hearing loss. However, it is probable that these patients will be admitted with repeating attacks due to the transmission of increased intracranial pressure through the enlarged vestibular aquaduct. Recently, viral etiological factors have been emphasized in etiology of SSNHL. Therefore, a preceding history of URTI was also obtained from patients in the study. It was revealed that almost ¾ of the subjects did not have such infection before the hearing loss. However, it is probable that the infection may be asymptomatic at certain times; therefore, this rate might actually be higher. It is also thought that in seasons in which URTI prevalence increases, it is more likely to experience SSNHL. Thus, the patients were evaluated to assess whether there is a seasonal abundance of diagnosis; however, such influence of the season was not determined in this study. Series with a higher number of subjects may help to clarify this issue.

None of the treatment options have been proven to be superior to each other in randomized clinical trials of SSNHL (6,7,11,16). Although more than 60 treatment modalities have been described, there is no consensus about the treatment

modality of choice (4). Steroids (systemic or intratympanic), rheological agents, vasodilators, antiviral agents, vitamin-electrolyte complexes, anticoagulants and hyperbaric oxygen therapy are the most commonly used treatment modalities for SSNHL treatment, in different combinations (3,10,14-16). Moreover, the necessity of the treatment is still controversial due to spontaneous recovery rates ranging from 32% to 70% in the literature (1,6,8-10). However, most of the time, hearing loss does not recover without treatment, and up to 10% of the cases may experience worsening of hearing despite treatment; therefore, clinicians usually do not take the risk of leaving the patient untreated (3,6,7). Multidrug therapy, also known as "shotgun" therapy, is the most common treatment of choice in SSNHL (6,17).

This uncertainty leads to the investigation of efficacy of commonly used agents, particularly systemic steroids. The randomized controlled study by Wilson et al. (2) in 1980 is known as a milestone in SHL treatment as high dose systemic steroid therapy, either oral, intravenous or parenteral, has been considered standard therapy (13). Although the exact mechanism is unknown, corticosteroids are thought to improve hearing loss by suppressing immune response, improving the decreased microcirculation, and reducing inflammation, edema and endolymphatic pressure in inner ear (14,15). On the other hand, there are some conflicts about the efficacy of systemic steroid therapy in SHL. Some authors discovered that steroids have no therapeutic advantage over placebo (3,8,9,16. It was also claimed in studies by Wilson et al. (2) and other researchers that the cure rates are roughly equal to the spontaneous cure rate (32-70%) (3).

Therefore, in this study, the role of systemic steroids on outcomes was evaluated. When hearing recovery was compared between steroid-administered and steroid-free groups, recovered or unchanged subject ratios were not statistically significant in both groups. On the other hand, the recovery rates of both groups are also consistent with spontaneous healing or placebo treatment results of the literature. It is always probable that there are a certain number of subjects in either group who recovered spontaneously. However, as it is extremely difficult to homogenize patient populations of SSNHL, outcomes with different agents or with combination treatments constitute wide ranges. Even with large series, it is not easy to achieve solid conclusions. One of the limitations of our patient group is again problem of heterogeneity. For instance, it is probable that pediatric patient group or endolymphatic hydrops cases might respond to identical treatment protocols differently. Moreover, certain systemic diseases such as diabetes mellitus, hyperlipidemia or hypertension which were also existent in our patient group are known risk factors for SSNHL. These co-morbidities might interfere with the microvascular supply of the inner ear and lead to hearing loss. Although their effect on prognosis of the disease is not well established, it may be speculated that negative prognostic effect may occur (17,18). Thus, despite steroids seeming to have no additional benefit in this paper, studies on more homogenous patient populations might contribute to the knowledge.

The severity of initial hearing loss has been associated with poorer prognosis in SSNHL (19,20). It is generally agreed that almost all patients with >90 dB hearing loss will not recover regardless of the therapy (21). There are also some studies showing that 70-80 dB hearing loss is a cut-off level affecting the outcome of SHL therapy (20,21). Not only the severity of hearing loss, but also the configuration of the initial audiograms appears to affect the outcome (20,22). It is suggested that patients with low-frequency hearing losses - upward sloping audiograms - or mid-frequency hearing losses - flat type audiograms - may have a better prognosis (21-23). It was also suggested that low- frequency hearing losses tend to have better recoveries as they have a better tolerance of impairment (24). Another possible mechanism explaining why patients with low-frequency loss were more likely to recover is differences in the vulnerability of hair cells. Hair cells in the basal turn are known to be more susceptible to ototoxic drugs and noise than those in the apex (23,24). Therefore, despite having more glucocorticoid receptors, basal turn damage - known as high-frequency losses - have a worse prognosis (24). Thus, the prognostic effect of initial configuration of PTA on outcomes was also evaluated in this study. In our study, it was found that patients with flat type audiograms had better relative hearing gain and, although statistically insignificant, patients with profound type hearing loss had the worst prognosis. These findings are consistent with the literature mentioned above. The negative prognostic effect of profound or total hearing loss is almost agreed worldwide. However, in the literature, there are certain studies which report poor prognosis with flat type or low frequency losses which is an inconsistent finding with the majority of the rest (18,25). This might be attributable, to a certain point, to various classification patterns or diverse treatment modalities utilized by different authors.

The time elapsing from the onset of hearing loss to the initiation of treatment is reported to be another important prognostic factor; the sooner treatment is initiated, the better the outcome (8,22). Treatment should be started as soon as possible and is probably not helpful after 30 days, as active disease may have resolved and damage may be permanent (21). In our patient group, an arbitrary cut-off value was determined as 5 days in order to define "early" and "delayed" treatment. Recovery rates of early and delayed treatment groups did not differ; however, there was a statis-

tically significant difference when unchanged patients were compared. As expected, starting therapy within the first 5 days lowered the number of patients who failed to respond to treatment. In a way, this might reflect that the initiation of therapy as soon as possible may not guarantee the probability of recovery but helps to lower the incidence of failure. Definition of "early" and "delayed" treatment of SSNHL is another issue which had not yet been standardized. Usually the cut-off values within the first 10 days are offered (26,27). Despite it being a common expectation that the timing of therapy is a prognostic factor, it was rarely found to have no effect on prognosis (28). Again, heterogeneity of the patient groups and study designs might be responsible for inconsistent outcomes.

Another controversial issue is the definition of "recovery". Wilson et al. (2) defined complete recovery as within 10 dB of baseline and partial recovery as thresholds within 50% or more of pre-therapy audiograms. Suckfüll et al. (11) accepted an increase of 15 dB or more as improvement. Apart from these studies, there are many various definitions. There are no standardized criteria and it is evident that the method of defining recovery has a significant impact on the reported outcome of the study. In this study, treatment failure was defined as hearing recovery less than 10 dB. When stricter values are used, these rates would obviously differ.

One of the limitations of the study might be the standard treatment protocol of the clinic, which excludes certain commonly used methods such as hyperbaric oxygen and intratympanic steroids. It is obvious that the application of these treatment modalities may affect outcomes. However, it should be kept in mind that the diversity of treatment protocols from separate centers usually give rise to similar differences. Additionally, a huge part of the patient population was not included due to absent or insufficient follow-up records. This is another possible factor altering the results of the study. In spite of these limitations, the study provides promising data for the certain prognostic factors that have been the focus of investigations.

In conclusion, SSNHL is usually an idiopathic disease and both its treatment and outcome parameters remain controversial. According to this patient series, oral steroid therapy does not have any influence on outcomes of SSNHL. However, mid-frequency hearing loss of flat type and initiation of treatment earlier than 5 days from the onset of symptoms, seem to have positive prognostic effects. Further randomized controlled subject groups might contribute to determine the prognostic factors of SSNHL.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of the university.

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