The Journal of Laryngology & Otology

cambridge.org/jlo

Plasma levels of endothelial cell-specific molecule-1 and pentraxin-3 in idiopathic sudden sensorineural hearing loss

F Gündoğan[1], A Bayram[2], M Kalkan[2] and İ Özcan[2]

[1]Department of ENT, Boğazlıyan State Hospital, Kayseri and [2]Department of ENT, Kayseri Training and Research Hospital, Turkey

Main Article

Dr A Bayram takes responsibility for the integrity of the content of the paper

Presented at the 39th Turkish National Congress of Otolaryngology Head and Neck Surgery, 8–12 November 2017, Antalya, Turkey.

Cite this article: Gündoğan F, Bayram A, Kalkan M, Özcan İ. Plasma levels of endothelial cell-specific molecule-1 and pentraxin-3 in idiopathic sudden sensorineural hearing loss. *J Laryngol Otol* 2018;**132**: 995–999. https://doi.org/10.1017/S002221511800186X

Accepted: 17 June 2018
First published online: 29 October 2018

Key words:
Hearing Loss, Sudden; Endothelium; Vascular Endothelial Cells

Author for correspondence:
Dr Ali Bayram,
Kayseri Training and Research Hospital,
Sanayi Mah. Atatürk Bulvarı Hastane Cad.
No: 78, Kayseri 38010, Turkey
E-mail: dralibayram@gmail.com
Fax: +90 352 3207313

Abstract

Objectives. To evaluate the plasma levels of endothelial cell-specific molecule-1 (ESM-1) and pentraxin-3 (PTX-3) in patients with idiopathic sudden sensorineural hearing loss, and to compare the pre- and post-treatment levels in patients responsive and non-responsive to therapy.

Methods. The study included 108 subjects: 51 with idiopathic sudden sensorineural hearing loss and 57 controls. For ESM-1 and PTX-3 analyses, blood samples were collected before and three months after treatment initiation in the idiopathic sudden sensorineural hearing loss group and once for the control group. Treatment response was evaluated three months after therapy initiation with pure tone audiometry, and the patients were divided into two groups: responsive and non-responsive to treatment.

Results. Serum ESM-1 levels were significantly higher in the idiopathic sudden sensorineural hearing loss group than the control group, whereas the difference was not significant for PTX-3. In the responsive and non-responsive groups, ESM-1 and PTX-3 levels were not statistically different before and after treatment.

Conclusion. To our knowledge, this is the first study investigating plasma ESM-1 and PTX-3 levels in idiopathic sudden sensorineural hearing loss. Increased plasma ESM-1 levels may confirm endothelial dysfunction involvement in idiopathic sudden sensorineural hearing loss pathogenesis, which could be associated with vascular impairment.

Introduction

Sudden sensorineural hearing loss (SNHL) is defined as an acute SNHL of 30 dB or more over at least three contiguous frequencies occurring within a 72-hour period.[1] Sudden SNHL is an otological emergency, with an estimated prevalence of 5–20 cases per 100 000 per year.[2] Although sudden SNHL exhibits spontaneous recovery, with a rate of 32–65 per cent,[3] various treatment modalities, including corticosteroids, vasodilators, hyperbaric oxygen therapy, antioxidants and carbogen therapy have been investigated, with varying results reported in the literature.[4]

Disturbance of cochlear blood flow, viral infection, autoimmune disease and Reissner's membrane rupture have been proposed as theories of underlying mechanisms.[5] However, the aetiology still remains unclear in the majority of patients and this condition is called idiopathic sudden SNHL. Despite the multitude of theories, the sudden and mainly unilateral nature of idiopathic sudden SNHL, with the possible spontaneous resolution pattern, suggests vascular involvement.[6] Quaranta *et al.* reported that idiopathic sudden SNHL should be considered as a microcirculation disorder based on endothelial dysfunction.[7] They showed signs of endothelial dysfunction that included high levels of adhesion molecules, hyperhomocysteinaemia and lower folate levels, an unbalanced oxidative status, a lower value for flow-mediated dilatation of the brachial artery, and a reduced percentage of circulating endothelial progenitor cells in patients with idiopathic sudden SNHL.

Endothelial cell-specific molecule-1 (ESM-1), also known as endocan, is a 50 kDa soluble proteoglycan, consisting of a 165 amino acid mature protein core (20 kDa) and approximately 30 kDa of a single dermatan sulphate chain linked to serine residues.[8] ESM-1 is secreted predominantly by vascular endothelial cells from the gastrointestinal tract, liver, lungs and kidneys, and can freely circulate in the bloodstream.[9] ESM-1 is considered to be a novel marker that has been reported to be overexpressed in various diseases characterised by endothelial dysfunction, such as cardiovascular disease, chronic kidney disease, cancer, Behçet's and psoriasis vulgaris.[9–12]

Pentraxin-3 (PTX-3) is a long secretory glycoprotein produced by vascular endothelial cells and macrophages, especially in response to injury and stress.[13] In contrast to its short-arm counterpart of C-reactive protein, which is primarily synthesised in the liver and thus reflects systemic inflammation, PTX-3 is synthesised locally in the vascular system, and therefore is thought to be closely linked to endothelial dysfunction.[14] Increased levels of PTX-3 have been related to the risk or progression of various diseases, including

cardiovascular, kidney and female reproductive system diseases, and severe traumatic brain injury.[15]

The present study hypothesised that plasma ESM-1 and PTX-3 levels could be elevated as a marker of endothelial dysfunction given the possible relationship between endothelial dysfunction and idiopathic sudden SNHL. To our knowledge, this is the first study investigating plasma ESM-1 and PTX-3 levels in idiopathic sudden SNHL patients. We also aimed to evaluate alterations of plasma ESM-1 and PTX-3 levels according to treatment response in the clinical course of idiopathic sudden SNHL.

Materials and methods

Patients

The present study was approved by the Ethics Committee of the Kayseri Erciyes University School of Medicine (reference number: 2017/270) and written informed consent was obtained from all participants. The study included 108 subjects, 51 in the idiopathic sudden SNHL group and 57 in the control group, aged 18–65 years. The idiopathic sudden SNHL group comprised patients who had at least a 30 dB SNHL in three consecutive frequencies occurring within 3 days of symptom onset.

A detailed medical history, which included details of audiovestibular and neurological symptoms, was obtained from all subjects. Complete otolaryngological examination was followed by pure tone audiometry and acoustic impedance. Temporal magnetic resonance imaging was performed on all patients, to rule out retrocochlear pathology.

Patients were excluded from the study if they had presented 10 days after symptom onset, or if they had a history of any retrocochlear disease, Ménière's disease, tumours, ototoxic drug use, acoustic trauma, barotrauma, bilateral hearing loss, or any other identifiable aetiology for sudden hearing loss. Subjects with diseases that could alter the serum levels of ESM-1 and PTX-3, such as cardiovascular disease, chronic kidney disease or malignancy, were also excluded from the study.

The control group consisted of age- and sex-matched healthy subjects without any ear disease, hearing loss or pathological condition that might influence ESM-1 and PTX-3 serum levels.

Audiometric evaluation

Pure tone audiometry was performed in a standard soundproof room, with a Grason-Stadler GSI-61 clinical audiometer (Madison, Wisconsin, USA), at 0.25, 0.5, 1, 2, 4 and 8 kHz, and a four-tone pure tone average was calculated across 0.5, 1, 2 and 4 kHz. Hearing loss was defined as normal at 25 dB or lower, mild at 26–40 dB, moderate at 41–55 dB, moderate-to-severe at 56–70 dB, severe at 71–90 dB, and profound at 91 dB or higher, as per the World Health Organization classification.[16] The initial audiograms were also classified according to the configuration as flat, up-sloping, down-sloping or total hearing loss.

Treatment protocol

According to our institution's standard treatment protocol, 1 mg/kg methylprednisolone, tapered by 20 mg every 3rd day until termination, was initiated for all patients in the idiopathic sudden SNHL group. On the 5th day of oral steroid administration, the patients with 15 dB or more improvement in pure tone audiometry were treated only with oral steroid therapy. For the patients with hearing improvement of less than 15 dB on the 5th day of oral steroid treatment, either intratympanic steroid (intratympanic steroid group) or hyperbaric oxygen (hyperbaric oxygen group) were added to oral steroid therapy as an early salvage therapy (the patient's preference was considered after detailed information regarding the salvage therapy modalities had been provided).

Intratympanic steroid injection was performed via a tympanostomy tube while the patient was lying flat in a supine position with their head tilted 45 degrees to the opposite side. Approximately 0.5–0.7 ml of 4 mg/ml dexamethasone (Dekort, Deva Holding, Istanbul) was instilled slowly through the tympanostomy tube, and the patient was instructed to keep the position for 30 minutes without swallowing. Each patient in the intratympanic steroid group underwent steroid injection every other day, with a total of five intratympanic steroid sessions.

In the hyperbaric oxygen group, a total of 20 hyperbaric oxygen sessions were administered in a multi-place hyperbaric chamber. For each subject, these daily sessions consisted of: 14 minutes' compression in air, followed by a treatment period at 2.4 atmospheres absolute for 75 minutes, and then a decompression period of 14 minutes' oxygen.

A final evaluation of hearing improvement was performed via pure tone audiometry three months after the initiation of treatment for all patients. Patients with less than 15 dB hearing recovery between the initial and three-month audiograms were considered as being non-responsive to the treatment (non-responsive group). A hearing gain of 15 dB and over was accepted as responsive to treatment (responsive group). Treatment outcomes were described according to Siegel's criteria, as follows: complete recovery – final threshold of more than 25 dB; partial recovery – gain of more than 15 dB, with a final hearing threshold of 25–45 dB; slight recovery –gain of more than 15 dB, with a final threshold of more than 45 dB; and no improvement – gain of less than 15 dB, with a final hearing threshold of more than 75 dB.[17]

Laboratory testing

For ESM-1 and PTX-3 analyses, blood samples were collected twice (before and three months after the initiation of treatment) for the idiopathic sudden SNHL group and once for the control group. After centrifugation of the blood samples at 4000 revolutions per minute for 10 minutes, the supernatants were placed at −80 °C. ESM-1 and PTX-3 levels in plasma samples were analysed using ESM-1 and PTX-3 enzyme-linked immunosorbent assay kits (Aviscera Bioscience, Santa Clara, California, USA) according to the manufacturer's instructions. The levels of ESM-1 and PTX-3 were compared between the idiopathic sudden SNHL group and the control group. A comparison was also performed of the levels before and three months after the initiation of treatment for patients in the responsive and non-responsive groups.

Statistical analysis

Statistical analysis was performed using SPSS software (version 21; SPSS, Chicago, Illinois, USA). Normally distributed data were expressed as means ± standard deviations. Abnormally distributed data were expressed as medians (quartile 1, quartile 3). A p-value of less than 0.05 was considered significant for all comparisons. The chi-square test was used for comparison of

https://doi.org/10.1017/S002221511800186X Published online by Cambridge University Press

Table 1. Demographic features of idiopathic sudden SNHL and control groups

Characteristic	Idiopathic sudden SNHL group*	Control group†	*P*-value
Age (mean ± SD; years)	43.3 ± 14.9	42.6 ± 11.9	0.803
Gender (female/male; *n*)	21/30	19/38	0.520

*$n = 51$; †$n = 57$. SNHL = sensorineural hearing loss; SD = standard deviation

categorical variables. The student's *t*-test was used to compare ESM-1 levels between the idiopathic sudden SNHL and control groups, whereas the Mann–Whitney U test was utilised for the comparison of PTX-3 levels. A paired-samples *t*-test was carried out for the comparison of pre- and post-treatment ESM-1 levels of responsive and non-responsive groups, while the Wilcoxon signed-rank test was used for the comparison of PTX-3 levels. The comparison between the responsive, non-responsive and control groups regarding ESM-1 and PTX-3 levels was made using the Kruskal–Wallis test.

Results

Demographic features of the idiopathic sudden SNHL and control groups are shown in Table 1. There was no significant difference between the groups regarding age and gender.

The distribution of patients according to the degree of hearing loss in the idiopathic sudden SNHL group was as follows: 10 patients with mild, 9 patients with moderate, 11 patients with moderate-to-severe, 12 patients with severe and 9 patients with total hearing loss. The most common audiometric configuration was the down-sloping type (31.4 per cent, $n = 16$), while the number of patients with total, up-sloping and flat configurations were 9, 14 and 12, respectively.

There were 18 patients with 15 dB or more hearing improvement on the 5th day of oral steroid administration. Among the 33 patients with hearing improvement of less than 15 dB on the 5th day of steroid therapy, 17 received intratympanic steroid therapy, whereas 16 patients underwent hyperbaric oxygen treatment in addition to oral steroid therapy.

At 3 months, 18 of the 51 idiopathic sudden SNHL group patients had 15 dB or less hearing recovery. According to the Siegel criteria, 18 patients healed with complete recovery, 7 showed partial recovery, 8 had slight recovery and 18 showed no improvement.

Serum ESM-1 levels were significantly higher in the idiopathic sudden SNHL group than in the control group, whereas the difference was not significant for PTX-3 (Table 2). Before treatment, there was a significant difference between responsive, non-responsive and control subjects in terms of ESM-1 levels. In responsive and non-responsive patients, ESM-1 levels were significantly higher than in the controls, but there was no difference between responsive and non-responsive groups regarding ESM-1 levels. Although PTX-3 levels were higher in the responsive and non-responsive groups than in the control subjects, the difference was not significant (Table 3). In the responsive group and the non-responsive group, ESM-1 and PTX-3 levels were not statistically different before and after treatment (Table 4).

Discussion

Although oral or intravenous corticosteroids are the most commonly used therapies in the management of idiopathic sudden SNHL, approximately 30–50 per cent of patients demonstrate a poor response to steroid therapy over a two-week period of time.[18] In the present study, 64.7 per cent of the idiopathic sudden SNHL patients showed a poor response to oral steroid therapy on the 5th day of admission, which is higher than the rates reported in the related literature. This could be because of the standard treatment protocol of our institution regarding the early initiation of salvage therapy in patients with hearing improvement of less than 15 dB on the 5th day of oral steroid therapy.

In idiopathic sudden SNHL, the early administration of primary or salvage therapy has been shown to be important for improving hearing results.[19–21] In our study, even with the addition of early salvage therapy, 18 out of 51 patients with idiopathic sudden SNHL (35.3 per cent) demonstrated no improvement in hearing status, which might be attributed to the high number of idiopathic sudden SNHL patients with moderate-to-severe, severe and total hearing loss, who constituted the majority of the patients in the idiopathic sudden SNHL group (62.7 per cent, $n = 32$). Generally, patients with greater hearing loss on the initial audiogram after sudden SNHL onset have a decreased rate of hearing improvement as compared to patients with mild losses.[2] In addition, patients with down-sloping and flat audiogram configurations have been shown to have lower recovery rates than those with low-frequency and mid-frequency hearing losses.[3] In the present study, 72.5 per cent of the patients in the idiopathic sudden SNHL group had down-sloping, total or flat type audiograms.

An endothelial dysfunction has been described in patients with idiopathic sudden SNHL, which supports a vascular involvement in idiopathic sudden SNHL aetiopathogenesis. Endothelial dysfunction may cause impaired labyrinth perfusion and reduced hearing capability in patients with idiopathic sudden SNHL.[7]

The association between endothelial dysfunction and idiopathic sudden SNHL pathogenesis has been demonstrated by several methods in the literature. Circulating levels of endothelial progenitor cells, which have the potential to proliferate and differentiate into mature endothelial cells, were found to be significantly lower in sudden SNHL patients than in controls.[22] Capaccio *et al.* reported an unbalanced oxidative stress status that could cause endothelial dysfunction and vascular impairment in patients with idiopathic sudden SNHL.[23] Gul *et al.* demonstrated an association between idiopathic sudden SNHL and oxidative stress, and suggested that hypoxia may cause further damage by inducing endothelial dysfunction within the inner-ear microcirculation in idiopathic sudden SNHL.[24] Quaranta *et al.* demonstrated an increased expression of circulating adhesion molecules, supporting the existence of endothelial dysfunction and vascular involvement in the pathogenesis of sudden SNHL.[25] Ciccione *et al.* showed that flow-mediated dilation of the brachial artery was significantly lower in idiopathic sudden SNHL patients than in controls, and concluded that the hearing loss seemed to be associated with vascular endothelial dysfunction and increased cardiovascular risk.[26] Similarly, Berjis *et al.* found that flow-mediated dilation was significantly lower in patients with idiopathic sudden SNHL than in controls.[27] These authors stated that endothelial dysfunction is associated with sudden SNHL, and that this association is independent from other cardiovascular risk factors, including diabetes and dyslipidaemia.[27]

ESM-1 is a novel biomarker of endothelial dysfunction, which was first identified and reported in 1996.[8] Endothelial dysfunction is considered the primary lesion in the

https://doi.org/10.1017/S002221511800186X Published online by Cambridge University Press

Table 2. ESM-1 and PTX-3 levels in idiopathic sudden SNHL and control groups before treatment

Parameter	Idiopathic sudden SNHL group*	Control group†	*P*-value
ESM-1 (mean ± SD; ng/ml)	3.22 ± 1.2	2.1 ± 0.68	<0.001
PTX-3 (mean (range); pg/ml)	2962 (2448–4150)	2651 (1954–3640)	0.106

*$n = 51$; †$n = 57$. ESM-1 = endothelial cell-specific molecule-1; PTX-3 = pentraxin-3; SNHL = sensorineural hearing loss; SD = standard deviation

Table 3. ESM-1 and PTX-3 levels in responsive, non-responsive and control groups before treatment

Parameter	Responsive group*	Non-responsive group†	Control group‡	*P*-value
ESM-1 (mean ± SD; ng/ml)	3.2 ± 1.33	3.26 ± 0.94	2.1 ± 0.68	<0.001
PTX-3 (mean (range); pg/ml)	2944 (2276–4102)	2966 (2322–5414)	2651 (1954–3640)	0.224

*$n = 33$; †$n = 18$; ‡$n = 57$. ESM-1 = endothelial cell-specific molecule-1; PTX-3 = pentraxin-3; SD = standard deviation

Table 4. ESM-1 and PTX-3 levels in responsive and non-responsive groups before and after treatment

Group	Parameter	Before treatment	After treatment	*P*-value
Responsive*	ESM-1 (mean ± SD; ng/ml)	3.2 ± 1.33	3.01 ± 1.49	0.662
	PTX-3 (mean (range); pg/ml)	2944 (2276–4102)	2748 (2217–3672)	0.837
Non-responsive†	ESM-1 (mean ± SD; ng/ml)	3.26 ± 0.94	2.97 ± 1.35	0.454
	PTX-3 (mean (range); pg/ml)	2966 (2322–5414)	2994 (2006–4549)	0.777

*$n = 33$; †$n = 18$. ESM-1 = endothelial cell-specific molecule-1; PTX-3 = pentraxin-3; SD = standard deviation

progression of atherosclerosis, and elevated ESM-1 levels have been associated with cardiovascular disease.[12] In addition, Kanbay *et al.* reported that ESM-1 may be a useful early novel marker for premature vascular endothelial dysfunction in patients with obstructive sleep apnoea syndrome.[28]

PTX-3 is a member of the long pentraxin family synthesised in the vascular system and thought to reflect endothelial dysfunction.[14] Elevated PTX-3 plasma levels, which correlated with endothelial dysfunction severity, were found in patients with chronic kidney disease and pre-eclampsia.[29,30] In addition, close associations have been reported between PTX-3 and markers of endothelial dysfunction, such as soluble vascular adhesion molecule-1, fibrinogen and flow-mediated dilation.[31,32]

- ESM-1 and PTX-3 plasma levels were evaluated in idiopathic sudden sensorineural hearing loss (SNHL) patients
- Endothelial dysfunction has been described in these patients, supporting vascular involvement in idiopathic sudden SNHL aetiopathogenesis
- ESM-1 and PTX-3 overexpression has been reported in various diseases characterised by endothelial dysfunction
- Serum ESM-1 levels were significantly higher in idiopathic sudden SNHL patients than in controls; the difference was not significant for PTX-3
- Increased plasma ESM-1 levels may confirm endothelial dysfunction involvement in idiopathic sudden SNHL pathogenesis, possibly associated with vascular impairment

In the present study, we hypothesised that plasma levels of ESM-1 and PTX-3 might be elevated in idiopathic sudden SNHL, indicating, and being the consequence of, endothelial dysfunction. Plasma ESM-1 levels were significantly higher in idiopathic sudden SNHL patients than in control subjects. Despite serum PTX-3 levels being higher in idiopathic sudden SNHL patients than in controls, the difference was not significant ($p = 0.106$). According to these results, we suggest that elevated plasma ESM-1 levels indicate a role of endothelial dysfunction in the aetiopathogenesis of idiopathic sudden SNHL.

This study also evaluated the possible association between plasma ESM-1 and PTX-3 and treatment response. The ESM-1 and PTX-3 levels were not statistically different before and after treatment in responsive and non-responsive patients. Although ESM-1 levels were significantly higher than in the controls in responsive and non-responsive patients before treatment, there was no significant difference between responsive and non-responsive patients. Thus, we conclude that plasma ESM-1 and PTX-3 levels might not be prognostic indicators for idiopathic sudden SNHL.

Conclusion

To our knowledge, this is the first study to investigate plasma ESM-1 and PTX-3 levels in idiopathic sudden SNHL patients. Increased plasma ESM-1 levels may confirm the involvement of endothelial dysfunction in the pathogenesis of idiopathic sudden SNHL, which could be associated with vascular impairment. Further studies with a larger population could better delineate ESM-1 and PTX-3 as diagnostic tools of vascular impairment and as prognostic indicators of clinical course in patients with idiopathic sudden SNHL.

Acknowledgements. The authors thank Dr Derya Koçer from the Department of Biochemistry, Kayseri Training and Research Hospital. This study was financially supported by Kayseri Training and Research Hospital (grant number: 2015/48).

Competing interests. None declared

References

1 Stachler RJ, Chandrasekhar SS, Archer SM, Rosenfeld RM, Schwartz SR, Barrs DM *et al.* Clinical practice guideline: sudden hearing loss. *Otolaryngol Head Neck Surg* 2012;**146**:1–35

https://doi.org/10.1017/S002221511800186X Published online by Cambridge University Press

2 Byl FM Jr. Sudden hearing loss: eight years' experience and suggested prognostic table. *Laryngoscope* 1984;**94**:647–61
3 Kuhn M, Heman-Ackah SE, Shaikh JA, Roehm PC. Sudden sensorineural hearing loss: a review of diagnosis, treatment, and prognosis. *Trends Amplif* 2011;**15**:91–105
4 Conlin AE, Parnes LS. Treatment of sudden sensorineural hearing loss: I. A systematic review. *Arch Otolaryngol Head Neck Surg* 2007;**133**:573–81
5 Chau JK, Lin JR, Atashband S, Irvine RA, Westerberg BD. Systematic review of the evidence for the etiology of adult sudden sensorineural hearing loss. *Laryngoscope* 2010;**120**:1011–21
6 Mattox DE, Simmons FB. Natural history of sudden sensorineural hearing loss. *Ann Otol Rhinol Laryngol* 1977;**86**:463–80
7 Quaranta N, De Ceglie V, D'Elia A. Endothelial dysfunction in idiopathic sudden sensorineural hearing loss: a review. *Audiol Res* 2016;**6**:151
8 Lassalle P, Molet S, Janin A, Heyden JV, Tavernier J, Fiers W *et al*. ESM-1 is a novel human endothelial cell-specific molecule expressed in lung and regulated by cytokines. *J Biol Chem* 1996;**271**:20458–64
9 Yang WE, Hsieh MJ, Lin CW, Kuo CY, Yang SF, Chuang CY *et al*. Plasma levels of endothelial cell-specific molecule-1 as a potential biomarker of oral cancer progression. *Int J Med Sci* 2017;**14**:1094–100
10 Balta I, Balta S, Koryurek OM, Demirkol S, Mikhailidis DP, Celik T *et al*. Serum endocan levels as a marker of disease activity in patients with Behçet disease. *J Am Acad Dermatol* 2014;**70**:291–6
11 Balta I, Balta S, Demirkol S, Mikhailidis DP, Celik T, Akhan M *et al*. Elevated serum levels of endocan in patients with psoriasis vulgaris: correlations with cardiovascular risk and activity of disease. *Br J Dermatol* 2013;**169**:1066–70
12 Yilmaz MI, Siriopol D, Saglam M, Kurt YG, Unal HU, Eyileten T *et al*. Plasma endocan levels associate with inflammation, vascular abnormalities, cardiovascular events, and survival in chronic kidney disease. *Kidney Int* 2014;**86**:1213–20
13 Mantovani A, Garlanda C, Bottazzi B, Peri G, Doni A, Martinez de la Torre Y *et al*. The long pentraxin PTX3 in vascular pathology. *Vascul Pharmacol* 2006;**45**:326–30
14 Yasunaga T, Ikeda S, Koga S, Nakata T, Yoshida T, Masuda N *et al*. Plasma pentraxin 3 is a more potent predictor of endothelial dysfunction than high-sensitive C-reactive protein. *Int Heart J* 2014;**55**:160–4
15 Liu S, Qu X, Liu F, Wang C. Pentraxin 3 as a prognostic biomarker in patients with systemic inflammation or infection. *Mediators Inflamm* 2014;**2014**:421429
16 World Health Organization. *International Classification of Impairments, Disabilities and Handicaps*. Geneva: World Health Organization, 1980;**73**
17 Siegel LG. The treatment of idiopathic sudden sensorineural hearing loss. *Otolaryngol Clin North Am* 1975;**8**:467–73
18 Li P, Zeng XL, Ye J, Yang QT, Zhang GH, Li Y. Intratympanic methylprednisolone improves hearing function in refractory sudden sensorineural hearing loss: a control study. *Audiol Neurootol* 2011;**16**:198–202
19 Nakagawa T, Yamamoto M, Kumakawa K, Usami S, Hato N, Tabuchi K *et al*. Prognostic impact of salvage treatment on hearing recovery in patients with sudden sensorineural hearing loss refractory to systemic corticosteroids: a retrospective observational study. *Auris Nasus Larynx* 2016;**43**:489–94
20 Dai Y, Lu L, Hou J, Yang X, Li H, Yang Y *et al*. Intratympanic methylprednisolone perfusion as a salvage treatment for profound idiopathic sudden sensorineural hearing loss. *J Laryngol Otol* 2017;**131**:404–10
21 Pezzoli M, Magnano M, Maffi L, Pezzoli L, Marcato P, Orione M *et al*. Hyperbaric oxygen therapy as salvage treatment for sudden sensorineural hearing loss: a prospective controlled study. *Eur Arch Otorhinolaryngol* 2015;**272**:1659–66
22 Quaranta N, Ramunni A, De Luca C, Brescia P, Dambra P, De Tullio G *et al*. Endothelial progenitor cells in sudden sensorineural hearing loss. *Acta Otolaryngol* 2011;**131**:347–50
23 Capaccio P, Pignataro L, Gaini LM, Sigismund PE, Novembrino C, De Giuseppe R *et al*. Unbalanced oxidative status in idiopathic sudden sensorineural hearing loss. *Eur Arch Otorhinolaryngol* 2012;**269**:449–53
24 Gul F, Muderris T, Yalciner G, Sevil E, Bercin S, Ergin M *et al*. A comprehensive study of oxidative stress in sudden hearing loss. *Eur Arch Otorhinolaryngol* 2017;**274**:1301–8
25 Quaranta N, Ramunni A, Brescia P, D'Elia A, Vacca A, Ria R. Soluble intercellular adhesion molecule 1 and soluble vascular cell adhesion molecule 1 in sudden hearing loss. *Otol Neurotol* 2008;**29**:470–4
26 Ciccone MM, Cortese F, Pinto M, Di Teo C, Fornarelli F, Gesualdo M *et al*. Endothelial function and cardiovascular risk in patients with idiopathic sudden sensorineural hearing loss. *Atherosclerosis* 2012;**225**:511–16
27 Berjis N, Moeinimehr M, Hashemi SM, Hashemi SM, Bakhtiari EK, Nasiri S. Endothelial dysfunction in patients with sudden sensorineural hearing loss. *Adv Biomed Res* 2016;**5**:5
28 Kanbay A, Ceylan E, İnönü Köseoğlu H, Çalışkan M, Takir M, Tulu S *et al*. Endocan: a novel predictor of endothelial dysfunction in obstructive sleep apnea syndrome. *Clin Respir J* 2018;**12**:84–90
29 Hamad RR, Eriksson MJ, Berg E, Larsson A, Bremme K. Impaired endothelial function and elevated levels of pentraxin 3 in early-onset preeclampsia. *Acta Obstet Gynecol Scand* 2012;**91**:50–6
30 Witasp A, Ryden M, Carrero JJ, Qureshi AR, Nordfors L, Näslund E *et al*. Elevated circulating levels and tissue expression of pentraxin 3 in uremia: a reflection of endothelial dysfunction. *PLoS One* 2013;**8**:e63493
31 Tong M, Carrero JJ, Qureshi AR, Anderstam B, Heimbürger O, Bárány P *et al*. Plasma pentraxin 3 in patients with chronic kidney disease: associations with renal function, protein-energy wasting, cardiovascular disease, and mortality. *Clin J Am Soc Nephrol* 2007;**2**:889–97
32 Suliman ME, Yilmaz MI, Carrero JJ, Qureshi AR, Saglam M, Ipcioglu OM *et al*. Novel links between the long pentraxin 3, endothelial dysfunction, and albuminuria in early and advanced chronic kidney disease. *Clin J Am Soc Nephrol* 2008;**3**:976–85

https://doi.org/10.1017/S002221511800186X Published online by Cambridge University Press