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Association between Macrophage Migration Inhibitory Factor Gene Variation and Response to Glucocorticoid Treatment in Sudden Sensorineural Hearing Loss

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Key Words
Sensorineural hearing loss · Macrophage migration inhibitory factor · Glucocorticoids · Treatment outcome

Abstract
Several lines of evidence suggest the role of the immune system in the pathogenesis of sudden sensorineural hearing loss (SSNHL). Macrophage migration inhibitory factor (MIF) mediates its role in various immune and inflammatory conditions by the regulation of immune reactions. Several studies have confirmed an association between MIF gene polymorphisms and susceptibility to various inflammatory and autoimmune disorders. The aim of this study was to explore the association between the MIF (–173 G/C) polymorphism (rs755622) and SSNHL in an Iranian population. In this case-control association study, SSNHL cases (n = 77) were included. Normal healthy subjects (n = 100) were also recruited from the same region. Genotyping for MIF (–173 G/C) polymorphism was carried out using the polymerase chain reaction-restriction fragment length polymorphism technique. The frequency of the MIF –173 C allele carriers (GC + CC genotype) was significantly elevated in SSNHL patients who responded to glucocorticoid treatment compared with the patients with no response to treatment. These results suggest that the MIF gene polymorphism is associated with a response to glucocorticoid treatment in patients with SSNHL.

Introduction

Sudden sensorineural hearing loss (SSNHL) is defined as a new onset of unilateral or bilateral hearing loss that develops rapidly within 24–72 h with a greater than 30-dB hearing loss at three consecutive frequencies. Although the etiology and pathogenesis of SSNHL are not known, various causes including viral infection, vascular disease and autoimmunity have been anticipated as the primary cause of the disease [Chien et al., 2012; Um et al., 2013]. However, it has so far been difficult to attribute one particular mechanism to individual cases. The fact that even an exact location (e.g. vascular, neuronal, inner ear, and/or cerebral malfunction) has not been apparent makes the identification of mechanisms involved more complicated. One of the main treatment options in SSNHL is the

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administration of high-dose steroids intravenously, orally or via intratympanic routes. However, in idiopathic SSNHL, the efficiency of steroids treatment has not yet been proven [Weiss et al., 2014]. Several pieces of evidence support the involvement of genetic factors in the presence of SSNHL as a complex multifactorial disease. The genetic markers attributed to SSNHL include prothrombin G20210A variant, factor V Leiden G1691A substitution and methylenetetrahydrofolate reductase (MTHFR) C677 polymorphisms [Chien et al., 2012]. Although the onset of disease is mostly in the elderly, it can occur at various ages [Weiss et al., 2014] and an incidence of 5–20 cases in 100,000 individuals each year has been estimated for the disease prevalence [Xenellis et al., 2006]. However, disease incidence should be much higher considering the number of ageing populations in industrialized countries and taking into account the misdiagnosis of the disease, especially in elderly people. Hearing recovery in idiopathic SSNHL is unpredictable, varying from complete or spontaneous recovery to nonrecovery [Weiss et al., 2014].

Macrophage migration inhibitory factor (MIF) is a small protein consisting of 115 amino acids encoded by a gene that maps to chromosome 22q11.2 in humans. Although T cells are known as the main source of MIF production, other cell types including macrophages are also involved in MIF production and secretion. MIF is also considered as a proinflammatory cytokine with a range of targets which modulate the expression of a number of inflammatory molecules, including TNF-α, IL-6, IL-1b, IL-2, IL-8, and IFN-γ [Wang et al., 2012; Zhang et al., 2013] and playing an important immune regulatory role in several inflammatory diseases such as rheumatoid arthritis and atherosclerosis [Xiao et al., 2011; Saeedi et al., 2013].

A single nucleotide polymorphism (rs755622) in the 5′ flanking region of the MIF gene at position –173 (G to C transition) has been associated with increased susceptibility to multiple organ-specific autoimmune diseases, including juvenile idiopathic arthritis, systemic lupus erythematosus, inflammatory bowel disease, glomerulonephritis, multiple sclerosis, psoriasis, sarcoidosis, systemic sclerosis, and scleroderma. In the T-lymphoblast cell line, it has been observed that the presence of the mutant C allele creates an AP-4 transcription factor binding site, resulting in a significantly increased MIF expression. It has also been reported that increased MIF concentration was associated with more severe clinical presentations and subsequently a poor outcome of the disease [Renner et al., 2005; Arikan et al., 2006; Wang et al., 2012; Bucala, 2013; Yazdani et al., 2013]. In contrast to other proinflammatory cytokines that are generally suppressed by glucocorticoids, MIF has a very specific counterregulatory effect on glucocorticoids. On the one hand, MIF expression and secretion are increased by low physiological concentrations of glucocorticoids [Choi et al., 2011]. Evidence of MIF upregulation as a result of endogenous glucocorticoid effect has been reported in rat adjuvant-induced arthritis. On the other hand, MIF displays antagonistic effects for glucocorticoids. In murine antigen-induced arthritis, exogenous MIF administration had a reversal effect on the histological severity of the disease which was as a result of glucocorticoid inhibition. Such a relationship between MIF and glucocorticoids is also observed in studies on humans. It has been observed that the inhibition of MIF by genetic deletion or anti-sense oligonucleotide treatment results in a significant change in the glucocorticoid dose response of TNF production in macrophages, which confirms the direct effect of MIF on regulating glucocorticoid sensitivity. The mechanism of the MIF counterregulatory effect on the anti-inflammatory actions of glucocorticoid is not yet fully understood. However, MIF and glucocorticoids may interact with each other through several different pathways [Vivarelli et al., 2008; Wang et al., 2012].

In the present study, we investigated for the first time whether the allelic frequency of the MIF (–173 G/C) polymorphism correlated with SSNHL and explored the relation between response to treatment with corticosteroids and the MIF polymorphism. The role of age, tinnitus, vertigo, and initial ideogrammatic pattern of patients as prognostic factors were also explored in connection with response to treatment.

Subjects and Methods

Patients and Controls

A total of 77 patients with SSNHL (mean age: 43.5 ± 14.7, 58.4% male and 41.6% female) participated in this study. The inclusion criterion was a hearing loss of 30 dB or greater in at least three contiguous frequencies. All patients were admitted to Amir Alam Hospital emergency ward (an affiliated hospital of Tehran University of Medical Sciences, Tehran, Iran) during the years 2012–2014 after the onset of SSNHL. The exclusion criteria were patients having previous history of hearing loss, pregnancy, diabetes, and immune system deficiency. All patients had negative MRI. The control group (n = 100) were collected from the same region and included individuals without a family history of SSNHL who had been examined by an expert clinician and did not have high blood pressure and a history of autoimmune disease, cancer or Alzheimer's disease at the time of recruitment. They had also been evaluated for anemia, diabetes, pregnancy, and lipid disorders and by

Table 1. Clinical characteristics of patients with SSNHL

Sex (M/F), n	45/32
Mean age, years	43.5±14.7
Unilateral/bilateral, n	75/2
Left ear involvement, n (%)	37 (48.1)
Right ear involvement, n (%)	38 (49.4)
Audiogram pattern, n (%)	
Descending	28 (36.4)
Ascending	13 (16.9)
Mid part	1 (1.3)
Flat	35 (45.5)
Accompanying signs, n (%)	
Vertigo	9 (11.7)
Tinnitus	34 (44.2)
Headache	1 (1.3)
Vertigo + tinnitus	12 (15.6)
Tinnitus + headache	2 (2.6)
Vertigo + headache	1 (1.3)
All	5 (6.5)
Total number of patients	77

physical, biochemical and urine test. All patients received prednisone at an initial dosage of 1 mg/kg or intratympanic dexamethasone of 4 ml or both treatments. The time range from symptom development to treatment was from 6 h to 1 month and in patients with symptoms for 1 and a half months or more no treatment was recommended. Dosage and duration of prednisone administration was the same for all patients. Hearing gain (10 dB in pure tone average or 10–15% in speech discrimination score) was used as the parameter for hearing recovery. Hearing loss outcome was controlled in a 3-step procedure – 1 week and 1 and 3 months after the onset of hearing loss. Informed consent was obtained from all participants before recruitment into the research protocol. The study was approved by the ethics committee of Tehran University of Medical Sciences in accordance with the Helsinki declaration. The questionnaire, consisting of demographic information, physical examination result, transverse myelitis condition, disease onset, history of diabetes mellitus and hypertension, history of smoking, accompanying signs like tinnitus, vertigo, family history of hearing loss, and history of trauma, was obtained from all patients. In addition, audiometry hearing testing was performed for all patients before treatment.

DNA Isolation

Genomic DNA was extracted from peripheral blood samples collected in EDTA (ethylenediaminetetraacetic acid) tubes as an anticoagulating agent using the salting-out method. The concentration of DNA was estimated by absorbance at 260 nm.

Polymorphism Genotyping

The MIF gene polymorphism was genotyped using the polymerase chain reaction (PCR)-restriction fragment length polymorphism method as described previously [Saeedi et al., 2013]. The PCR reaction mixture contained 200 ng DNA, 0.3 mM of each primer, 0.2 mM dNTPs, 1 unit Taq polymerase (Fermentas), 2 ml 10× PCR buffer (Fermentas) with 2.5 mM magnesium chloride in a total reaction volume of 25 ml. The MIF-173 forward and reverse primers were as follows: 5′-ACT-AAG-AAA-GAC-CCG-AGG-C-3′ and 5′-GGG-GCA-CGT-TGG-TGT-TTA-C-3′, respectively. The cycling conditions were the following: 95°C for 10 min followed by 30 amplification cycles at 95°C for 45 s, 60°C for 45 s and 72°C for 45 s and a final extension at 72°C for 10 min. The amplified PCR products (8 µl) were then digested in a 10-µl final reaction volume using 1.5 µl of 10× reaction buffer and 5 units of *Alu* I restriction enzyme (Roche Diagnostics GmbH, Penzberg, Germany) at 37°C overnight. Controls of known genotype were included for every set of digestions carried out and finally the digested products were resolved on a 3.0% agarose gel stained with ethidium bromide and visualized using UV transillumination.

The PCR products for the GG genotype had a consistent restriction site resulting in 98- and 268-bp fragments, three fragments of the size 205, 98 and 63 bp for the CC genotype and four fragments of the size 268, 205, 98, and 63 bp for the GC genotype.

Statistical Analysis

The strength of association between different groups and alleles or genotypes of the MIF gene polymorphism was estimated using odds ratios (OR) and 95% confidence intervals (CI). Levels of significance were determined using contingency tables by either the χ^2 test or Fisher's exact analysis. All analyses were carried out using SPSS software (version 16.0).

Results

Characteristics of patients are summarized in table 1. There were only 4 patients who had a positive family history of sudden hearing loss in their first-degree relatives. The mean length of time to treatment was 5.1 ± 5.3 in responders and 5.8 ± 4.5 in nonresponders. The 3 patients without a follow-up audiogram were excluded from the study. MIF (–173 G/C) gene polymorphism genotype frequency was determined in patients and controls. Allele and genotype frequencies conformed to Hardy-Weinberg equilibrium in all groups ($p > 0.7$).

Accompanying Signs and Audiogram Pattern with Response to Treatment

The most frequent accompanying signs with hearing loss were tinnitus (34/44.2%; table 1). No significant relation was observed between accompanying signs and response to treatment with glucocorticoid ($p = 0.3$). A flat audiogram pattern was the most frequent pattern (35/45.5%). The audiogram pattern was connected with response to treatment ($p = 0.054$) and an ascending pattern showed the most probability in successful response to treatment (10/76.9%; table 1).

Table 2. Allelic frequency of MIF gene variant in patients compared with controls

	GG	GC	CC
Controls, n (%)	59 (59)	31 (31)	10 (10)
Patients, n (%)	47 (61)	27 (35)	3 (4)

MIF Genotype Frequencies in Patients with SSNHL Compared with Controls

A total of 77 SSHNL patients (45/58.4% males and 32/41.6% females) and 100 healthy controls subjects were analyzed for the MIF gene polymorphism allele and genotype frequencies. The genotype frequencies showed no significant differences between patients and controls (table 2). A notably high prevalence of G/G genotype were found in our patients but the differences were not statistically significant (p = 0.7, OR = 1.05, 95% CI: 0.4–1.7).

Allele Frequencies and Recovery from Sudden Hearing Loss

The association between the MIF gene polymorphism in relation to hearing recovery after treatment with glucocorticoid was investigated in patients with no improvement (n = 38) in hearing loss compared with the group showing response to glucocorticoid treatment (n = 39). There was a significant difference for the frequency of the MIF gene variant (CC + GC vs. GG) between patients with response to glucocorticoid treatment and those without response (p = 0.02, OR = 3.06, 95% CI: 1.04–9.2; table 3). Multivariate analysis showed no deviation from OR after adjustment for confounding factors, including sex, age, severity, and treatment modality. Comparison of mean age between patients with and without response after glucocorticoid treatment also showed no significant differences (p > 0.05; table 4).

Discussion

In this study a functional variant in the MIF gene promoter was assessed for association with SSNHL. Although no significant difference was observed for the frequency of the MIF gene polymorphism between SSNHL patients and normal healthy controls subjects, an association with response to glucocorticoid treatment was detected.

Most cases of SSNHL have no identifiable cause for being diagnosed as idiopathic. Some factors, including viral infection, vascular impairment, immune-mediated mechanisms, and inner ear and central nervous system abnormalities, have been identified as the most commonly associated causes [Xenellis et al., 2006; Um et al., 2013].

MIF is regarded as an innate cytokine and one of its main roles includes counterregulating the immunosuppressive effect of glucocorticoids and the inhibition of apoptosis. Previous studies have shown significant relationships between increased MIF expression and inflammatory responses. Because of its role in the regulation of the immune system, the genetic variation of MIF has been associated with several inflammatory diseases [Bucala, 2013; Lan et al., 2013; Yazdani et al., 2013].

Previous studies confirmed the association between the MIF (–173 G/C) polymorphism and increased susceptibility of several disorders including nephrotic syndrome in Turkish [Berdeli et al., 2005] and Italian [Vivarelli et al., 2008] populations, biliary atresia [Arikan et al., 2006], Chagas disease (a meta-analysis in Colombian and Peruvian cohorts [Torres et al., 2009]), Ménière's disease in an Iranian population [Yazdani et al., 2013], erythema nodosum secondary to sarcoidosis in a Spanish population [Amoli et al., 2002], chronic hepatitis B or HBV-induced liver cirrhosis in a Chinese population [Zhang et al., 2013], and male psoriasis and late-onset psoriasis in a Han population in northeastern China [Wu et al., 2009].

This study is the first to report an association between the MIF polymorphism and response to glucocorticoid treatment in patients with SSNHL. It is well known that response to glucocorticoid and steroid hormones varies extensively among individuals and almost 30% of people show a weak response to glucocorticoid treatment. Although little is known about the molecular basis of this variation, it is clear that glucocorticoid action is largely being made through the glucocorticoid receptor as a result of transcription factor activation. Therefore, regulatory polymorphisms are likely to play a key role in this process. Differences in lymphocyte glucocorticoid sensitivity as a consequence of variation in transcriptional response have been reported as a result of a glucocorticoid-dependent regulatory polymorphism which is acting in cis relative to RBMS3 and in trans to affect the transcriptional response of multiple distant genes [Maranville et al., 2013].

In vitro studies have identified several distinct pathways for the interaction between glucocorticoids and MIF. However, the exact mechanism has not yet been identified. Unlike other proinflammatory cytokines, the regulatory effect of MIF on glucocorticoids is in a bipha-

Table 3. The genotype frequency of MIF gene variant in patients with response after glucocorticoid treatment compared to patients with no response

	GG	GC + CC	Total
Response to glucocorticoid treatment, n (%)	20 (51.3)	19 (48.7)*	39 (100)
No response to glucocorticoid treatment, n (%)	29 (76.3)	9 (23.7)	38 (100)

* p = 0.02; OR = 3.06; 95% CI: 1.04–9.2.

sic manner, with suppression at high concentrations and induction at lower concentration of glucocorticoids [Berdeli et al., 2005].

The counterregulatory effect of MIF on immune suppressive properties of glucocorticoid makes it an interesting target for pharmacological intervention as the inhibition of MIF may be especially beneficial in inflammatory conditions, including asthma or rheumatoid arthritis resistance to steroid treatment. MIF expression is also induced by glucocorticoids and in a study performed on systemic lupus erythematosus, a positive correlation between circulating MIF levels and steroid dosage was reported. Therefore, the discovery of glucocorticoid congeners that preserve the immunosuppressive but not the stimulatory activity of MIF will be useful as a novel and more efficient approach for the treatment of inflammatory diseases [Leng et al., 2009].

The correlation between increased MIF level, MIF gene polymorphism and steroid resistance has been reported in several autoimmune diseases and in human CEM (isolated from continuous culture of human lymphoblasts) T-cell lines [Wang et al., 2012].

Several reports present the effect of the MIF polymorphism on glucocorticoid nonresponder or resistant responsive patients with autoimmune diseases. MIF signaling seems to be mediated through two distinct pathways – one pathway includes interaction with the intracytoplasmic receptor after its endocytosis while the other pathway is mediated through binding to its surface receptor. Therefore, it could be assumed that MIF differentially induces the signaling cascades in glucocorticoid-resistant and glucocorticoid response patients [Ishiguro et al., 2006].

We observed the association of the C allele with glucocorticoid response. This may propose that the MIF polymorphism may influence signaling cascade inducement in response to glucocorticoid treatment.

Although the MIF impact on steroid response has been revealed, some investigations indicate controversial

Table 4. Comparison of mean age between patients with and without recovery

	Response (n = 39)	No response (n = 38)	Total (n = 77)
Mean ± SD	44.4±14.3	42.6±15.3	43.5±14.7

p > 0.05.

results for MIF polymorphism association with response to glucocorticoid treatment. Choi et al. [2011] found no association between the MIF (–173 G/C) polymorphism and steroid responsiveness in Italian patients with nephrotic syndrome, although another study revealed contrary data [Berdeli et al., 2005]. The MIF (–173 G/C) polymorphism did not contribute to prednisone and glucocorticoid poor response in vivo in childhood acute lymphoblastic leukemia [Ziino et al., 2005] and idiopathic thrombocytopenic purpura [Lao et al., 2013], respectively. It seems that although MIF has a distinct role in the inflammatory cascade in different disorders, other proinflammatory mediators might prevail over some of the MIF actions, including the regulation of glucocorticoid response. In addition, the source of MIF level measurement, e.g. in synovial fluid [De Benedetti et al., 2003], peripheral blood [Edwards et al., 2010] or the site of intra-articular steroid injection [De Benedetti et al., 2003] versus intratympanic steroid injection [Xenellis et al., 2006] might be an important factor contributing to the observed differences. The discrepancies observed might also be due to the MIF gene frequency difference in various populations. For example, in some populations the frequency of the –173 G allele was 75–90%, which was quite higher than the –173 C allele (15–20%). In two studies carried out in Japan, the frequency of the –173 C allele (19.3 and 22.3%) was almost twice as high as that among the white population from the UK (12%), while it

was almost the same as the frequency of the –173 C allele in a German population [Renner et al., 2005]. This might have been due to variations in ethnic and geographic distribution.

Targeting MIF successfully in SSNHL patients who are refractory to steroid-using bioengineered soluble receptors or receptor antagonists and specific antibodies like other soluble proinflammatory cytokines [Santos and Morand, 2006] would be of potential interest in future studies. The benefits of such therapeutic strategies include the early introduction of second-line medication and protection from negative side effects of unnecessary drug administration. Another strategy for targeting MIF in SSNHL patients might be allele-specific targeting, which needs to be further examined.

A further possible explanation is that SSNHL might have an underlying physiopathology different from that seen in other autoimmune diseases. According to the literature [Chien et al., 2012; Um et al., 2013], other genes might also have an impact on the presence of SSNHL, emphasizing that more studies are necessary to learn about the precise pathogenesis of SSNHL.

Conclusions

These results suggest an association of the MIF polymorphism with response to glucocorticoid treatment in patients with SSNHL, which may bring new insights into the molecular pathogenesis of SSNHL. In addition, this finding might indicate the involvement of various autoimmune and nonautoimmune mechanisms in the pathogenesis of the disease and highlight the role of the MIF gene in patients with autoimmune SSNHL with a better response to glucocorticoid. Furthermore, studies on larger sample sizes should be performed to explore the association of the MIF polymorphism with the risk of SSNHL in different populations. The association which has been observed in this study must be interpreted with caution due to the study limitation and variability of etiologies involved in SSNHL. Studies on very large cohorts might be needed to further confirm the results observed in our study. These results might help in understanding the MIF biology, which itself may lead to new insights into the etiology of many chronic, disabling human disorders and also to the development of novel therapeutic approaches to treat such conditions.

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