



Original Article

Inner Ear Involvement in Children with Familial Mediterranean Fever

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OBJECTIVE: Familial Mediterranean fever (FMF) is the most common and best understood disease of hereditary periodic fever syndromes. Various degrees of sensorineural hearing loss can be seen in the progression of some hereditary periodic fever syndromes. There are very limited and controversial studies in the literature with regard to hearing loss in patients diagnosed with FMF. We aimed to evaluate cochlear function in children with FMF.

MATERIALS and METHODS: Forty-nine patients diagnosed with FMF and 49 age- and sex-matched controls were included in the study. All of the children had undergone a routine ear-nose-throat examination. Patients with pathological findings in the otologic examination or a history of recurrent otitis media; using proven ototoxic drugs; or having an abnormal tympanometry finding were excluded from the study. Following audiologic evaluation, tympanometry and distortion product otoacoustic emissions testing were conducted on all subjects. Pure-tone and high-frequency audiometry were carried out on 40 subjects from both groups who could cooperate in the testing.

RESULTS: Hearing thresholds of FMF patients were found to be increased at all frequencies (250 to 16,000) ($p < 0.001$). The difference between the hearing thresholds of the two groups could be seen more prominently at higher frequencies, and despite a statistically significant difference, the hearing thresholds of the two groups were within the normal range of tonal audiometry frequencies. In the otoacoustic emission evaluation, the distortion products and signal/noise ratio of children with FMF were lower in the tested frequencies from 1000 to 4000 Hz ($p < 0.001$).

CONCLUSION: Our results demonstrated that FMF disease may cause hearing loss in children with FMF. Hearing loss in children with familial Mediterranean fever has been observed, showing increased hearing thresholds at all frequencies in audiometry, together with decreased distortion products and signal: noise ratios, demonstrated by distortion product otoacoustic emissions testing. We think this might be due to cochlear involvement. Regular follow-up of auditory function in FMF children may be helpful for determining early possible hearing loss.

KEY WORDS: Familial Mediterranean fever, hearing loss, childhood, audiometry, otoacoustic emission

INTRODUCTION

Familial Mediterranean fever (FMF) is characterized by recurrent attacks of self-limited periodic fever and abdominal, articular, and thoracic pain with inflammation of serous membranes. The disease is an autosomal recessive disorder caused by mutations in the MEditerranean FeVer gene (MEFV), which encodes a protein termed pyrin, and almost completely affects non-Ashkenazi Jews, Armenians, Arabs, and Turkish populations (i.e., people of Mediterranean origin) but can also be seen in other ethnic groups from outside of the Mediterranean region around the world due to widespread intercontinental migration in the early period of the 20th century [1,2].

The most concentrated population of FMF patients in the world is probably in Turkey. It is anticipated that more than 100,000 patients with FMF exist in Turkey [2,3].

The thought of cochlear involvement in FMF is a new and interesting idea in the otologic field. Is this a possibility? To our knowledge, only three studies exist (having controversial findings) in the literature with regard to children with FMF [4-6]. Development of vasculitic disease is seen with increasing frequency in patients with FMF [4,5,7]. Also, various degrees of sensorineural hearing loss (SNHL) can be seen in the progression of some hereditary periodic fever syndromes (HPFS), and FMF is the most common disease of HPFS [3-5]. So, reasonable questions remain on this topic. Distortion product otoacoustic emissions (DPOAEs) and high-frequency audiometry (HFA) testing can help to establish cochlear involvement at an early period of a patient with a risk of hearing loss. In this study, we aimed to evaluate hearing function in children with a diagnosis of FMF using tonal and high-frequency audiometry and DPOAEs.

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Submitted: 04.01.2014 Accepted: 04.06.2014 Available Online Date: 16.07.2014

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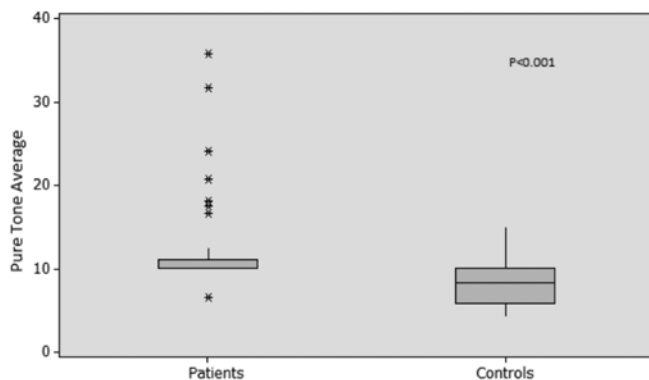
Table 1. Demographic and audiometric data of the groups (audiometric testing revealed a significant difference in hearing levels between groups)

Variables	Hearing levels in dB		"p" value
	Control group	Patient group	
Age (year)	9.86±2.79	11.08±3.12	-
Hz 250	12.45±0.61	16.06±0.67	**
Hz 500	8.90±0.68	12.69±0.74	**
Hz 1000	8.18±0.76	12.75±0.83	**
Hz 2000	8.18±0.81	12.13±0.88	**
Hz 4000	9.23±1.38	15.19±1.51	**
Hz 8000	9.84±1.65	20.25±1.81	**
Hz 10000	13.44±1.93	26.06±2.12	**
Hz 12000	14.27±1.87	27.94±2.05	**
Hz 14000	16.20±1.76	31.06±1.93	**
Hz 16000	17.19±1.80	33.63±1.98	**
PTA	8.23±0.65	12.48±0.71	**

PTA: pure tone average

-: p>0.05 (not significant)

**: p<0.001

**Figure 1.** Pure tone averages of the groups

MATERIALS and METHODS

The present study was conducted in the Otorhinolaryngology and Pediatric Clinics of Afyon Kocatepe University Faculty of Medicine Hospital. A total of 49 patients diagnosed with FMF from the Pediatric Clinics and 49 age- and sex-matched healthy children that were admitted to the Otorhinolaryngology and Pediatric Clinics were included in the study. The mean age of the patient group was 11.08±3.12 (range 6-16) years and 9.86±2.79 (range 6-16) years for the control group. Patients with FMF were diagnosed according to Tel Hashomer criteria, and genetic mutations were detected. The study protocol was approved by the ethics committee of the Afyon Kocatepe University Faculty of Medicine and conducted in accordance with the ethical principles described by the Declaration of Helsinki. Uniform consent was obtained from all parents and the children, if feasible. The patients and the control group were evaluated in the Otolaryngology Department of our center. The patients with a pathologic finding at the otologic examination or history of recurrent otitis media; using proven ototoxic drugs; or having an abnormal tympanometry finding were excluded from the study. All of the children had

undergone a routine ear-nose-throat examination. Following audiologic evaluation, tympanometry, tonal and high-frequency audiometry, and DPOAE testing were conducted.

Auditory Evaluation

Primarily, tympanograms of the patients ("Maico MI 34 diagnostic GmbH impedance meter" Maico diagnostic GmbH, GERMANY) were obtained to prove that middle ear function was normal. Tonal and high-frequency audiometry was performed for 40 subjects who could cooperate in testing with a type "A" tympanogram for both groups. For these tests, an Interacoustics Clinical Audiometer AC 40 device and TDH-39P headphones (Interacoustics A/S, DENMARK) were used. During the high-frequency audiometry, earphones were changed to "Koss R80" digital headphones, and the test was continued with a stimulant. Audiometric evaluation including high frequencies (250, 500, 1000, 2000, 4000, 8000, 10,000, 12,500, and 16,000 Hz) was performed in a soundproof test room. Pure-tone average (PTA) was used to determine the hearing loss. A hearing level of <25 dB was considered normal in the tested frequencies.

Otoacoustic Emission Measurements

Measurements of distortion product otoacoustic emissions (DPOAEs) were carried out for all subjects while the subjects were seated in a soundproof test room (Otodynamics ILO 288 Echoport equipment, Otodynamics Ltd., Hateld, UK). DPOAEs were measured at five different frequencies, ranging from 1000 to 4000 Hz (1000, 1400, 2000, 2800, 4000). By calculating the difference between distortion products (DP) and the noise for two standard deviations, the signal-to-noise ratio (SNR) for each frequency was determined.

Statistical Analysis

Continuous variables were presented as mean±SD. Kolmogorov-Smirnov test was used to evaluate the distribution of variables. Independent sample t-test was used for continuous variables with normal distribution, and Mann-Whitney U-test was used for continuous variables without normal distribution. p<0.05 value was accepted as a significant level. For statistical calculations, MINITAB Statistical Software (Minitab Release 14 Statistical Software 2004) was used.

RESULTS

The age distribution (p>0.05) was not significantly different between the two groups (Table 1). There were statistically significant differences between FMF patients and the control group in terms of hearing levels at all frequencies (250 to 16,000 Hz) in the tonal and high-frequency audiometry (p<0.001). Also, a substantial difference was found in terms of pure tone average between both groups (p<0.001). The hearing thresholds of both groups are shown in Table 1. Pure tone averages of the groups are shown in Figure 1. Statistically significant differences (p<0.001) were also found between FMF patients and the control group in DPOAE measurements at all frequencies DP (1 to 4 kHz) and in SNR measurements at all frequencies (1 to 4 kHz). Table 2 and Figure 2 show the results of the DPOAE and SNR measurements in both groups.

DISCUSSION

FMF can be due to tissue injury by vasculitic, amyloidotic, or thrombophilic pathways^[8]. Cochlear involvement may be possible by these mechanisms. In FMF, pyrin appears to play a major role in the inflam-

Table 2. Comparison of average DPOAE results of the patients with FMF and the controls

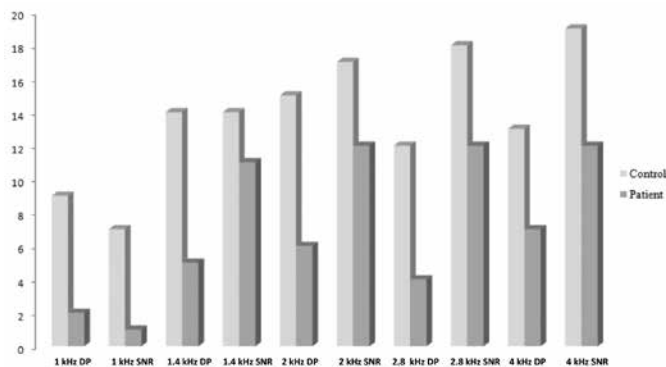
Variables	Control group	Patient group	"p" value
1 kHz DP	9.44±1.32	2.56±1.32	*
SNR	7.12±1.56	1.59±1.56	*
1.4 kHz DP	14.70±1.39	5.84±1.39	**
SNR	14.84±1.68	11.02±1.68	*
2 kHz DP	15.32±1.39	6.19±1.39	**
SNR	17.37±1.60	12.57±1.60	**
2.8 kHz DP	12.15±1.27	4.10±1.27	**
SNR	18.57±1.42	12.29±1.42	**
4 kHz DP	13.22±1.20	7.04±1.20	*
SNR	19.07±1.22	12.54±1.22	**

DP: distortion product ; SNR: signal-to-noise ratio

*: p<0.01

**: p<0.001

DPOAE results of the patients with FMF and the controls revealed a significant difference in terms of DP and SNR measurements between groups

**Figure 2.** DPOAE results of the groups

matory pathways, with regulation of the production of proinflammatory cytokines, such as interleukin 1 β (IL-1 β), tumor necrosis factor- α (TNF- α), and interleukin 6 (IL-6); uncontrolled release of chemoattractants for inflammatory cells; and caspase activation [3, 8].

It is known that the continuity of normal blood supply is vital for normal cochlear function [9]. The spiral ligament (SL) and stria vascularis constitute the cochlear lateral wall, and SL fibrocytes (SLFs) have a pivotal role in the continuity of cochlear homeostasis. In the inflammatory condition, IL-1 β and TNF- α are secreted in the early period of inflammation. These proinflammatory cytokines may act on SLFs to produce various chemoattractants that could activate inflammatory cells and could break down neighboring vascular endothelial cells. This state is like a vicious circle that increases inflammatory cell trafficking from circulation to inflammatory sites [10].

Some vasculitic disorders appear to be more frequent in FMF patients. Henoch-Schönlein purpura (HSP) has been seen in 2.6%-5.0% of pediatric patients with FMF, and 0.8%-1.0% of children with FMF have presented with polyarteritis nodosa (PAN). Another type of vasculitis, protracted febrile myalgia, may be accompanied by FMF. The physiopathology of vasculitis in FMF patients has not been clearly defined [3]. Behçet's disease (BD) has a vasculitic component in the

physiopathologic mechanism and is also seen more often in FMF patients. Both syndromes have a higher prevalence in the ancient silk road, and some MEFV mutations may increase susceptibility in BD [11]. Cochlear involvement has been shown to be present by audiological assessment in the course of BD [12, 13]. Also, in a retrospective study, cerebral stroke in FMF patients has been shown to have a higher prevalence than in the general population. Other studies have reported an increase of early markers of atherosclerosis, such as increased intima-media thickness of the carotid artery, increased endothelial dysfunction, and increased aortic wall stiffness in FMF patients. In another interesting study, a relationship between stroke and high serum fibrinogen levels has been shown in non-FMF patients. Moreover, as in all inflammatory diseases, inflammation is a common prothrombotic condition. Also, the development of amyloidosis is the most serious complication of FMF, and the cochlea is not considered a preserved organ [8].

In the literature, some HPFSs, including FMF, have been associated with hearing loss [14]. One of them, CINCA (or NOMID), was associated with hearing loss of various degrees in 75% of patients in a study by Prieur et al. [15]. Ahmadi et al. found hearing loss at high frequencies related to cochlear damage in patients with NLRP3 (known as CIAS1)-mediated CAPS. Unregulated autoinflammation mediated by interleukin-1 has accounted for cochlear involvement and hearing loss in CAPS [14]. MWS is another member of HPFSs and is related to mutations in the NLRP3 gene, which encodes cryopyrin. Cryopyrin, like pyrin, regulates the production of proinflammatory cytokines, such as IL-1 β . Different degrees of SNHL were shown in 85% of MWS patients in the late period of the disease. The notable recovery of hearing loss with anakinra, a blocker of the activation pathways of cytokines, in patients with MWS was reported. Based on this, cytokines could be potential therapeutic targets for this group of disorders [16]. In addition, Akalin et al. reported recurrent episodes of SNHL in a patient with active FMF who also had the M694V MEFV mutation [17]. Singh-Grewal et al. presented two patients with FMF coexisting with MEFV and CIAS1 mutations and suffering from progressive SNHL [18]. Also, Hornigold et al. [19] presented bilateral SNHL in a patient with familial systemic amyloidosis. All of these could be accepted as rare presentations. But, recently, Ulu et al. [20] first presented hearing loss with involvement of the inner ear via endothelial dysfunction using pulse wave velocity, which is an early marker for determining endothelial dysfunction, in adult patients with FMF.

To our knowledge, three studies of cochlear involvement in children with a diagnosis of FMF exist [4-6]. Uysal et al. [5] presented similar results between a control group and patients with FMF for mean TEOAE correlation percentage, signal-noise ratio, and TEOAE amplitudes at 1, 1.5, 2, 3, and 4 Hz frequency values. On the other hand, Koybası et al. found increased hearing thresholds, including high frequencies (8000, 10,000, 12,500, and 16,000 Hz) in HFA, and showed decreased distortion products and signal-noise ratios for FMF children, including frequencies (1400 Hz to 4000 Hz) in the otoacoustic emission evaluation [4]. Recently, Cevik et al. [6] showed normal DPOAE values ranging from 1020 Hz to 5040 Hz and normal hearing values in an auditory evaluation including HFA between children with FMF and controls. In contrast, in our study using DPOAEs and HFA, in pediatric patients with FMF, hearing levels were clearly lower than in the healthy control group, including frequencies of 1000 Hz to 4000 Hz,

suggesting cochlear involvement. According to our results, we have first presented increased hearing thresholds including all frequencies (250 to 16,000 Hz) in pediatric patients with FMF. Also, as analyzed in Table 1, the difference between the hearing thresholds of the two groups can be seen more prominently at higher frequencies, and despite a statistically significant difference, the hearing thresholds of the two groups were within the normal range at tonal audiometry frequencies. These findings may indicate clear and objective cochlear involvement in children with FMF.

DPOAEs are easily applicable and more valuable for detecting the cochlear component of hearing loss and prove objectively small changes in the cochlea compared to other audiological procedures. HFA can reveal early findings of cochlear damage and is useful for assessment of the population at risk of hearing loss ^[7].

Moreover, children diagnosed with FMF use colchicine for long periods. The effect of colchicine treatment on the cochlea has not been clearly shown and must also be investigated.

In conclusion, our study demonstrated that FMF disease may cause hearing loss in children with FMF. We think this might be due to cochlear involvement. These findings also suggest that regular follow-up of auditory function in FMF children may be helpful in determining early possible hearing loss. Also, this area of research is a novel field, and the reports so far are controversial. Therefore, prospective, multicenter, controlled studies with long-term follow-up and larger participation are needed to clarify this issue.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of Afyon Kocatepe University / 09.01.2013-B.30.2.AKÜ.0.20.05.04/02.

Informed Consent: Written informed consent was obtained from parents of the patients who participated in this study.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept - A.B., A.B.; Design - Ş.U., A.A.; Supervision - A.A., M.S.; Materials - A.B., Ş.U.; Data Collection and/or Processing - A.B., M.S.T., R.K.; Analysis and/or Interpretation - A.B., Ş.U.; Literature Review - A.B., Ş.U.; Writing - A.B.; Critical Review A.A.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study has received no financial support.

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