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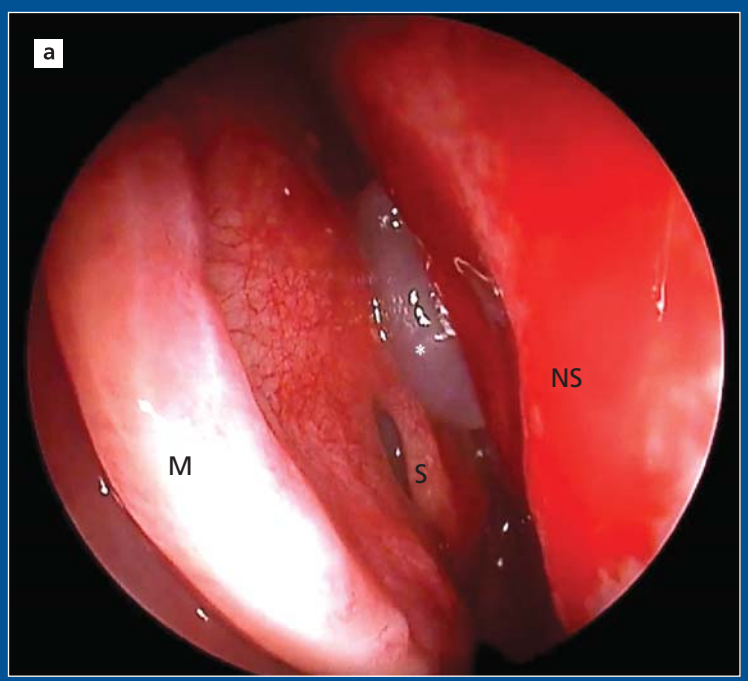

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Description

ENT Updates (formerly Journal of Medical Updates), is a periodical of the Continuing Education, and Scientific Research Association (CESRA), Turkey, which is published in both printed (p-ISSN 2149-7109) and electronic (e-ISSN 2149-6498) versions three times a year on April, August, and December. A peer-reviewed system is used to select manuscripts. The language of the journal is English. The journal is currently indexing and abstracting in Emerging Sources Citation Index (ESCI) by Thomson Reuters, TUBITAK ULAKBIM Turkish Medical Index, Proquest, EBSCO Host, Index Copernicus and Google Scholar.

Aims and Scope

The goal of the journal is to present and improve collective scientific knowledge and the scientific background dealing with otorhinolaryngological disorders and related subjects (allergy, pediatrics, neurology, psychiatry, neurosurgery, radiology, anesthesiology, pulmonology, etc.) via experimental and clinical studies, reviews, case reports, short communications and letters to the editor. The initial aim of this journal is to form a countrywide education platform and to share the recent information and learn about the treatment of various local or rare diseases in aware of the fact that a disease may be rare to a certain region while it is very common to another. The second aim of this journal and Continuous Education and Scientific Research Association (CESRA), a nonprofit organization serving for continuous education, is to represent our country in international arena of science and knowledge with the published papers. We aimed to undertake a novel effort in the international representation and attribution of published articles. That is why we have set an international editorial board from all over the world beside the national board spread to each corner of the country. The target readers of the ENT Updates include otorhinolaryngology specialists and residents as well as all other physicians working in the field of otorhinolaryngology or in related specialities.

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On the Front Cover: Fig. 1. (**a**) Endoscopic view of nasal polypoid lesion (meningoencephalocele sac) between middle turbinate and nasal septum. **M:** middle turbinate, **S:** superior turbinate, **NS:** nasal septum. *Meningoencephalocele sac. İmre A, Pınar E, Ece AA. Ethmoidal meningoencephalocele and cerebrospinal fluid leak after septoplasty: a rare complication. ENT Updates 2017;7(2):108–111.

Experimental Study

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Can local administration of humic acid shorten recovery time of mandibular fractures? Experimental study

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Abstract

Objective: The aim of the present pilot study was to evaluate the effects of a single local dose administration of humic acid on healing of subcondylar mandibular fractures in rats.

Methods: In this study, a randomized experimental protocol was used. The study was conducted with 16 male Wistar-albino rats that were 16–18 weeks old. The rats (n=16) were randomly divided into two groups: Group HA received humic acid (0.3 cc/site, n=8) and Group C received no additional medical administration (control group, n=8). A full-thickness surgical osteotomy was performed in the subcondylar area. A single dose of humic acid (0.3 cc/site) was administered locally by spraying on the bone surfaces of the fracture line. Mandible was dissected on postoperative day 21. Then, fractured hemimandibles were obtained for histopathological examination.

Results: The median score of bone fracture healing was 7.16 (range: 7 to 8) in the Group HA and 7.50 (range: 7 to 8) in the Group C. When the groups were compared in terms of bone healing scores, there was no statistical difference between the Group HA and the Group C (p>0.05).

Conclusion: Results of this study showed that local administration of humic acid was not efficient for healing of bone fractures. However, we are of the opinion that it is required to conduct more comprehensive studies, including humic acid's different concentrations and administration manners, evaluating the effects of humic acid on tissue both histopathologically and in terms of inflammatory and proinflammatory cytokine levels.

Keywords: Humic acid, subcondylar mandibular fractures, fracture healing.

Özet: Lokal hümik asit uygulaması mandibula kırıklarının iyileşme zamanını kısaltabilir mi? Deneysel çalışma

Amaç: Bu pilot çalışmanın amacı tek bir lokal hümik asit dozunun sıçanlarda subkondiler mandibula kırıkları üzerine etkilerini değerlendirmektir.

Yöntem: Bu çalışmada randomize deneysel protokol kullanıldı. Çalışma 16–18 haftalık 16 erkek Wistar albino sıçanlarıyla yürütüldü. Sıçanlar iki gruba randomize edildi. HA grubuna hümik asit (0.3 cc/bölge, n=8) uygulanırken C grubuna (kontrol grubu, n=8) herhangi bir ilave ilaç verilmedi. Subkondiler alanda tam kalınlıkta cerrahi osteotomi yapıldı. Kırık hattının kemik yüzeylerine lokal olarak tek doz hümik asit (0.3 cc/bölge) püskürtüldü. Postoperatif 21. gün mandibula diseke edildi. Daha sonra mandibulalar iki yarıma bölünerek histopatolojik inceleme yapıldı.

Bulgular: Kemik kırığı ortanca iyileşme skorları HA grubunda 7.16 (aralık: 7–8) ve C grubunda 7.50 (aralık: 7–8) idi. Gruplar iyileşme skorları açısından karşılaştırıldığında HA ile C grubu arasında istatistiksel açıdan herhangi bir anlamlı farklılık yoktu (p>0.05).

Sonuç: Bu çalışmanın sonuçları lokal hümik asit uygulamasının kemik kırıklarının iyileşmesinde etkili olmadığını göstermiştir. Ancak, hümik asidin farklı konsantrasyonları ve uygulama yöntemleri dahil, hem histopatolojik olarak hem de enflamatuar ve proenflamatuar sitokin düzeyleri açısından hümik asidin etkilerini değerlendiren daha kapsamlı çalışmaların yürütülmesi gerektiği düşüncesindeyiz.

Anahtar sözcükler: Hümik asit, subkondiler mandibüler kırıklar, kırık iyileşmesi.

Fracture healing is an exceptional biological course described by three intersecting phases: inflammatory reaction, callus arrangement, and bone remodeling.[1] Bone regeneration is influenced by growth factors, cytokines and molecular signaling.[2–4] Numerous factors are included in regeneration and healing of the bone fracture. As

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per, TGF-β is in charge for of mesenchymal stem cell stimulation, engaging osteoprogenitors, osteoblast and chondrocyte differentiation, chemotaxis, and bone matrix production.[5] Proinflammatory cytokines, including interleukin-1 (IL-1), IFN-γ and tumor necrosis factor-α (TNF-α) inhibit osteoblastic collagen production and interrupt formation of the bone matrix.[6,7] These cytokines also increase osteoclastic bone resorption.[7,8] As a result, a clear correlation exists between advanced inflammation and developed resorption of the bone. Thus, immune system activation and inflammation persuaded after bone fracture undesirably affect bone regeneration.

Humic acids (HA) are a group of high-molecular-weight polymers that are primarily derived from the decomposition of dead plants. HA is a dark-brown, carbon-rich material that mostly exists in peat, soil, and well water.[9] HA has been demonstrated to exist in the gastrointestinal tract of humans and animals and could circulate in the blood.[10] HA contains some trace elements that are important for human's health.[11] HA has been used therapeutically for a very long time. Some of its health-related effects are still unclear. Some studies showed that HA causes stimulation of lymphocytes and has antiviral, anti-allergic, anti-ulcerogenic, anti-inflammatory, and antibacterial properties.[12–14] In their study, Çalışır et al. showed that the systemic effects of HA have strong anti-inflammatory and osteoblastic activity.[11]

Mandibular fractures are the most common facial fractures. These fractures can be treated by using a conservative technique or surgery.[15] The most appropriate approach for treatment of subcondylar mandibular fractures has still been a matter of debate today.[16] Regardless of the method selected, possibility of development of various complications is present. In recent years, there has been an increase in the number of studies conducted by using the combinations of various techniques along with the method chosen for treatment of these fractures to shorten recovery time and reduce complications. In the study conducted by Altuntaş et al., for this purpose, which is involved in the present study, it was shown that subcondylar mandibular fractures recovery time was shortened by extracorporeal shock wave therapy.[17]

The results obtained from study of Çalışır et al. indicated that HA in systemic administration could stimulate bone recovery by causing an increase at anti-inflammatory cytokine levels like IL-10 but a decrease at proinflammatory cytokine levels like IL-1β.[11] In our literature reviews, we also could not found a study revealing the effect of local administration of humic acid on recovery of bone fractures.

We aimed to seek an answer for the question "Can HA show this effect when it is also administered to surfaces of fractures locally?" in the present study in order to shorten recovery time of subcondylar mandibular fractures. We hypothesize that administration of HA can function as a novel treatment in bone fracture healing and shorten recovery time of subcondylar mandibular fractures.

Materials and Methods

Experimental animals

The experiments were carried out according to the National Institute of Health (NIH) Guide for the care and use of Laboratory Animals (NIH Publications No. 80-23 Revised 1996). The protocol of the study was approved by the Institutional Review and Animal Ethics Use Committee of Faculty of Medicine of Cumhuriyet University (65202830-050.04.04-19; date: 19.02.2015), and the study was conducted according to accepted guidelines for the care and use of laboratory animals for research.

In this study, a randomized experimental protocol was used. The study was conducted with 16 male Wistar-albino rats that were 16–18 weeks old and had an average body weight of 230±10 g. Wistar albino rats (n=16) were randomly divided into two groups: Group HA received humic acid (0.3 cc/site, n=8) and Group C received no additional medical administration (control group, n=8).

The rats were kept under standard laboratory conditions (12-h light/dark cycles, 24±2 °C, 35–60% humidity). Because of the broken jaws, all the animals were fed only with soft food and water for the first 7 days of experiment. The animals began their normal diets (a standard laboratory diet and available drinking water) after the first week.

Drug and chemicals

Humic acid was obtained from SigmaTau (Rome, Italy). The humic acid solution (0.3 cc/site) was administered locally by spraying on the bone surfaces of the fracture line.

Operation procedure and the study protocol

The animals were anesthetized with intraperitoneal injections of ketamine (7.5 mg/kg) (Ketalar®, Pfizer, Istanbul, Turkey) and xylazine (6 mg/kg) IM (Rompun®, Bayer, Istanbul, Turkey). Each right buccal area of the rats was

shaved and prepared with an antiseptic solution (povidone iodine). Following an approximately 10-mm incision made along the inferior border of the mandible and division of the masseter muscle, a full-thickness surgical osteotomy was made by using mosquito forceps in the subcondylar area, which was confirmed by condyle fragment mobility. Hemostasis was observed both on the fracture line and connected soft tissues, and a single dose of humic acid (0.3 cc/site, n=8) was sprayed in the Group HA by administering an injection. Nothing was administered to the Group C.

The wound was not syringed and no debris was removed. Finally, the skin flap was replaced and sutured. Intramuscular penicillin injections were administered with all the rats for the first 3 days after procedure.

After postoperative 21 day, the animals were euthanatized with the intraperitonial injections of pentothal sodium (200 mg/kg). Mandible was dissected and all soft tissues were removed after sacrificing process. Then, fractured hemimandibles were obtained for histopathological examination.

Histopathological examination

The histological analyses were performed by two (HO, ET) pathologists blind to the samples. All tissue examples were immediately fixed in 10% formalin. After the fixation, specimens were kept at 10% nitric acid, decalcification was completed in 4 days and the specimens were embedded in paraffin. The specimens were cut in the sagittal sections into 5-µm thick sections, transferred to slides for conventional hematoxylin-eosin (H&E) staining and examined by light microscopy (Eclipse 80I; Nikon, Tokyo, Japan). Digital camera and auxiliary equipment (USB (H) EXT 1/0; Nikon, Tokyo, Japan) were used with microscope to obtain digital images of the sections. The amount of the ossification for each section was scored out of 10 as described by Huo and Troiano[18] (Table 1). The total score of the scale ranged from 1 point (fibrous tissue) to 10 points (mature bone).

Table 1. Histological scoring system for the evaluation of fracture healing.

Score	Histological findings of the fracture zone
1 point	Fibrous tissue
2 points	Mainly fibrous tissue and small amount of cartilage tissue
3 points	Equal amount of fibrous and cartilage tissues
4 points	Completely cartilage tissue
5 points	Mainly cartilage tissue and small amount of immature (woven) bone
6 points	Equal amount of cartilage tissue and immature bone
7 points	Significantly immature (woven) bone and small amount of cartilage
8 points	Completely immature (woven) bone
9 points	Immature bone and small amount of mature bone
10 points	Mature (lamellar) bone

Statistical analysis

The data were analyzed by using Statistical Package of Social Science (SPSS Inc., Chicago, IL, USA) for Windows version 22.0. Sections of all specimens stained with hematoxylin-eosin were scored. Mean scores were calculated for both groups and the differences between the groups were statistically analyzed. The data were expressed as mean, median, and minimum-maximum values. Bone fracture healing scores were analyzed by using Mann-Whitney U test. Level of significance was set at $p<0.05$.

Results

Two rats in the Group HA and two rats in the Group C died three days after the surgery due to dehydration and nutritional problems. Therefore, histological examination was not accomplished on these rats. Finally, 6 rats in both groups were included in the present study. All rats well tolerated the administration and no significant weight loss was observed until the end of the experiment.

Table 2 shows the histological scores of all specimens stained with H&E in terms of bone fracture healing.

Table 2. Histological scores of fracture healing for both groups.

	Minimum	Maximum	Median	Mode	Mean	p-value (MW)
Group HA, (n=6)	7	8	7	7	7.17±0.41	12.000
Group C, (n=6)	7	8	7.5	7*	7.5±0.55	0.394

*Because the number of samples who received 7 and 8 points was equal, the smaller one was chosen.

The median score of bone fracture healing was 7.16 (range: 7 to 8) in the Group HA and 7.50 (range: 7 to 8) in the Group C. When the groups were compared in terms of bone healing scores, there was no statistical difference between the Group HA and the Group C ($p>0.05$).

Discussion

This study was designed to investigate the effect of a single dose administration of HA on bone healing and the histolopathological features of the new bone. The present study showed that the controls and the rats administered with a single dose of HA did not show any significant difference in terms of bone healing scores.

The number of studies examining the effects of HA on bone tissue is rather limited. It was determined in study of Tkachenko et al.[19] that even though a significant increase was observed in recovery and formation of osteocyte when HA was administered to experimentally formed fracture line for a week, it caused a decrease in osteogenesis when administration time was extended. On the contrary, in the study on Kel'ginbaev et al.,[20] HA was observed to have a positive effect on regeneration of bone tissue. Similarly, in their study, Çalışır et al.[11] also observed that daily oral administration of 80 and 150 mg/kg HA decreased the alveolar bone loss and increased osteoblastic activity. The effect of systemic HA administration on bone recovery was examined in all three studies; however, we could not find a study evaluating local administration. Therefore, this is the first study examining the effect of local HA administration on bone.

It is known that proinflammatory and anti-inflammatory cytokine levels have an effect on recovery of bone fractures.[7] HA are the most common forms of organic carbon found in nature.[9] They exhibit strong anti-inflammatory effects by inhibiting IL-1β and TNF-α secretion activated by leukocytes.[21] Çalışır et al.[11] determined in their study that HA caused an increase in anti-inflammatory cytokine (IL-10) level and on the other hand, a decrease in proinflammatory cytokine (IL-1β) levels when different doses of HA (20, 80 and 150 mg/kg) were administered via gastric feeding for 15 days in experimental rat periodontitis model. In the light of these results, they pointed out that 80 mg/kg/day HA administration had strong anti-inflammatory characteristics. Depending on this finding, they drew attention that HA could increase anti-inflammatory cytokine level and also enhance osteogenesis by decreasing production of proinflammatory cytokine. The study of Çalışır et al.[11] was a significant reference point in terms of our study's hypothesis. However, we could not observe a similar effect in local single dose administration of HA.

There are studies in the literature, which indicates topical and spray forms of HA and its derivatives may be effective in wound healing, psoriasis, dermatitis, and rheumatoid arthritis treatment.[22] Therefore, the results of this study showed that local administration of HA was not efficient for healing of bone fractures. However, we are of the opinion that it is required to conduct more comprehensive studies, including HA's different concentrations and administration manners, evaluating the effects of HA on tissue both histopathologically and in terms of inflammatory and proinflammatory cytokine levels.

Conclusion

The aim of the present pilot study was to investigate the effects of local administration of HA on bone fracture healing in an experimental model of subcondylar mandibular fractures in rats.

Despite the fact that the results of the present study showed that single dose local administration of HA did not have a positive effect on recovery of subcondylar mandibular fractures, it should be kept in mind that there are studies in the literature indicating HA is effective on bone recovery in systemic administration. For this reason, with the locally repeated HA administrations or methods, which may provide longer contact of HA with fracture surface during recovery time, in future, we think that the efficiency of HA should be examined in more details.

Conflict of Interest: No conflicts declared.

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Clinical Research

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Cytokine gene variants/expressions and non-syndromic microtia – is there a link?

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Abstract

Objective: Although many genetic and environmental factors are investigated the etiopathogenesis of microtia, it still remains unclear. We investigated the relationship between the variants/expression of pro- and anti-inflammatory cytokines [interleukin (IL) 6, IL-10, tumor necrosis factor-alpha (TNF-α), transforming growth factor beta (TGF-β1), interferon gamma (IFN-γ)] and susceptibility non-syndromic microtia in a Turkish cohort.

Methods: Nineteen unrelated cases with microtia and 40 healthy controls were included in the present study. Cytokine variants were tested by polymerase chain reaction with sequence-specific primers (PCR-SSP) method.

Results: It was found that IL-6 (-174) GG genotype (high expression) was higher in microtia cases than the controls (p=0.010) while IL-6 (-174) GC (high expression) genotype was lower in patients (p=0.003). For IL-6 (-174), patients with GG genotype had a 5895-fold increased risk for microtia. IFN-γ (+874) variant AA genotype (low expression) was lower in microtia cases (p=0.009). IL-6 (-174) G allele was more prevalent in patient group compared to controls while C allele was lower in patients than controls (p=0.003). IFN-γ (+874) variant T allele was more prevalent in cases while A allele was lower in cases (p=0.017).

Conclusion: We have demonstrated for the first time that the cytokine variants constitute risk factors for developing microtia. Our study suggests that the IFN-γ (+874) and IL-6 (-174) variants may be considered as a risk factor for microtia in a Turkish cohorts.

Keywords: Non-syndromic microtia, cytokine, variant, expression.

Özet: Sitokin gen varyantları/ekspresyonları ve non-sendromik mikrotia – Bir ilişki var mıdır?

Amaç: Mikrotianın etyopatogenezinde birçok genetik ve çevresel faktörler araştırılmasına rağmen hala belirsizlik vardır. Bu çalışmada bir Türk kohortunda pro- ve anti-enflamatuar sitokinlerin [interlökin (IL) 6, IL-10, tümör nekroz faktör alfa (TNF-α), transforme edici büyüme faktörü beta (TGF-β1), İnterferon gama (IFN-γ)] varyant/ekspresyonu ve sendromik-olmayan mikrotiaya yatkınlık arasındaki ilişkiyi araştırdık.

Yöntem: Çalışmaya akraba olmayan 19 mikrotiyalı olgu ve 40 sağlıklı gönüllü kontrol dahil edildi. Sitokin varyantları dizi spesifik primer-polimeraz zincir reaksiyonu (PCR-SSP) metodu kullanılarak analiz edildi.

Bulgular: IL-6 (-174) GC genotipi (yüksek ekspresyon) mikrotia vakalarında daha düşükken (p=0.003), IL-6 (-174) GG genotipi (yüksek ekspresyon) mikrotia vakalarında kontrolden daha yüksek olarak bulundu (p=0.010). IL-6 (-174) için, GG genotipi taşıyan hastalar mikrotia için 5895 kat yüksek riske sahipti. IFN-γ (+874) varyant AA genotip (düşük ekspresyon) mikrotia vakalarında düşüktü (p=0.009). IL-6 (-174) C alleli hastalarda kontrollere göre düşükken, G alleli hasta grubunda kontrole göre daha yaygındı (p=0.003). IFN-γ (+874) varyant A alleli hastalarda düşükken, T alleli hastalarda daha yaygındı (p=0.017).

Sonuç: Burada mikrotia gelişimi için sitokin varyantlarının risk faktörü teşkil edeceğini ilk defa gösterdik. Sonuçlarımız IFN-γ (+874) ve IL-6 (-174) varyantlarının Türk toplumunda mikrotia gelişimi ile ilişkili olabileceğini öne sürmektedir.

Anahtar sözcükler: Sendromik olmayan mikrotia, sitokin, varyant, ekspresyon.

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Microtia, manifested by a small, abnormally shaped auricle, is among the most common external ear anomalies; the estimated prevalence varies between 0.8 and 4.2 per 10,000 births depending on the population.[1] It is more common in males, particularly the isolated form. The right ear is more frequently involved.[2] Many factors have been implicated in the etiology, including genetic mutations, vascular abnormalities, and teratogenic agents. Multifactorial inheritance is usually thought to be the most possible cause; however, this is still debatable.[3]

Cytokines are crucial regulators of both maternal receptivity and embryo competence for implantation. There are now numerous studies reporting that cytokines play a role in embryo development, implantation, trophoblast invasion and placental development. Interleukin 6 (IL-6) is a cytokine, secreted by endometrial epithelial cells. It was shown to be related with improved blastocyst development and implantation rates. IL-10 is a pleiotropic cytokine and was shown to regulate resistance to inflammatory stimuli as lipopolysaccaride by down-regulating the amount of pro-inflammatory cytokines in the uterus and placenta.[4] The transforming growth factor beta (TGF-β) superfamily of growth factors contains more than 30 different members. The ligands and their downstream pathway components are very well preserved during evolution, and they regulate various cellular functions. Their actions are regulated during embryonic development, resulting in a variety of astonishing cellular responses.[5] Interferon gamma (IFN-γ) is a pro-inflammatory cytokine produced in the utereus during early gestation. Studies in mice reported that a localized and punctual synthesis of IFN-γ by uterine natural killer cells plays a role in normal placental development and pregnancy outcome.[6] Tumor necrosis factor-alpha (TNF-α) is a cytokine with numerous functions and was identified in the ovary, fallopian tubes, uterus, and placenta, and it is expressed in embryonic tissues almost at all stages of development.[7]

We investigated the relationship between the variants of key pro- and anti-inflammatory cytokines [IL-6 (-174), IL-10 (-1082,-819,-592), IFN-γ (+874), TGF-β1 (codon 10 and 25), TNF-α (-308)] and susceptibility microtia in a Turkish cohort. In addition, expression levels of these cytokines signified in kit procedure were evaluated.

Materials and Methods

Study population

The study group consisted of 19 subjects with microtia, and 40 unrelated healthy control subjects with no personal or family history of dysmorphic disorders. Subjects with microtia were recruited consecutively and prospectively from those who were treated and followed-up in the Plastic, Reconstructive and Aesthetic Surgery Department. All subjects, patients and controls were of Turkish origin. Healthy control group was recruited from the patients living in the same geographical areas, and they were well-matched with the patient group in terms of gender, age and ethnicity. The protocol of this study was approved by the Institutional Ethics Committee, and all subjects gave written informed consent before enrolling in the study.

Genotyping

Whole blood was collected in EDTA tubes and genomic DNA was extracted using salting out method[8] and stored at -20oC until analysis. Cytokine genotyping was performed by the polymerase chain reaction sequence-specific primer method (PCR-SSP), using the Cytokine Genotyping Tray kit according to the manufacturer's instructions. Single nucleotide variants for five cytokines IL-6 (-174), IL-10 (-1082,-819,-592), IFN-γ (+874), TGF-β1 (codon 10 and 25), TNF-α (-308) were analyzed previously described by Karaoglan et al.[9] The expression levels of these cytokines signified in kit procedure were evaluated.

Statistical analysis

Statistical analysis was performed using software SPSS version 18.0 for Windows (SPSS Inc., Chicago, IL, USA). The statistical significance of the differences among the groups was estimated by logistic regression analysis. Odds ratio (OR) and 95% confidence interval (CI) were also calculated. Differences in the genotype distribution among the two groups were compared with chi-square test and, when needed, Fisher's exact test was used. The Hardy-Weinberg equilibrium (HWE) was determined using a software analysis.[10] The level of significance was set at $p \leq 0.05$.

Results

Genotype distributions and allele frequencies of TNF-α (-308), IL-6 (-174), and IFN-γ (+874) variants are presented in Table 1. TNF-α (-308) genotype distribution was not significantly different between microtia cases and healthy controls. All cases and controls were in HWE (HWEpa: 0.739, HWEpb: 0.906). A statistically significant difference in the genotype distribution between microtia cases and healthy controls was found for IL-6 (-174) variant. It was noted that IL-6 (-174) GG genotype (high expression) was higher in microtia cases than the

Table 1. Genotype distribution of TNF-α (-308), IL-6 (-174) and IFN-γ (+874) variants between cases and controls.

	Genotype-expression	Microtia cases n^a (%)	Controls n^b (%)	OR*	%95 CI*	p*
TNF-α (-308)	GG (high)	18 (94.7)	36 (89.2)			
	AG (high)	1 (5.3)	4 (10.8)	0.052	0.052–4.807	1.000
IL-6 (-174)	GG (high)	17 (88.2)	20 (50)	5.895	1.482–23.442	**0.010**
	GC (high)	2 (11.8)	17 (43.2)	0.176	0.036–0.870	**0.033**
	CC (low)	0 (0)	3 (6.8)	0.925	0.847–1.010	0.544
IFN-γ (+874)	TT (high)	5 (26.3)	5 (12.2)	2.500	0.625–9.996	0.266
	AT (intermediate)	12 (63.2)	17 (43.2)	2.319	0.754–7.132	0.170
	AA (low)	2 (10.5)	18 (44.6)	0.144	0.029–0.707	**0.009**

TNF-α: tumor necrosis factor-alpha, IL-6: interleukin-6, IFN-γ: interferon gamma.
n^a=19, n^b=40, *Fisher's exact test.
The statistically significant results are showed in bold.

controls (p=0.010, OR: 5.85, 95% CI: 1.482–23.442). IL-6 (-174) GC (high expression) genotype was lower in patients, (p=0.003, OR: 0176, 95% CI: 0.036–0.870). The genotype distribution among all cases and the controls was concordant with the HWE (HWEpa: 0.808, HWEpb: 0.813).

There was a significant difference for genotype distribution of (+874) variant of IFN-γ gene between groups. IFN-γ (+874) variant AA genotype (low expression) was lower in microtia cases (p=0.009, OR: 0.144, 95%CI: 0.029–0.707). All groups were in HWE (HWEpa: 0.191, HWEpb: 0.754).

Statistical analysis showed that IL-10 (-1082, -819, -592) and TGF-β (codon 10 and 25) genotypes did not significantly differ between the patient and control groups [data not shown (p>0.05).]. When the IL-10 and TGF-β1 haplotype expressions were compared, no statistically significance was found between the groups. IL-10 deviated from HWE in the groups. The genotype distribution of TGF-β1 among the groups was in line with HWE.

Allele frequencies of TNF-α (-308), IL-6 (-174) and IFN-γ (+874) variants are given in Table 2. It was found that allele frequencies of IL-6 (-174) and IFN-γ (+874) variants showed statistically significant difference between the microtia cases and the controls. IL-6 (-174) G allele was higher in microtia group compared to controls while C allele was lower in microtia groups than controls (p=0.003, OR: 7.263, 95% CI: 1.614–32.680). IFN-γ (+874) variant T allele was more prevalent in cases while A allele was lower in cases (p=0.017, OR: 0.370, 95% CI: 0.168–0.819).

Table 2. Allele distribution of TNF-α (-308), IL-6 (-174) and IFN-γ (+874) variants between cases and controls.

	Alleles	Microtia cases n^a (%)	Controls n^b (%)	OR*	%95 CI*	p*
TNF-α (-308)	G	37 (97.37)	76 (95.00)			
	A	1 (2.63)	4 (5.00)	1.947	0.210–18.042	**1.000**
IL-6 (-174)	G	36 (94.74)	57 (71.25)			
	C	2 (5.26)	23 (28.75)	7.263	1.614–32.680	**0.003**
IFN-γ (+874)	T	22 (57.89)	27 (33.75)			
	A	**16 (42.01)**	**53 (66.25)**	**0.370**	**0.168-0.819**	**0.017**

TNF-α: tumor necrosis factor-alpha, IL-6: interleukin-6, IFN-γ: interferon gamma.
n^a=38, n^b=80, *Fisher's exact test.
The statistically significant results are showed in bold.

Discussion

Microtia is a congenital malformation of the ear, ranging from minimal abnormalities to major structural changes or even total absence of the external ear (anotia).[11] Furthermore, most of the cases with microtia also have conductive hearing loss on the affected side.[12] Microtia may be isolated, or manifested as an element of anomalies or a syndrome.[11] Several genetic methods have been used to study microtia, such as linkage analysis, direct sequencing of DNA, investigation of single gene disorders associated with microtia, searching for cytogenetic rearrangements in patients, and the study of animal models. Data for a crucial genetic relationship with microtia revealed higher concordance in monozygotic twins compared to dizygotic twins, 38.5% and 4.5%, respectively.[11,13] Familial cases with autosomal recessive or dominant modes of inheritance with variable expression and incomplete penetrance were also reported.[14] Prevalence of familial cases was estimated between 3 and 34%.[11,15] Mouse models showed that mutations in specific genes could result in microtia.

Immunologic system has a crucial function that enables normal pregnancy development and promotes the development of complications. Success in pregnancy outcome seems to be closely related to a distinct balance between the cytokines Th1 and Th2, both involved in fetal growth and development. In this study, we investigated the relation between the IL-6 (-174), IL-10 (-1082,-819,-592), IFN-γ (+874), TGF-β1 (codon 10 and 25), and TNF-α (-308) variants and susceptibility to microtia in a Turkish cohort. Furthermore, we evaluated expression levels of these cytokines signified in kit procedure.

IL-6 is a marker of inflammation and it plays a pro-inflammatory and anti-inflammatory mediator role. IL-6 is expressed in a various cell types, including blood cells, fibroblasts, macrophages and adipose cells. IL-6 was also shown to be expressed in the fallopian tubes of humans and pigs. IL-6 synthesized in endometrial epithelial cells is associated with improved blastocyst development and implantation rates.[16] IL-6 was also reported to enhance cell number and decrease apoptosis in mouse blastocyts.[17] IL-6 knockout mice are fertile; however, their fertility is diminished, implantation rates are low and miscarriage rates in mid-gestation are high. The human IL-6 gene has about 50 variants in its promoter region.[18] A functional -174GC (rs1800795) variant is related to the fundamentally IL-6 transcription rate, which could affect the level of serum IL-6. Compared to -174CC genotype carriers, -174 GG/GC carriers have a higher IL-6 expression.[17] In the present study, we found that IL-6 (-174) variant genotype distribution was related with microtia (Table 1). IL-6 (-174) GG genotype (high expression) was higher in microtia cases than the controls (p=0.010) while IL-6 (-174) GC (high expression) genotype was lower in patients, (p=0.003). It seems that GC genotypes create protection advantage of heterozygosity for microtia. Also, IL-6 (-174) G allele was more prevalent in microtia group compared to control group while C allele was lower in microtia cases than controls (p=0.003) (Table 2).

IFN-γ is crucial in several cellular processes, such as inducing innate and adaptive immune responses, hindering cell proliferation and stimulating apoptosis.[19] It is mainly secreted by CD4 +Th cells, CD8+T cytotoxic cells, and natural killer cells. Research in mice suggested that a localized and punctual production of IFN-γ by uterine natural killer cells facilitates normal placental development and pregnancy outcome.[6] The human IFN-γ gene has a variant in the first intron at its 5' end, next to a CA repeat region (+ 874 A>T, rs2430561) that affects the synthesis of IFN-γ and had been associated with several autoimmune and chronic inflammatory conditions.[20] Investigation of the biological role of this variant showed that + 874 T allele carriers had higher production of IFN-γ.[20] We found that IFN-γ (+874) variant AA genotype (low expression) was lower in cases (p=0.009) (Table 1). It was thought that IFN-γ AA genotype had protective role against microtia. Also, IFN-γ A allele was lower in microtia cases (p=0.017) (Table 2).

TNF-α is a cytotoxic protein which arises after endotoxin treatment in rabbit serum. TNF-α acts as a mediator in apoptosis processes and is involved in infection and immune reactions. It plays a significant role in the etiopathogenesis of several diseases: sepsis, multiple sclerosis, osteoporosis, some types of cancer and diabetes.[21] Studies conducted in the past few years have noted the importance of TNF-α in reproductive medicine. It seems to have an impact on pregnancy. Therefore, TNF-α protein, TNF-α RNA and also its receptors TNF-R1 and TNF-R2 are expressed during the pregnancy in various tissues including ovaries, endometrium, placenta and in the fetus itself.[21] It has been known that TNF-α wields deleterious effects on pre-implantation embryo development. TNF-α given to mice during early pregnancy had a detrimental effect on implantation or reduced litter size in mice and rats.[22] TNF-α has been held responsible in embryopathies occurring due to developmental toxicants, various stresses, and maternal metabolic derangements. TNF-α appears to involve in the differentiation and growth processes in a normal pregnancy. In the present

study, TNF-α genotype distribution showed no association between microtia cases and controls (p>0.05). Also, we found no significant difference according to haplotype analysis between groups (Tables 1 and 2).

In humans, IL-10 is encoded by five exons and four introns and is located at the 1q31-32 position. IL-10, a pleiotropic cytokine, affects in the process of inflammation and immunoregulation. It is likely that IL-10 is a major cytokine for the maintenance of pregnancy thanks to its protective effect on the feto-placental unit. It hinders the synthesis of inflammatory cytokines including IL-6, TNF-α and IFN-γ. Along with IL-4 and IL-13, IL-10 seems to regulate trophoblast invasion and to facilitate placental development.[23] Recent studies reported that some biologically important variants were present in the IL-10 gene. These variants may affect the interleukin-10 production rate. Synthesis of IL-10 is modulated at transcriptional, posttranscriptional and translational levels.[24] These variants are found at positions -592 (rs1800872, A/C), -819 (rs1800871, T/C) and -1082 (rs1800896, A/G) (24). In this study, we noted no association between IL-10 genotype distribution/haplotype analysis and microtia (p>0.05).

TGF-β superfamily is a group of signaling factors such as TGF-β and bone morphogenetic proteins (BMPs) with a significant capability to stimulate cartilage and bone.[25] In the embryonic phase, chondrocytes develop in distinct phases of cell proliferation, condensation and maturation to proliferating chondroblasts synthesizing collagen type II and proteoglycans. Exogenous TGF-β induces embryonic development in vitro, facilitating blastocyst proliferation and development and raising the number of blastocysts.[26] Several TGF-β superfamily members, their receptors and Smads are expressed in embryos during late phases. They also found to be involved in gastrulation and organogenesis.[26] In this study, we identified no statistically significant association between the cases and the control subjects according to genotype distribution and haplotype analysis of the TGF-β1 (codon 10 and 25).

Conclusion

While the precise pathogenesis of microtia remains ill-defined, it is believed to be a multifactorial malformation in which environmental and genetic factors are involved. As far as we know, the association between cytokine variants and microtia has not been investigated previously in a Turkish population. Our data suggest that the IL-6 (-174) and IFN-γ (+874) variants may have a functional effect in microtia. Our data provide a genetic basis for the hypothesis that cytokine variants may play a role in the formation of microtia. Larger studies in different ethnic populations are needed to confirm our findings.

Conflict of Interest: No conflicts declared.

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Efficacy and safety of combined treatment of acute rhinosinusitis by herbal medicinal product Sinupret and mometasone furoate nasal spray

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Abstract

Objective: Herbal medicinal products have a well-established role in therapy of upper airway inflammations. Current evidence supports the use of intranasal corticosteroids for improvement in clinical symptoms of uncomplicated acute rhinosinusitis (ARS). We aimed to evaluate efficacy and safety of combined therapy by mometasone furoate nasal spray (MFNS) and oral herbal medicinal product Sinupret in comparison to MFNS monotherapy when treating mild to moderate ARS.

Methods: Forty-six ARS patients were divided into two groups. Group 1 (n=23) received herbal drug Sinupret, 160 mg per os, three times daily and MFNS 200 µg twice daily for 7 days. Group 2 (n=23) received only MFNS 200 µg twice daily for 7 days. We assessed total symptom score (TSS), individual symptom scores for each symptom (nasal obstruction, rhinorrhea, postnasal drip, facial pain/pressure, impaired sense of smell) and endoscopic findings (mucosal edema, mucopurulent secretion), before and after treatment.

Results: Significant improvement of all clinical parameters was found after both treatment modalities (p<0.000). We observed lower post-treatment TSS (p=0.002), nasal obstruction (p=0.001), rhinorrhea (p=0.001), facial pain (p=0.001), impaired sense of smell (p=0.002), mucosal edema (p=0.003) and mucopurulent secretion (p=0.001) in MFNS/Sinupret group than in MFNS group. We found no adverse events in MFNS/Sinupret group, while only 1 patient reported mild epistaxis and 1 patient reported dryness in the nose in MFNS Group.

Conclusion: Our results suggest better efficacy of combined MFNS/Sinupret therapy of ARS on nasal symptoms and endoscopic findings, with the absence of adverse events in comparison to MFNS monotherapy.

Keywords: Glucocorticoids, inflammation, medicinal plants, rhinitis, sinusitis.

Özet: Akut rinosinüzit tedavisinde bitkisel tıbbi ürün Sinupret ile mometazon furoatın kombine kullanımının etkinliği ve güvenilirliği

Amaç: Bitkisel tıbbi ürünlerin üst solunum yolu enflamasyonlarındaki etkinliği bilinmektedir. Güncel bilgilerimiz komplike olmayan akut rinosinüzitte, intranazal kortikosteroidlerin semptomları iyileştirdiğini desteklemektedir. Bu çalışmadaki amacımız, hafif ve orta şiddetteki akut rinosinüzitte mometazon furoat sprey ve oral bitkisel ilaç Sinupret'in birlikte kullanımını mometazon furoat sprey monoterapisi ile karşılaştırmaktır.

Yöntem: Kırk altı akut rinosinüzitli hasta iki gruba ayrıldı. Grup 1 (n=23) günde 3 kez Sinupret, 160 mg oral ve günde 2 kez mometazon furoat sprey 200 µg kullandı. Grup 2 (n=23) ise sadece 7 gün süreyle günde 2 kez mometazon furoat sprey 200 µg kullandı. Çalışmada tedavi öncesi ve sonrası semptomlar ayrı ayrı (nazal obstrüksiyon, rinore, postnazal akıntı, fasiyal ağrı koku bozukluğu), toplam semptom skoru ve endoskopik bulgular (mukoza ödemi ve mukoprülan sekresyon) değerlendirildi.

Bulgular: Tedavi sonrası her iki tedavi grubundaki tüm klinik parametrelerde düzelme gözlendi (p<0.000). MFNS/Sinupret grubunda MFNS grubundan daha düşük toplam semptom skoru (p=0.002), burun tıkanıklığı (p=0.001), burun akıntısı (p=0.001), yüz ağrısı (p=0.001), koku bozukluğu (p=0.002), mukozal ödem (p=0.003) ve mukopürulan akıntı (p=0.001) olduğu gözlemlendi. MFNS/Sinupret grubunda hiç bir yan etki görülmezken, sadece MFNS grubunda 1 hastada hafif epistaksis ve 1 burun kuruluğu gözlendi.

Sonuç: Sonuçlarımız akut rinosinüzitte MFNS/Sinupret kombine tedavisinin semptomlar ve endoskopik bulgular üzerinde daha etkili olduğunu göstermiştir. MFNS monoterapisine kıyasla hiçbir advers olay bildirilmemiştir.

Anahtar sözcükler: Glukokortikoidler, inflamasyon, tıbbi bitki, rinit, sinüzit.

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Acute rhinosinusitis (ARS) is an inflammatory disease with a sudden onset including the mucosal membrane of paranasal sinuses and both nasal cavities. About 98 to 99.5% of the cases of ARS are caused by viruses, especially rhinoviruses, coronaviruses, parainfluenza, and influenza viruses, and adenoviruses.[1] Secondary bacterial infection is observed in about 0.5 to 2% of cases.[2] The pathophysiology of ARS is complex with a dominant role of inflammatory mucosal swelling, confining of natural sinus ostia in the area of ostiomeatal complex and sphenoethmoidal recess, and impaired mucociliary transport.[3] Viral infections disturb the function of ciliated cells of the pseudostratified respiratory epithelium, leading to mucociliary clearance impairment. This results in increase of cytokine and chemokine production, neutrophil chemoattraction, and bradykinin and leukotrienes releases. Therefore, vessel dilatation leads to higher mucosal swelling. Transudation and mucosal gland secretion accumulation within the sinuses favor the development of bacteria which release toxins to develop inflammation, leading to a cruel circle effect.[3]

Antibiotics are the most common treatment agents in ARS. However, as ARS is mostly a viral disease, the moderate benefits of antibiotics should be weighed against associated risks such as allergic reactions, gastrointestinal diseases and the development of resistant bacterial germs.[4] There is a reasonable evidence of use of intranasal corticosteroids in the treatment of ARS. Meltzer et al.[5] demonstrated the efficacy of mometasone furoate nasal spray as an effective monotherapy in uncomplicated ARS, maintaining a proposal to decrease recommending antibiotics for patients presenting with these clinical outcomes. The other authors suggest the use of steroid and a topical antibiotic combination into the nasal cavity healing uncomplicated bacterial ARS.[6]

Herbal medicines have been used for centuries for the treatment of many disorders. However, to date there are only several controlled, randomized analyses which evaluated the effectiveness of herbal medicine in therapy of ARS. Sinupret is a trademarked herbal preparation developed in Germany, available in tablet and drop forms, and composed of five herbal extracts: gentian (*Gentiana lutea*, root); primrose (*Primula veris*, flower); common sorrel (*Rumex acetosa*, herb); elder (*Sambucus nigra*, flower); European vervain (*Verbena officinalis*, herb). Previous investigations clearly demonstrated mucolytic, secretomotoric, anti-inflammatory, antiviral and antibacterial effects of this medicinal product.[7–10] These characteristics, as well as the results of two double-blind, placebo-controlled studies recommended the use of Sinupret as a good treatment option in both ARS and chronic rhinosinusitis (CRS).[11,12] The aim of our study was to evaluate the efficacy and safety of combined mometasone furoate nasal spray (MFNS) and oral Sinupret therapy in comparison to MFNS monotherapy when treating mild to moderate ARS. To our knowledge, this is the first such study presented in the literature.

Materials and Methods

Study design

This was a non-interventional, non-placebo controlled, case-control study of two consecutive case series, based on the treatment of ARS. We conducted a retrospective analysis of prospectively collected data at three institutions from January to December 2016. This investigation was conducted in accordance with the Declaration of Helsinki. The local Ethics Committee approved the study protocol (MFVMA06/16-18/) and we obtained written informed consent from each patient.

Study participants

Forty-six (n=46) adult patients with diagnosis of ARS according to the criteria of the European Position Paper on Rhinosinusitis and Nasal Polyps (EPOS 2012),[13] aged from 18 to 61 years were enrolled in the study. Patients had inflammation of the nasal cavity/paranasal sinuses for 7 or more days and less than 12 weeks with at least two of the following symptoms: nasal obstruction, anterior nasal secretion/postnasal drip, facial pain/pressure, and/or impaired or loss of the sense of smell. On nasal endoscopic examination, patients could have mucosal edema and mucopurulent secretion predominantly in the middle meatus.

The patients were divided into two groups. Group 1 (n=23) received herbal medicinal product Sinupret® forte tablets of 160 mg (Bionorica, Neumarkt, Germany), three times daily and MFNS (Nasonex®, Merck Sharp & Dohme, Hertfordshire, UK) 200 µg twice daily (two puffs in each nostril in the morning and in the evening) for 7 days. Group 2 (n=23) received only MFNS 200 µg twice daily for 7 days.

Exclusion criteria were: younger than 18 and older than 65 years, CRS with or without nasal polyps, nasal/paranasal sinus surgery within 6 months before study, nasal septum deviation and/or middle turbinate hypertrophy significantly impairing nasal airflow and corticosteroid spray application, systemic diseases affecting the nose (cystic fibrosis, Churg-Strauss syndrome, Wegener's granulomatosis, etc.), seasonal allergic rhinitis, bronchial asthma, aspirin sensitivity, hypersensitivity to study medications, the use of oral or

topical antibiotics, antihistamines, corticosteroids and leukotriene antagonists within the four weeks before the start of the study, the use of mucolytics, decongestants and analgesics within the 7 days before the investigation, pregnancy and lactation, diabetes mellitus, and smoking. Subjects were excluded if they had symptoms or signs of severe bacterial ARS (fever >38°, persistent severe unilateral facial or tooth pain, facial swelling, profuse unilateral mucopurulent secretion).

Clinical evaluation

Intensity of 5 rhinosinusitis symptoms (nasal obstruction, rhinorrhea, postnasal drip, facial pain/pressure, impaired sense of smell) was assessed at the start of the study (visit 1) and within the two days after the end of investigation (visit 2) using a visual analogue scale (VAS) (0–10 cm; from 0=absent to 10=maximum intensity). Patients indicating their symptoms' score to be from 0 to 3 were diagnosed as "mild ARS". Symptoms in the score range from 4 to 7 were diagnosed as "moderate ARS" while the score from 8 to 10 with fever of above 38°C for at least 3 days were diagnosed as "severe ARS". The patients with severe disease were excluded from investigation.

At visits 1 and 2, a rhinologist with proven experience in nasal endoscopy used a 4 mm 0° endoscope to evaluate the presence of mucosal edema and mucopurulent secretion in the middle meatus. A four-point scales were used for assessment of endoscopic findings: mucosal edema scored from 0=no edema to 3=severe edema; mucopurulent secretion from 0=none to 3=profuse. The maximum endoscopic score is 6, bilaterally for each endoscopic sign. According to the EPOS 2012 recommendations, radiological examinations (X-ray, CT, and MRI) or bacteriological examination were not used in the diagnostics of ARS.[13]

During the investigation, patients recorded their symptom scores on diary cards twice daily, in the morning and in the evening, and the same specialist recorded scores at the visit 2.

The efficacy endpoints were mean total symptom score (TSS; sum of the scores for nasal obstruction, rhinorrhea, postnasal drip, facial pain/pressure, impaired sense of smell), individual symptom score (score for each nasal symptom) and endoscopic score for each sign (mucosal edema, mucopurulent secretion), at the visit 1 and visit 2.

Safety

Reported adverse events were recorded throughout the study, with severity grades as mild, moderate and severe. At visit 2, nasal examination, laboratory tests and vital signs assessment were performed. Therefore, the development of any medical complications associated with progression of rhinosinusitis (orbital, endocranial or bone complications) were also recorded during the study.

Statistical analysis

The parameters have been expressed as mean±standard deviation. For between-group comparison, a non-parametric Mann-Whitney U test was used. The paired comparisons within a group were performed using the Wilcoxon's test. P values <0.05 were considered significant. The analysis was performed by using the SPSS software (Statistical Package for the Social Sciences, version 15.0; SPSS Inc., Chicago, IL, USA).

Results

Forty-six patients (26 men and 20 women), aged between 18 and 61 years (mean age 41.06±28.91) diagnosed with ARS were included in this investigation. All numerical data presenting the demographic characteristics, total symptom score, individual symptom scores and endoscopic findings (mucosal edema, mucopurulent secretion), before and after two different treatment modalities are presented in Table 1. Results concerning all parameters' statistical significances before and after the MFNS and MFNS/Sinupret treatment are presented in Table 2.

At the visit 1, we found no significant difference regarding the TSS, nasal obstruction score, rhinorrhea score, postnasal drip score, facial pain/pressure score and loss of the sense of smell score (p>0.05 for all parameters) between two investigation groups. We also found no significant difference between the MFNS and MFNS/Sinupret group regarding the mucosal edema (p>0.05) and mucopurulent secretion (p>0.05) (Table 1).

After the treatment, we found highly significant decrease of all clinical parameters in both MFNS and MFNS/Sinupret groups (p<0.000 for all parameters) (Figs. 1–3).

At the visit 2, we observed significantly lower levels of TSS (p=0.002), nasal obstruction score (p=0.001), rhinorrhea score (p=0.001), facial pain/pressure score (p=0.001), impaired sense of smell score (p=0.002), mucosal edema (p=0.003) and mucopurulent secretion (p=0.001) in MFNS/Sinupret group than in MFNS group. On the other hand, we found significantly lower postnasal drip score (p=0.018) in ARS patients receiving only MFNS in comparison to those receiving MFNS and Sinupret (Table 1).

Table 1. Demographic characteristics of study population and clinical parameters before and after therapy.

Parameter	MFNS (n=23) mean±SD (range)	MFNS+Sinupret (n=23) mean±SD (range)	p-value
Male/female	13/10	13/10	1.000
Age	42.70±2.43 (18–61)	40.39±2.60 (18–61)	0.524
Nasal obstruction (B)	6.48±0.14 (5–7)	6.13±0.21 (4–7)	0.299
Nasal obstruction (A)	3.00±0.15 (2–4)	2.09±0.06 (2–3)	0.001
Rhinorrhea (B)	6.61±0.10 (6–7)	6.22±0.17 (5–7)	0.094
Rhinorrhea (A)	4.13±0.13 (3–5)	3.30±0.18 (2–5)	0.001
Postnasal drip (B)	6.43±0.16 (4–7)	6.43±0.12 (5–7)	0.701
Postnasal drip (B)	2.87±0.10 (2–4)	3.30±0.15 (2–5)	0.018
Facial pain/pressure (B)	6.70±0.15 (4–7)	6.48±0.11 (6–7)	0.052
Facial pain/pressure (A)	2.96±0.13 (2–4)	1.91±0.11 (1–3)	0.001
Impaired sense of smell (B)	6.35±0.12 (5–7)	6.13±0.17 (5–7)	0.402
Impaired sense of smell (A)	3.04±0.13 (2–4)	2.04±0.12 (1–3)	0.001
Total symptom score (B)	32.57±0.41 (29–35)	31.39±0.53 (26–34)	0.078
Total symptom score (A)	15.17±0.40 (12–19)	13.48±0.25 (12–16)	0.002
Mucosal edema (B)	5.61±0.10 (5–6)	5.52±0.12 (4–6)	0.682
Mucosal edema (A)	2.70±0.13 (1–4)	2.22±0.09 (2–3)	0.003
Mucopurulent secretion (B)	4.83±0.16 (4–6)	4.96±0.15 (4–6)	0.522
Mucopurulent secretion (A)	2.87±0.11 (2–4)	1.83±0.14 (1–3)	0.001

A: after treatment, **B:** before treatment, **MFNS:** mometasone furoate nasal spray, **SD:** standard deviation

The safety of two different treatment modalities was also evaluated. None of the patients of MFNS/Sinupret group reported any adverse events, and all their vital signs and laboratory tests were normal. Among the participants of MFNS group, 1 patient had mild epistaxis and 1 patient reported the sense of dryness in the nose. All patients in this group had normal vital signs and laboratory tests.

Discussion

Currently, nasal corticosteroid has turn out to be a conventional adjuvant therapy in the treatment of both ARS and CRS. Pharmacologically, novel nasal steroids [i.e. MFNS and fluticasone propionate (FPNS)] seem to have considerably advanced lipid solubilities and topical potencies, and reduced systemic bioavailabilities than old generation nasal steroids.[14] Previous investigations with patients suffering from uncomplicated ARS suggest that MFNS can be better monotherapy option than antibiotic therapy.[5] MFNS 200 µg twice daily monotherapy is well accepted and extensively stimulated excessive alleviation of utmost ARS symptoms compared with placebo and amoxicillin.[5] The results of our study demonstrated that 7-days MFNS monotherapy improves all nasal symptoms and endoscopic findings in patients with uncomplicated form of ARS. However, we also showed that combined use of herbal drug Sinupret with MFNS improve the efficacy of ARS treatment regarding the almost all symptoms and local signs of acute sinonasal inflammation. The results suggest that addition of Sinupret to MFNS leads to better improvement of nasal obstruction, rhinorrhea, facial

Table 2. Radiologic findings of patients with paranasal sinus fungus ball.

Parameter	MFNS	MFNS+Sinupret
Nasal obstruction (B-A)	-3.46 (p<0.000)	-4.05 (p<0.000)
Rhinorrhea (B-A)	-2.09 (p<0.000)	-3.30 (p<0.000)
Postnasal drip (B-A)	-3.54 (p<0.000)	-3.13 (p<0.000)
Facial pain/pressure (B-A)	-3,74 (p<0.000)	-4.57 (p<0.000)
Impaired sense of smell (B-A)	-3.31 (p<0.000)	-4,09 (p<0.000)
Total symptom score (B-A)	-17.4 (p<0.000)	-17.91 (p<0.000)
Mucosal edema (B-A)	-2,91 (p<0.000)	-3.3 (p<0.000)
Mucopurulent secretion (B-A)	-1.96 (p<0.000)	-3.15 (p<0.000)

B-A: before treatment-after treatment, **MFNS:** mometasone furoate nasal spray

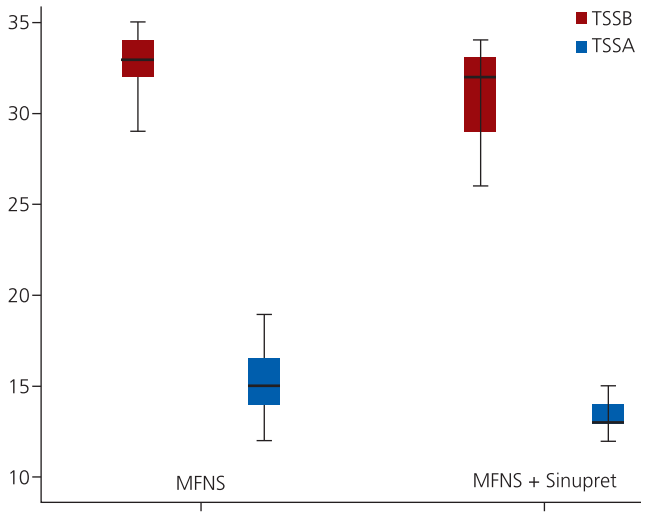

Fig. 1. Total symptom score (**TSS**), before and after two different treatment modalities. **A:** after treatment; **B:** before treatment; **MFNS:** mometasone furoate nasal spray; **TSS:** total symptom score.

pain/pressure and impaired sense of smell, as well as better resolution of mucosal edema and mucopurulent secretion from the nasal middle meatus. Therefore, TSS is significantly lower after the combined treatment in comparison to MFNS monotherapy.

Sinupret has been developed using the extraction of the phytopharmaceuticals contained in five herbs: gentian *(Gentiana lutea)*, primrose *(Primula veris)*, common sorrel *(Rumex acetosa)*, elder *(Sambucus nigra)*, and European vervain *(Verbena officinalis)*. The antiinflammatory action of Sinupret has been demonstrated in experimentally induced pleural inflammation in rats. The rats in which this herbal drug was administered orally one hour before treatment showed a lower volume of pleural effusion, less infiltration of polymorphonuclear leukocytes and decreased levels of prostaglandins in the exudates.[15] This antiinflammatory effect can be attributed to the polysaccharides and tannins in sorel and the iridoids in vervain.[15] Also, Sinupret has antiviral effect against adenoviruses, human rhinoviruses, respiratory syncytial virus, coxsackievirus, influenza and parainfluenza virus.[9] The mechanism of this action is inhibition of neuraminidase, an important enzyme for process of viral replication.[9] Sinupret has bactericidal effects on Gram-positive and Gram-negative bacteria, but this medication is not effective against *Escherichia coli*.[10] These antiinflammatory and antimicrobial effects of Sinupret lead to a better reduction of nasal obstruction, rhinorrhea, facial pain and impaired sense of smell in patients on combined therapy. The better resolution of mucopurulent middle meatus discharge in our patients from MFNS/Sinupret group can be explained by antibacterial action of this herbal drug.

However, after the treatment (visit 2), our patients receiving MFNS alone had lower postnasal drip score in comparison with those treating with Sinupret and MFNS.

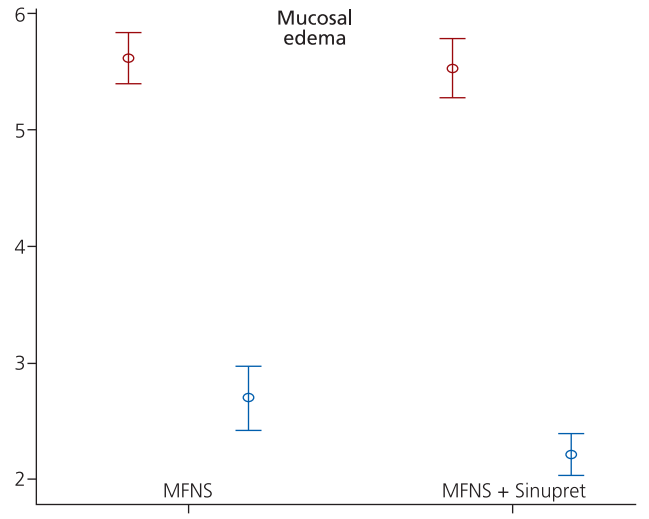

Fig. 2. Mucosal edema, before and after two different treatment modalities.

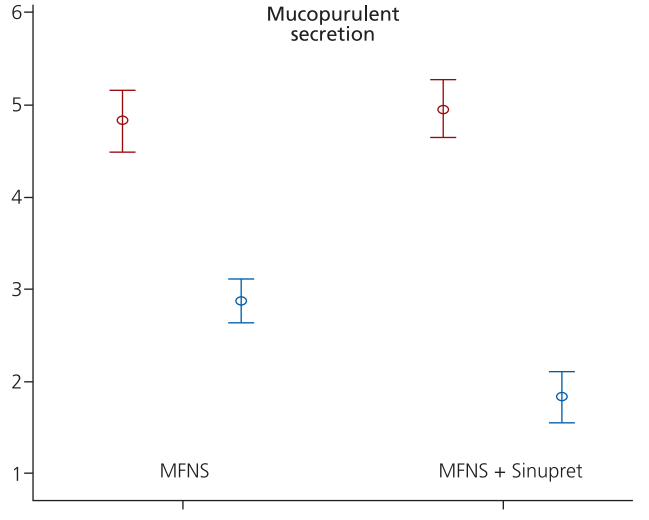

Fig. 3. Mucopurulent secretion from the middle nasal meatus, before and after two different treatment modalities.

This finding is not in accordance with lower rhinorrhea and mucopurulent secretion score in MFNS/Sinupret group after the treatment. Besides the fact that in patients with ARS/CRS clinical findings sometimes are not in accordance with subjective senses, this interesting phenomenon could be explained by strong secretolytic and secretomotoric activity of Sinupret. Dysfunctional mucociliary transport is a common pathophysiologic process developed as a results of infection and inflammation in ARS and CRS. Transport of the mucus layer within the airway surface liquid covering respiratory epithelia is influenced by the transepithelial secretion of ions, especially chloride ions (Cl^-). Primary Cl^- channel in respiratory epithelium responsible for good mucoliliary transport is the 'cystic fibrosis transmembrane conductance regulator' (CFTR), which is dysfunctional or absent in patients with cystic fibrosis resulting in a significant reduction of ciliary beat frequency.[7,16] Improvement of mucociliary clearance represents an important therapeutic strategy for patients with sinonasal inflammation by accelerating clearance of inflammatory products and pathogenic bacteria. Bioflavonoids, the main pharmacological components in Sinupret, strongly activate transepithelial Cl^- secretion in airway epithelial cells resulting in hydration of airway surface liquid and reduction of nasal fluid viscosity.[7,16] Therefore, Sinupret stimulates the ciliary beat frequency of human epithelial cells in vitro, with a significant increase only 10 minutes post-application and dose-dependent effects lasting up to 1 hour.[8] So, in patients treated with Sinupret and MFNS, accelerate nasal fluid clearance and low nasal secretion viscosity annul the inhibitory corticosteroid effects on mucosal gland secretion and inflammatory exudation, resulting in subjective sense of increased postnasal drip. Accordingly, the patients with combined therapy have higher postnasal drip score in the post-treatment period in comparison to ARS patients treated only by MFNS.

We observed no adverse events in patients from MFNS/Sinupret group in contrary to two participants from MFNS group which had the mild epistaxis and the sense of dryness in the nasal cavity. Nasal corticosteroid treatment have an antiinflammatory effect and inhibitory effect on nasal mucosa gland secretion. The application of the double dose of MFNS (400 µg daily) in patients with ARS could result in a mild level of nasal epithelium atrophy and consecutive mild nasal bleeding. The results of an experimental animal study by Yaremchuk et al.[17] demonstrated that Sinupret oral drops applied during acute rhinitis attenuate atrophic and destructive changes of the ciliated epithelium. This could be an explanation of a protective role of Sinupret in combined treatment of ARS.

Conclusion

Our results demonstrated better efficacy of combined MFNS/Sinupret therapy on nasal obstruction, rhinorrhea, facial pain/pressure and impaired sense of smell, as well as on endoscopic findings in patients with ARS in comparison to MFNS monotherapy. The absence of adverse events suggests a better safety of combined treatment comparing to nasal corticosteroid monotherapy in patients with uncomplicated form of ARS.

Conflict of Interest: No conflicts declared.

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Which temporal bone anatomical structures and pathologies could be best visualized by applying reconstruction to cross-sections obtained on an axial plane?

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Abstract

Objective: In this study, we aimed to identify the position in which temporal bone anatomical structures and pathologies could be best visualized by applying reconstruction to cross-sections obtained on an axial plane in temporal bone computed tomography (CT) scans.

Methods: Sixty patients were examined with temporal bone CT between July 2008 and March 2009. We obtained multiplanar reformatted images by applying retro-reconstruction on various planes from the axial plane sections.

Results: We determined that the reconstructed images increased the anatomical and pathological details and significantly contributed to evaluating the relationship between anatomical structures and their pathologies with other normal components.

Conclusion: Obtaining multiplanar reformatted images by retro-reconstruction decreased the need for visualization of coronal sections used in standard temporal bone CT exams since the anatomical details were diversified using the new planes. In addition, the dose of radiation received by the patients and the duration of the examination could be reduced by eliminating routine coronal plane sections and obtaining new images using retro-reconstruction.

Keywords: Temporal bone, computed tomography, reconstruction, anatomy.

Özet: Aksiyel düzlemde elde edilen kesitlerin rekonstrüksiyonuyla hangi temporal kemik anatomik ve patolojik oluşumları en iyi görüntülenebilir?

Amaç: Bu çalışmada temporal kemik anatomik ve patolojik yapılarının aksiyel düzlem temporal kemik bilgisayarlı tomografi (BT) taramalarında elde edilen kesitlere rekonstrüksiyon uygulayarak bu oluşumların hangi pozisyonda en iyi görüntülenebildiğini saptamayı amaçladık.

Yöntem: Temmuz 2008 ile Mart 2009 arasında 60 hasta temporal kemik BT'si ile incelendi. Değişik aksiyel düzlem kesitlerinden retrokonstrüksiyon yöntemiyle çok düzlemli yeniden formatlanmış görüntüler elde ettik.

Bulgular: Rekonstrükte görüntülerin anatomik ve patolojik ayrıntıları daha iyi gösterdiğini ve anatomik oluşumların ve patolojilerinin diğer normal öğelerle ilişkilerinin değerlendirilmesine önemli katkı sağladığını belirledik.

Sonuç: Retrokonstrüksiyon yöntemiyle birden çok düzlemde görüntülerin yeniden formatlanması, yeni düzlemlerde farklı anatomik ayrıntılar görüntülendiğinden standart temporal kemik BT incelemelerinde kullanılan koronal kesitleri görüntüleme gerekliliğini azaltmıştır. İlaveten, rutin koronal düzlem kesitleri gereksizleştirerek ve retrokonstrüksiyon yöntemiyle yeni görüntüler elde ederek hastaların aldığı radyasyon dozu ve inceleme süresi azaltılabilir.

Anahtar sözcükler: Temporal kemik, bilgisayarlı tomografi, rekonstrüksiyon, anatomi.

Temporal bone imaging using computed tomography (CT) has recently advanced significantly. CT is an imaging modality that plays an important role in diagnosis, differential diagnosis, treatment planning, and monitoring of temporal bone anatomy and pathology. In daily practice, CT imaging of the temporal bone is obtained using standard axial and coronal sections. However, many of the anatomical details cannot be observed clearly.[1] In recent years, with advances in multidetector CT, new images can be obtained using reconstruction of the derived section in many planes.[2] The middle and inner ear anatomical structures can be observed in more detail and can be evaluated easily.[1,3]

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In our study, we generated temporal bone CT images obtained in the axial plane which were sagittal, coronal, oblique semi-oblique, parallel to the course of the vestibular aqueduct, parallel to the second part of the facial nerve, and parallel to the manubrium malleie reconstructions. In the reformatted images, we determined which reconstruction plane improved visualization of the anatomical structures and pathologies of the temporal bone. The multiplanar reconstruction method requires only axial sections during the CT examination. This approach reduced both the radiation dose received by the patient and the examination duration by eliminating the coronal sections used in daily standard temporal bone CT imaging practices.

Materials and Methods

In the present study, 60 patients who were directed by clinicians to our CT unit for temporal bone CT examinations between July 2008 and March 2009 were examined. A total of 39 (65%) cases were female, and 21 (35%) were male, with a mean age of 35.8 years. The youngest patient was 12 years old, and the oldest was 76 years old. All patients were examined via axial sectional images using our CT (Siemens mark Somatom-Emotion model spiral CT; Siemens Healthcare, Erlangen, Germany). The examination was performed in a supine, neutral position, parallel to the superior orbital-meatal line without tilting of the chin. Scanning was performed from the beginning of the petrous pyramid to the mastoid. In each case, consecutive sections were obtained at 1-mm slice thickness in the axial plane. A 130 KV, 135 mAs, and 512×512 matrix was used. The rotation time was 1 second, and the average examination time was 40 seconds. To assess bone structures, the 'bone algorithm' was used. All examinations were performed without using intravenous contrast materials.

Evaluation was performed by two radiologists together. Reference angles on the left temporal bone were evaluated. A standard reconstruction algorithm was used. After the exam, we applied reconstruction on three reference planes (axial, sagittal, and coronal) to the images obtained on the axial plane, which were opened in 0.1-mm intervals. Primary and secondary reference planes were determined. In the reference plane, the left vector of the horizontal axis was defined as 0, and the right vector was defined as 180. The oblique planes were detected, in which the temporal bone anatomical structures (ossicle chain, stapes-oval window, round window, cochlea, vestibular aqueduct, semi-circular ducts, and facial nerve) and their pathologies were optimally evaluated.

Results

The coronal reconstructed images obtained from the axial 150° and sagittal 85° reference planes are required to assess the head, neck, and manibrium of the malleus.

Optimal assessment of the incus body, long process, incudostapedial joint and stapedial footplate can be performed using coronal reconstructed images obtained from the axial 150° and sagittal 60° reference planes.

'Molar tooth' formation, which also shows the incudomalleolar joint formed by the malleus and incus, can be observed using the sagittal reconstructed images obtained from the axial 60° and coronal 120° reference planes (Fig. 1).

The long axis projection of the stapes-oval window complex, which also includes stapedial anterior and posterior crosses with the stapedial footplate, can be observed based on the axial reconstructed images obtained from the coronal 30° and sagittal 150° reference planes (Fig. 2). The short axis projection could be observed based on the sagittal reconstructed images obtained from the axial 65° and coronal 120° reference planes.

The round window and adjacent anatomical structures, such as the labyrinthing segment of the facial nerve canal

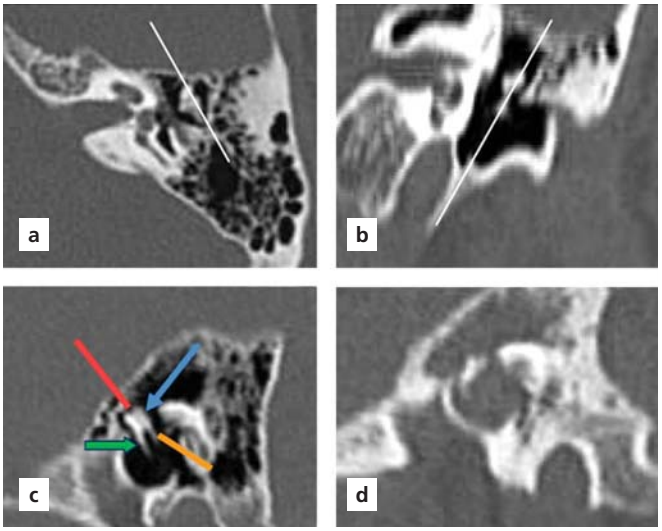

Fig. 1. (**a**–**d**) Double oblique sagittal views of the malleus and incus (**a**, **b**). Orthogonal axial 60° (**a**) and coronal 120° (**b**) reference planes (white lines). Double oblique sagittal (**c**) reconstructed view, which resembles the 'molar tooth' appearance; incus body (**blue arrow**), incudomalleolar joint (red line), manubrium mallei (**green arrow**), and incus long process (**orange line**). Reconstructed double oblique sagittal (**d**) view of a patient showing destruction of the partial incus body and total incus long process secondary to smooth tissue in the middle ear cavity. The clearness of the incudomalleolar joint is reduced, and there is a lateral subluxation of the manubrium mallei. [Color figure can be viewed in the online issue, which is available at www.entupdates.org]

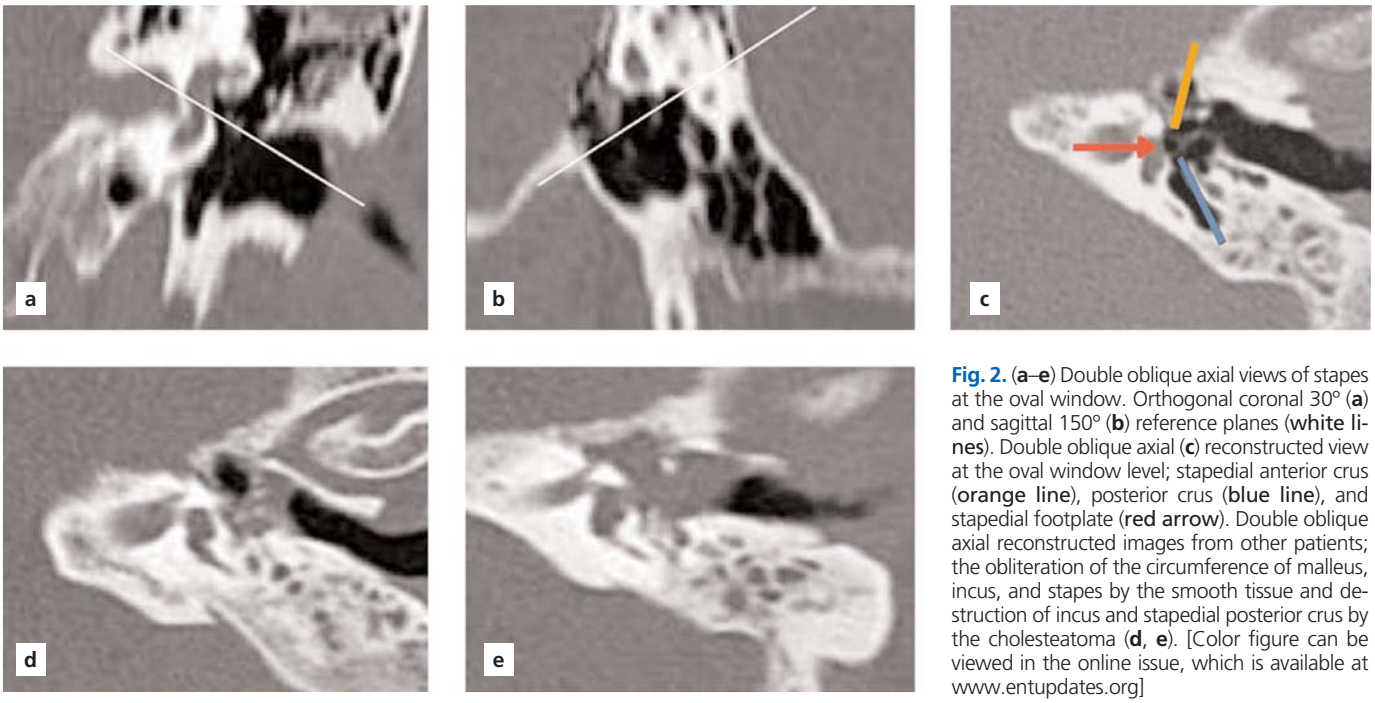

Fig. 2. (**a**–**e**) Double oblique axial views of stapes at the oval window. Orthogonal coronal 30° (**a**) and sagittal 150° (**b**) reference planes (**white lines**). Double oblique axial (**c**) reconstructed view at the oval window level; stapedial anterior crus (**orange line**), posterior crus (**blue line**), and stapedial footplate (**red arrow**). Double oblique axial reconstructed images from other patients; the obliteration of the circumference of malleus, incus, and stapes by the smooth tissue and destruction of incus and stapedial posterior crus by the cholesteatoma (**d**, **e**). [Color figure can be viewed in the online issue, which is available at www.entupdates.org]

and superior vestibular nerve canal, can be observed using the sagittal reconstructed images obtained from the axial 60° reference planes.

The short axis projection of the apical turn, middle turn, and basal turn of the cochlea can be observed based on the coronal reconstructed images obtained from the axial 30° and sagittal 75° reference planes and the long axis projection can be observed based on the sagittal reconstructed images obtained from the axial 120° reference planes.

The sagittal reconstructed images obtained from the axial 135° reference plane (Fig. 3) are required to assess the superior semi-circular canal.

Axial reconstructed images obtained from the coronal 180° reference plane are required to assess the lateral semi-circular canal.

The sagittal reconstructed images obtained from the axial 40° reference plane (Fig. 4) are required to assess the posterior semi-circular canal.

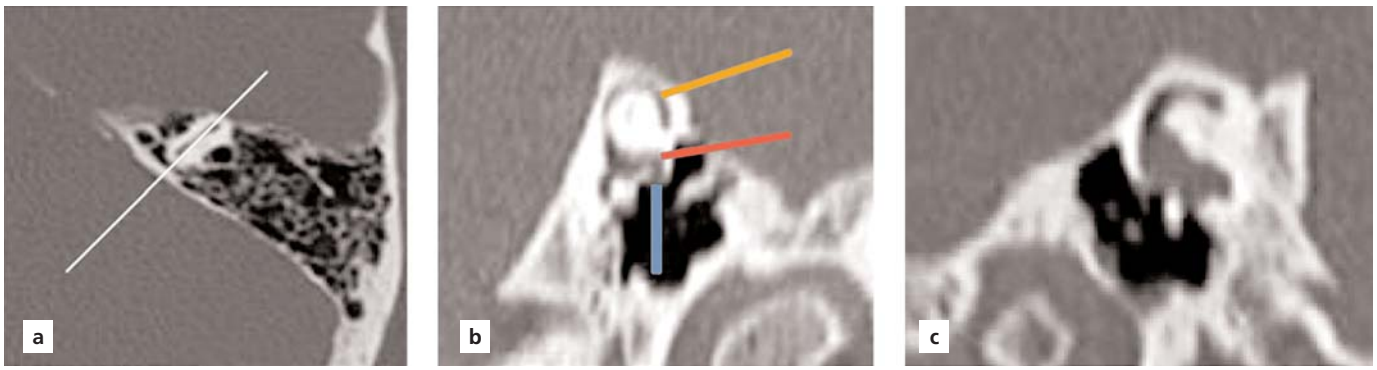

Fig. 3. (**a**–**c**) Single oblique-sagittal views of the superior semi-circular canal. Orthogonal axial 135° (**a**) reference plane (**white line**) parallel to the roof of superior semi-circular canal. Single oblique sagittal (**b**) reconstructed view; the bone continuity at the roof of superior semi-circular canal (**orange line**), facial nerve (**blue line**), and lateral semi-circular canal (**red line**). Single oblique sagittal (**c**) reconstructed images of another patient showing the deformity and the short rotation of the superior semi-circular canal. [Color figure can be viewed in the online issue, which is available at www.entupdates.org]

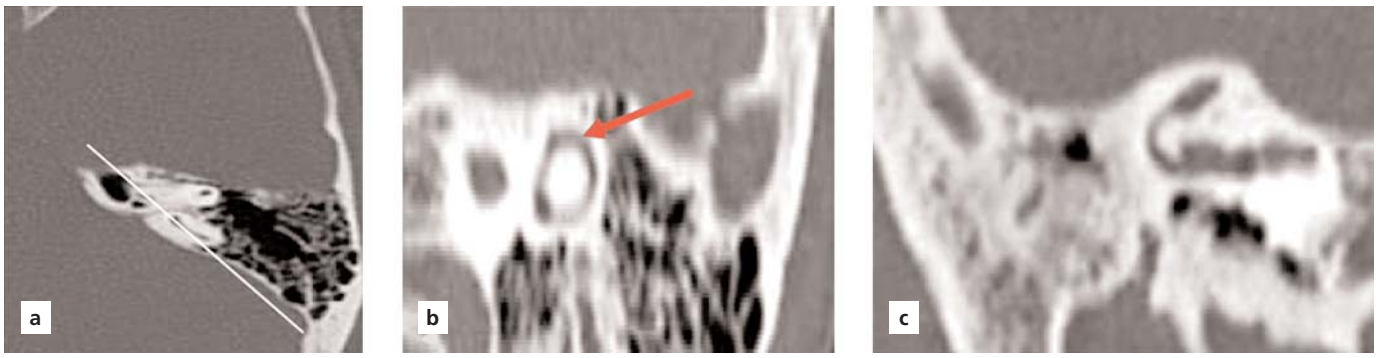

Fig. 4. (**a**–**c**) Single oblique-sagittal views of the posterior semi-circular canal. Orthogonal axial 40° (**a**) reference plane (**white line**) parallel to the roof of the posterior semi-circular canal. Single oblique sagittal (**b**) reconstructed view; posterior semi-circular canal (**red arrow**). Single oblique sagittal (**c**) reconstructed images of another patient with a common cavity deformity in the right ear showing the deformity and the short rotation of the posterior semi-circular canal. [Color figure can be viewed in the online issue, which is available at www.entupdates.org]

The sagittal reconstructed images obtained from the axial 90° reference plane (Fig. 5) are required to assess the vestibular aqueduct.

Visualization of the tympanic and mastoid segments of the facial nerve are provided by the sagittal reconstructed images obtained from the axial 60° and coronal 95° reference planes.

Discussion

Temporal bones have a complex anatomy, which includes hearing and balance organs. In addition, temporal bones contain functional spaces, plurality of holes, and channels through which blood vessels and nerves pass.[1,4]

At the end of the 1950s when politomography became more common, temporal bone imaging emerged as a specialized area within radiology departments. The recommended tube angulation during assessment of the temporal bone varies depending on the region examined, but in daily use, standard techniques include axial and coronal projections.[1,5] To visualize the anatomical structures, improved additional projections were developed. These projections, which are not orthogonal, were supported by temporal bone politomography pioneers.[1,5–7]

Other planes known in classical otologic radiology were investigated for the first time by Zonneveld in 1983.[7] This report discussed observations of classical autoradiological planes using proper patient positioning techniques

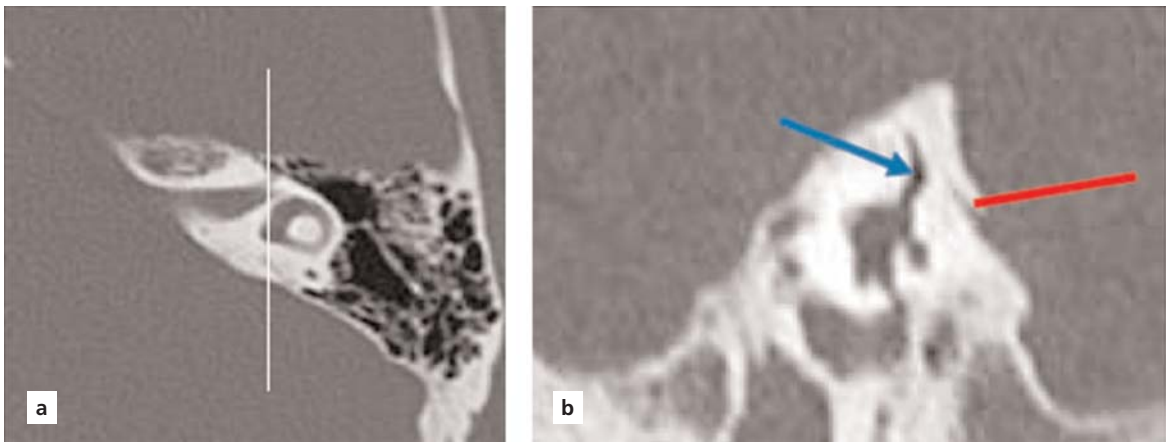

Fig. 5. (**a**, **b**) Single oblique-sagittal views of the vestibular aqueduct. Orthogonal axial 90° (**a**) reference plane (**white line**) including the vestibule medial wall and vestibular aqueduct. Single oblique sagittal (**b**) reconstructed view; vestibular aqueduct (**red line**) and common crus (**blue arrow**). [Color figure can be viewed in the online issue, which is available at www.entupdates.org]

in direct CT.[6,7] Autoradiological planes used with direct CT include transverse (Hirtz), coronal, sagittal, semiaxial (Guillen), semilongitudinal (Zonneveld), axiopetrosal (Pöschl), and longitudinal (Stenvers).[6–12] To achieve these planes using CT, the device was surrounded by a plate that rotates the patient through the sectional plane centre around the vertical axis.

The majority of temporal bone structures can be observed in the transverse (axial) plane.[6,7,9,10] This plane is ideal for basic assessment of temporal bones, since it provides the patient with comfort and enables comparison of the bilateral petrous bone in a single plane.[6,7,9,10] When a single-sectional plane is used, the structures parallel to the sectional plane are partially visible or absent. Therefore, temporal bone CT imaging requires at least two positions.[6,7] The choice of the second tomographic plane depends on the results of the fundamental assessment in the transverse plane, as well as the clinical information that can reveal which additional planes provide useful information.[6,7]

CT technology has developed rapidly since its introduction. Over time with evolving CT technology, it has become possible to reconstruct in different planes with slice thicknesses in millimeters. Thus, a detailed evaluation of temporal bone anatomical structures (ossicle chain, the stapes oval window complexes, round window, cochlea, vestibular aqueduct, semi-circular canal, and facial nerve canal) and pathologies, as well as the increased accuracy of CT for diagnosis, was provided.[1,4,5,12–17] With the introduction of high-resolution CT (HRCT) algorithms, studies have been performed with a spatial resolution of less than 1 millimeter; these are known as thin-section thicknesses with 'edge enhanced' filters. In addition, reconstruction programs can be applied to these studies.[1,4,5,7,8] In recent years, three-dimensional (3D) multiplanar reformatted imaging obtained from conventional cross-sectional CT data has been used at an increasing frequency.

Many anatomical structures of the middle and inner ear cannot be properly assessed using standard temporal bone imaging techniques, which are performed using axial and coronal sections. Obtaining these sections simultaneously increases both the radiation dose received by the patient and the duration of the examination.[3,18–21] In addition, many patients cannot maintain the position in which the head is brought to backward flexion in the prone position, which is required to obtain coronal images.[1,3,5] Since the dental region is within the field, there will be artefacts in the direct coronal sections of patients with a dental apparatus.[3] To eliminate these restrictions, instead of direct coronal imaging, the concept of obtaining coronal reconstructions from the axial images using thin-slice thickness has been proposed.[2,20,22–29]

Venema et al. attempted to address the question, 'Can coronal reconstructions obtained from the axial spiral CT data in 0.5-mm-slice thickness take the place of direct coronal sections?' in a study conducted in 1999.[3] Direct coronal sections and reconstructed coronal images of axial sections were compared by five observers. They also compared the contributions of two group images for diagnosis. It was concluded that there is no significant difference in the image quality between direct coronal sections and reconstructed coronal data. Within the framework of these results, coronal reconstructions obtained from axial images can replace direct coronal sections. Similar results were obtained by Shinaver et al. in 1997.[22]

Fatterpekar et al. in 2006 indicated that three-dimensional (3D) multiplanar reformatted imaging obtained from conventional CT data and 3D volume rendered CT images were used at an increasing frequency. They also emphasized that with the ability to perform rapid reformatting in many planes and to interfere with the spatial orientation, a detailed assessment of temporal bone anatomical structures was provided.[4]

Zhen et al. in 2007 presented three adult cadaver bones scanned by generating petrous bone using multislice CT (MSCT), and a multiplanar reformatted image with a 0.6-mm thickness was obtained.[2] The temporal bone cadaveric specimens were then sliced in cross-sections 0.1 mm in thickness. A total of 50 micro-anatomical structures that could not be assessed with clarity by CT images, obtained using thicker slices, were compared with the multiplanar reformatted (MPR) images. We found that the images obtained by MPR were similar to those in anatomical specimens, and it was concluded that MPR images were adequate for diagnostic knowledge and surgical anatomy.

Lane et al. in 2006 used MSCT with a 64-slice detector to show axial images of the temporal bone acquired in 100 cases and then applied in multiplanar reconstruction. They concluded that the convenient reconstructed images could be used to assess the anatomical structures. As a result, they indicated a need for an additional series for the development of diagnostic accuracy of middle and inner ear diseases by CT.[1]

Layton et al. indicated in 2011 that with improved CT technology, excellent multiplanar reformatting from sin-

gle axial acquisition data could reduce imaging times and motion artefacts. Small temporal bone structures could be identified confidently using the reformatted images in different planes.[30]

Lim et al. in 2013 evaluated the feasibility of MPR imaging with temporal bone CT for the diagnosis of temporal bone fractures. In the case of a temporal bone fracture in the middle ear cavity, MPR imaging parallel to the fracture line was recommended for further evaluation. The serial oblique images were acquired rectangularly to a fracture line with 0.5-mm intervals in the axial temporal bone scan.[31]

Zhou et al. in 2014 evaluated the oblique axial and coronal planes, on which the tympanic bone remnant was shown, and the ossicular mass appeared to be the largest in size. HRCT evaluation using MPR provided significant benefits. Preoperative measures for individual patients could provide guidance for canaloplasty and tympanoplasty procedures.[32]

In our study, we obtained axial images of temporal bones from patients who were directed to our clinic for temporal bone CT imaging. At the workstation, we opened these images using 0.1-mm intervals. We recognized the left vector of the horizontal axis to be 0º, while the right vector was 180º. We determined the reference planes and reformatted the images, which can reveal the anatomical structures and pathologies of the temporal bone. Our findings were similar to the study performed by Lane et al. in 2006 using a 64-slice detector MSCT.[1] Additionally, the reconstruction of posterior and lateral semi-circular canals was first described by us.

The limitation of our study was the low image quality of the reconstructed images which were performed by spiral CT device.

Using multiplanar reformatted imaging, it is posssible to perform reconstructions in coronal and other planes. Decreasing the radiation exposure and the examination duration allows us to examine more patients and eliminates restrictions associated with patient positioning.[27,29,33] The optimal assessment of temporal bone anatomical structures and pathologies was provided, and the contribution of CT in diagnostic accuracy of temporal bone pathologies increased. Based on the advantages of multiplanar reformatted imaging, radiologists are playing an active role in directing the medical and surgical treatment of middle ear diseases.

Conflict of Interest: No conflicts declared.

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Assessment of chemosensory disorders in allergic rhinitis

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Abstract

Objective: Allergic rhinitis (AR) is a globally common inflammatory disease that has a considerable effect on an individual's quality of life. It is estimated that AR affects 10% to 25% of the general population. Both gustatory and olfactory disorders affect the social activities and job performance resulting in impaired quality of life in patients suffering from AR. We think that these problems have not been sufficiently investigated in the past. We, therefore, decided to evaluate the smell-taste disorders in patients suffering from AR. Our objective is to evaluate the chemosensory perception in patients suffering from allergic AR.

Methods: Fifty-four patients with AR and 34 healthy controls were enrolled for the current study. "Sniffin' sticks" test and taste strips were used for chemosensory assessment.

Results: According to the "Sniffin' sticks" test results, patients with AR had significantly lower scores for odor threshold and identification subtasks, whereas there was no difference between the two groups regarding odor discrimination scores ($p<0.001$, $p<0.001$, and $p=0.3$, respectively). After evaluating the taste strip test results, we found that taste scores were significantly low in patients with AR when compared to controls for sweet, salty, bitter and sour tastes.

Conclusion: This study showed clinically important deficiency of chemosensory sensitivity in AR patients. Since chemosensory deprivation in AR patients has tended to be overlooked in the past, these outcomes suggest that chemosensory disorders should be part of the standard evaluation of patients with AR.

Keywords: Allergic rhinitis, chemosensory disorders, taste and smell disorders.

Özet: Alerjik rinitte kemosensöryal bozuklukların değerlendirilmesi

Amaç: Alerjik rinit (AR) bireylerin yaşam kalitesini hatırı sayılır derecede etkileyen ve dünya ölçeğinde sık görülen bir enflamatuvar hastalıktır. AR'nin dünya ölçeğinde genel popülasyonun %10–25'ini etkilediği tahmin edilmektedir. Hem tat alma hem de koku alma bozuklukları sosyal aktiveleri ve mesleki performansları etkileyerek AR'den rahatsız hastaların yaşam kalitesinin bozulmasına yol açmaktadır. Bu sorunların geçmişte yeterince araştırılmadığını düşünmekteyiz. Bu nedenle AR'den rahatsız hastalarda koku ve tat alma bozukluklarını değerlendirmeye karar verdik. Amacımız alerjik AR hastalarında kimyasal duyumsama algısını değerlendirmekti.

Yöntem: Bu çalışmaya 54 AR hastası ve 34 sağlıklı kontrol alınmıştır. Kimyasal duyumsama değerlendirmesi için kokulu çubukları koklama ve tat stripleri kullanılmıştır.

Bulgular: Kokulu çubukları koklama testi sonuçlarına göre AR hastalarının koku eşik ve tanımlama testleri skorları anlamlı derecede düşük olup iki grup arasında koku ayrım skorları açısından herhangi bir farklılık yoktu (sırasıyla $p<0.001$, $p<0.001$, $p=0.3$). Tat strip testi sonuçlarını değerlendirdikten sonra kontrollerle karşılaştırıldığında AR hastalarında tatlı, tuzlu, acı ve ekşi tatlarına ilişkin skorlar anlamlı derecede daha düşüktü.

Sonuç: Bu çalışma alerjik rinit hastalarında kimyasal duyumsama algısında klinik açıdan önemli bozulma olduğunu göstermiştir. Geçmişte alerjik rinit hastalarında kimyasal duyumsama yoksunluğu göz ardı etme eğilimi yaşandığından bu sonuçlar alerjik rinit hastalarının rutin değerlendirmesinde kimyasal duyumsama bozukluklarının da ele alınması gerektiğini akla getirmektedir.

Anahtar sözcükler: Alerjik rinit, tat ve koku bozuklukları, kemosensör bozukluklar.

Allergic rhinitis (AR) has a substantial effect on quality of life (QOL). Approximately 25% of the world's population is influenced by this condition.[1] In addition to the characteristic symptoms of the disease (sneezing, nasal obstruction, rhinorrhoea, and pruritus), other atypical and less common symptoms may affect a patient's QOL, including

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halitosis, fatigue, malaise, irritability, and smell-taste disorders.[2,3]

Smell and taste are important to our perception of the outside world, and the loss of smell and taste can be a deep blow to one's QOL. Among AR patients, 21–23% suffer from olfactory disorders.[2] Block of the airflow reaching the olfactory epithelium and allergic inflammation that damages the olfactory epithelium can cause reduced olfaction.[4] Smell and taste are closely related senses; impaired olfactory function has a considerable effect on taste perception.[2–5]

Olfactory and gustatory complaints can affect the QOL of patients with AR. We believe that these problems have not been recognized adequately in the past. Thus, we decided to evaluate smell-taste disorders in patients with AR.

Materials and Methods

Subject selection

This study was conducted according to the principles of the Helsinki Declaration and was approved by the Clinical Trials Committee of our hospital (09/07/2014, no. 63). Details of the study protocol were explained to all subjects and written informed consent was obtained before participation.

In total, 54 patients with AR and 34 healthy controls were enrolled. A medical history was taken to assess the occurrence of systemic disorders. All participants verified that they were not suffering from any known disease and were not taking any treatment. Patients with additional anatomical or systemic diseases that might decrease olfactory and/or gustatory function, including a previous head injury, stroke, head and neck radiotherapy, chemotherapy, major surgery of the head and neck, sinusitis, nasal polyposis, and nasal septal deviation were excluded. For all patients, a standardized otorhinolaryngological assessment was performed by the same ear, nose, and throat specialist. The age- and sex-matched control group consisted of people at the otolaryngology clinic for other reasons that met the above criteria.

Assessment of allergic rhinitis

The inclusion criteria were the diagnosis of AR based on history, physical examination, and allergy tests (sensitivity to at least one and maximum three of the tested allergens). The allergy (skin prick) tests involved six major allergens: *Alternaria* (a mold), *Oleacea* (olive tree), *cereals* (rye), *Dermatophagoides farinae* (dust mite), *Dermatophagoides pteronyssinus* (dust mite), and *graminées* (grass). Individuals in the control group underwent the same allergy tests after their physical examinations to ensure that they were free from allergies. We excluded subjects using any AR medication, including intranasal steroids and antihistamines, during the study.

Chemosensory assessment

The validated "Sniffin' sticks" test, in which odorants are presented in commercially available felt-tip pen-like devices (Sniffin' sticks; Burghart, Wedel, Germany),[6–8] were used to assess olfactory function. This test has been validated in a Turkish population[9] and consists of one threshold and two suprathreshold subtests: a test for the threshold of phenyl ethyl alcohol, a test for odor discrimination (16 triplets with two different odors), and a test for odor identification (16 common odors, presented in a four-choice, forced-choice procedure).[7] The maximum score for the subtests was 16, so the maximum composite score was 48 (threshold, discrimination, and identification [TDI] score). 'Normal' values for the TDI composite score are >30.3, with a cut-off between anosmia and hyposmia at 16.5.[7]

"Taste strips" were used to assess taste[10] (Taste strips; Burghart). This test consists of four concentrations each of the four basic taste qualities. Concentrations used for the taste strips were: 0.4, 0.2, 0.1, and 0.05 g/mL of sucrose (sweet); 0.3, 0.165, 0.09, and 0.05 g/mL of citric acid (sour); 0.25, 0.1, 0.04, and 0.016 g/mL of sodium chloride (salty); and 0.006, 0.0024, 0.0009, and 0.0004 g/mL of quinine hydrochloride (bitter). Distilled water was used as the solvent, and the taste solutions were prepared freshly at regular intervals. The left or right side of the anterior third of the extended tongue was tested using the strips, resulting in a total of 32 trials.[10] The mouth was rinsed before each use of the strips. Increasing concentrations were used. Taste qualities were applied in a randomized fashion at each of the four concentration levels and alternating the side of the presentation. Patients had to identify the taste from a list of four descriptors: sweet, sour, salty, and bitter (multiple forced choice). To obtain an impression of overall gustatory function, the number of correctly identified tastes per side was added up to a "taste score".[10] A total threshold of <9 was classified as hypogeusia. Inter-test reliability has been shown to be high (r=0.68).[10]

Statistical analysis

Data analyses were performed using SPSS software (ver. 21.0; SPSS Inc., Chicago, IL, USA). The normal distribution of variables was first evaluated using the Shapiro-Wilk test. Data are presented as means ± standard deviations for continuous variables, and the number of cases was used for categorical variables. Differences between groups were analyzed using t or χ^2 tests, as appropriate.

Results

The study cohort consisted of 88 subjects, 34 men and 54 women, with a mean age of 36 (range: 18 to 47; median: 36.9±13.3) years. There was no significant difference between the AR and control groups in terms of age or sex. Of the patients, 46% were allergic to *D. pteronyssinus*, 34% to *D. farinae*, 38% to *Alternaria*, and 31% to *graminées*.

As shown in Table 1, when the "Sniffin' sticks" results were evaluated, patients with AR had significantly lower scores for odor threshold and identification subtasks (p<0.001 and 0.001, respectively), whereas there was no difference between the groups in the odor discrimination scores (p=0.3; Fig. 1). On evaluating the taste strip test results, taste scores were decreased significantly in patients with AR versus controls for sweet, salty, bitter, and sour tastes (Figs. 2 and 3).

Discussion

Allergic rhinitis is a global public health issue. It is a common condition, affecting more than 400 million people worldwide. High prevalence rates have been noted in both industrialized and developing countries. Moreover, recent reports have revealed an increase in the prevalence of AR over the last four decades.[11] AR can be a substantial source

Table 1. Taste scores in patients and control group.

	Allergic rhinitis n=54	Control group n=34	p-value
Age	37.1±11.6	36.5±14.4	0.6
Gender (F/M)	34/20	20/14	0.7
TDI score	27.8±2.3	35.3±2.6	0.001
Total taste score for right side	9.3±4.2	13.1±1.7	<0.001
Total taste score for left side	9.5±4.1	13.2±1.6	<0.001

TDI: Treshold Discrimination Identification Score

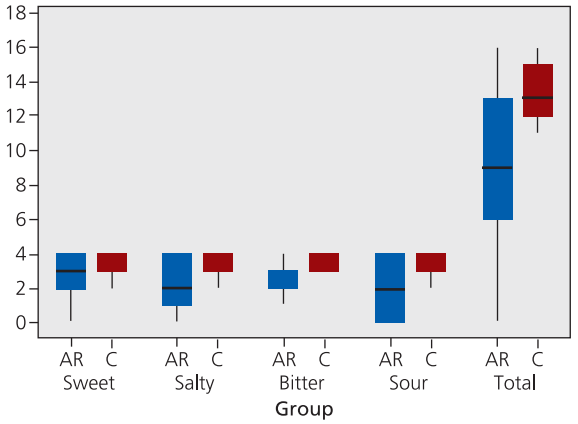

Fig. 2. Taste scores for the right side of the tongue.

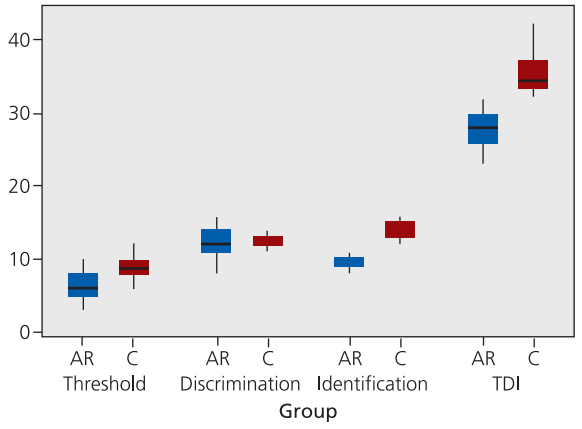

Fig. 1. Sniffin' Sticks olfatory testing scores according to groups.

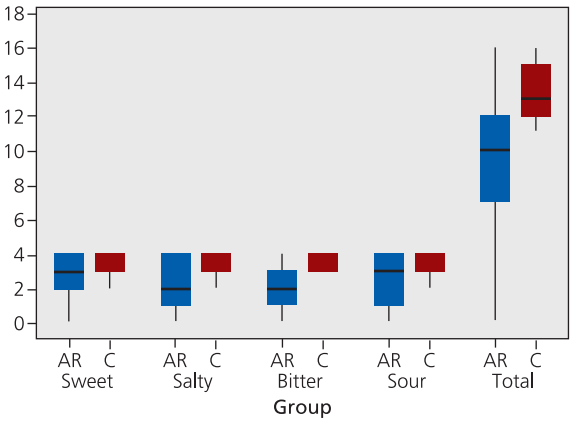

Fig. 3. Taste scores for the left side of the tongue.

of morbidity in poorly managed patients. Although not life-threatening, the symptoms of AR impair social and work function and can affect patient QOL significantly. In affected patients, one or more symptoms, including rhinorrhoea, sneezing, nasal itching, and congestion, may influence the QOL.[12]

AR may also be associated with smell-taste disorders. Olfactory dysfunction is a common symptom in AR: up to 23% of patients suffer from a reduced sense of smell.[11–13] Olfactory dysfunction in AR patients is believed to be caused by block of the airflow to the olfactory epithelium, secondary to nasal mucosal edema due to inflammation. However, medical or surgical treatments that decrease nasal blockage may not adequately treat hyposmia. These conclusions, verified in numerous studies, suggest that nasal blockade is not the individual mechanism of olfactory dysfunction in patients with AR. Another mechanism is the damage of the olfactory epithelium by allergic inflammation, directly triggering olfactory dysfunction.[4] Although it remains unclear, the pathogenesis of olfactory dysfunction seems to involve obstruction and inflammation.

We used the "Sniffin' sticks" test, which has been approved by the German Olfactory and Gustatory Committee. This test assesses the sense of smell quantitatively concerning threshold, discrimination, and identification. It is a suitable and accurate method for analyzing olfactory dysfunction, which may be linked to various diseases. However, several factors can affect the test including age, smoking status, and environment.[11] Thus, we sought to exclude all variables that might affect performance scores. We found that olfactory function was decreased regarding threshold and identification in patients with AR, whereas there was no significant change in discrimination scores.

Most patients who complain of a loss of taste actually have some degree of smell dysfunction as well. Most of a food's flavor comes from our ability to smell it. The tongue can sense only salty, sweet, sour, bitter, and umami. This is why it is difficult to sense a food's flavor when one has a stuffy nose. Most gustatory dysfunction is, in fact, caused by smell disorders instead of taste perception. One of the furthermost mutual reasons of olfactory dysfunction is AR. However, any situation that causes in a compromised situation for the chemosensory mediators (e.g., neurotransmitters, neural pathways, oral mucosa, saliva, and tongue) can result in impaired taste perception.[14] Thus, we excluded all other conditions that may cause taste disorders. We found that gustatory function was decreased in all parameters in patients with AR. However, this decrease may not only be related to olfactory dysfunction. Further research is needed to fully understand taste dysfunction in AR.

Conclusion

Our study demonstrates clinically important chemosensory perception disorders in AR patients; these impairments may cause a reduced QOL. Due to the chemosensory disorders in AR, and particularly their impacts on QOL, they have been ignored in the past, and our results propose that chemosensory disorders would be part of the standard evaluation of AR patients.

Conflict of Interest: No conflicts declared.

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Evaluation of the vascular contacts of the facial nerve on three-dimensional fast imaging employing steady-state acquisition MRI in Bell's palsy

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Abstract

Objective: The purpose of this study was to demonstrate the vascular contact patterns of the facial nerve (FN) on three-dimensional fast imaging employing steady-state acquisition (3D-FIESTA) magnetic resonance imaging (MRI) and evaluate the correlation between these patterns, House-Brackmann (HB) grades and outcomes in Bell's palsy (BP).

Methods: Fifty-two patients with BP and 25 healthy controls were included in the study. Besides, a third group was formed by the asymptomatic sides of 52 patients. The vascular contact patterns of the FN on 3D-FIESTA MRI were classified with regard to the presence, number and anatomic location of the contact.

Results: A significant difference was found between the groups in terms of vascular contact patterns of the FN ($p<0.001$). Multiple vascular contacts were more prominent in the symptomatic sides of the patients. There was a positive statistical correlation between vascular contact patterns and HB grades at presentation and at the 3rd week and 3rd month follow-ups ($r=0.335$; $p=0.015$, $r=0.587$; $p<0.001$ and $r=0.493$; $p<0.001$).

Conclusion: Multiple vascular contacts of the FN on 3D-FIESTA MRI were found to be more common and associated with poor recovery in BP. Thus, 3D-FIESTA MRI may provide prognostic information in BP.

Keywords: 3D-FIESTA MRI, Bell's palsy, facial nerve, vascular contacts.

Özet: Bell felcinde kararlı-durum eldeli MRG ile hızlı üç boyutlu görüntülemede fasiyal sinire vasküler basının değerlendirilmesi

Amaç: Bu çalışmanın amacı, üç boyutlu kararlı-durum eldeli hızlı manyetik rezonans görüntülemede (3D-FIESTA) fasiyal sinirin vasküler bası kalıplarını göstermek, bunun yanı sıra bu kalıplar, House-Brackmann (HB) derecelendirmeleri ve Bell felcindeki (BP) sonuçlar arasındaki korelasyonu değerlendirmektir.

Yöntem: Çalışmaya 52 BP hastası ve 25 sağlıklı kontrol dahil edildi. Ayrıca 52 hasta da sağlıklı (asemptomatik) taraf üçüncü grubu oluşturdu. Vasküler temasın varlığı, sayısı ve anatomik yerleşimine göre fasiyal sinirin vasküler temas kalıpları 3D-FIESTA MRG'de sınıflandırıldı.

Bulgular: Yüz sinirinin vasküler bası kalıpları bakımından gruplar arasında anlamlı bir farklılık saptandı ($p<0.001$). Hastaların semptomatik taraflarında çoklu vasküler basılar daha belirgindi. Hasta geldiğinde, 3. hafta ve 3. aydaki kontrollerde vasküler bası kalıplarıyla HB dereceleri arasında pozitif istatistiksel korelasyon mevcuttu ($r=0.335$; $p=0.015$, $r=0.587$; $p<0.001$ ve $r=0.493$; $p<0.001$).

Sonuç: 3D-FIESTA MRG'de fasiyal sinirin çoklu vasküler basısının çok daha sık olduğu ve BP'de düşük iyileşme oranlarıyla ilişkili olduğu saptanmıştır. Bu nedenle, 3D-FIESTA MRG BP'de prognostik bilgi sağlayabilir.

Anahtar sözcükler: 3D-FIESTA MRG, Bell felci, vasküler bası, yüz siniri.

Bell's palsy (BP) is a rapid unilateral facial nerve paresis/paralysis with idiopathic etiology. The most common cause of unilateral peripheral facial weakness is BP, and BP leads to the inability of voluntary movements of the affected side of the face.[1] Other etiologies of unilateral peripheral facial weakness include trauma, iatrogenic injuries, infections, neoplastic diseases, autoimmune diseases, and otologic diseases.[2]

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Idiopathic acute facial palsy, known as BP, is primarily hypothesized to occur as an inflammatory response to *Herpes simplex* virus type 1 (HSV-1) infection with subsequent blockage of the neural activity. The underlying mechanism of BP, such as microcirculatory failure of the vasa nervorum and ischemic neuropathy, still remain unknown even if the viral etiology has been discussed by several authors.[3] Furthermore, it was suggested that causes of secondary facial palsy and BP may coexist, and while patients with BP present with facial paresis/palsy as a primary complaint, not all patients with facial paresis/palsy have BP. Thus, the presence of contributing factors such as coexisting anatomical differences along the course of the facial nerve is an open question.

The cerebellopontine angle (CPA) cistern or internal auditory canal (IAC) crossed by the facial and vestibulocochlear nerves may be involved in various pathologies, such as neurogenic and glomus tumors, leptomeningeal disease and vascular lesions. Vertebrobasilar dolichoectasia, aneurysm and vascular loops may produce vestibulocochlear symptoms such as sensorineural hearing loss, vertigo or tinnitus, as well as facial palsy.[4] The branches of the anterior inferior cerebellar artery (AICA) and the posterior inferior cerebral artery (PICA) in the CPA cistern usually run between the facial and vestibulocochlear nerves and may have contact with them. The three-dimensional fast imaging employing steady-state acquisition (3D-FIESTA) magnetic resonance imaging (MRI) technique is valuable for demonstrating the course of the facial nerve from the brain stem to the IAC and provides a clear depiction of these neurovascular contacts.

The purpose of our study was to compare 3D-FIESTA MRI scans between patients with and without a history of facial palsy and to determine whether these vascular contacts may contribute to the risk for this disease. We also analyzed whether there was a correlation between the vascular contact patterns of the facial nerve and House-Brackmann (HB) facial nerve grading scores, outcomes and recovery of the patients or not. To our knowledge, this study is the first to demonstrate the vascular contact patterns of the facial nerve on 3D-FIESTA MRI and evaluate the correlation between these patterns and the grade of facial palsy and outcomes in patients with facial palsy.

Materials and Methods

This single center retrospective study was conducted at the Radiology, Otorhinolaryngology and Neurology departments of our institution. The study protocol was approved by the institutional ethical committee and written informed consent was waived due to its retrospective nature.

The medical records of 52 patients with unilateral Bell's palsy and 25 healthy controls were retrospectively evaluated. Patients presenting with acute onset of idiopathic unilateral facial palsy and who subsequently underwent temporal bone MRI were included in the study. Patients with any evidence of congenital, autoimmune, neurovascular, traumatic, neoplastic or infectious etiologies and with a history of temporal bone surgery, history of facial palsy on the opposite side or bilateral nerve palsy were excluded. All patients in the study received 10 days of oral prednisone therapy (60 mg oral prednisone for 5 days with 5 days of gradually decreasing doses) initiated within 72 hours of symptom onset and were followed up for at least 3 months. Also, according to the records of topographic test results, the facial nerve was affected proximal to the geniculate ganglion in all patients. The grade of facial nerve palsy was recorded at presentation, at 3rd week and at 3rd month after initial symptom onset, according to the House-Brackmann (HB) facial nerve grading system.[5]

Patients who were referred for brain MRI with complaint of headache and reported to be otherwise healthy, and those without a history of facial palsy were included in the control group. Both sides of the 25 patients in the control group were evaluated separately, constituting a group of 50 facial nerve sides. Besides the facial palsy and control groups, a third group was formed by the asymptomatic sides of the 52 patients with facial palsy. All subjects were evaluated for vascular contacts of the facial nerve on 3D-FIESTA MRI.

Magnetic resonance imaging was performed on a General Electric (GE) Signa 1.5 T MRI scanner (GE Healthcare, GE Medical Systems, Milwaukee, WI, USA) with an eight-channel head coil. For high-resolution MR images of the IAC, axial 3D-FIESTA sequence was used with the following scanning parameters: repetition time, 5.5 ms; echo time, 2.1 ms; bandwidth, 244 Hz/px; section thickness, 0.8 mm; slice gap, 0.6 mm; matrix size, 256×256; number of excitations, 4; flip angle, 65°; field of view, 220 mm.

All images were interpreted retrospectively based on the consensus of two national board-certified radiologists with five and ten years of experience in head and neck radiology, respectively. The radiologists knew that the patients all had acute facial palsy; however, they were blinded to the original MRI reports and clinical findings. Each study was recruited from the Picture Archiving and Communication System (Centricity PACS; GE Healthcare, Milwukee, WI, USA) and loaded onto a dedicated workstation with three

3MP high-resolution monitors (Barco, Inc., Kortrijk, Belgium). The vascular contact patterns of the facial nerve were classified with regard to the presence, number and anatomic location of the neurovascular contact (Table 1, Fig. 1). In order to demonstrate the course of the facial nerve from the brain stem to the IAC and to depict the neurovascular contacts, sagittal, semi-sagittal and semi-coronal reconstructions were created on axial 3D-FIESTA images with the scanner console.

Analysis of the results was performed using the IBM SPSS Statistics Version 21.0 software for Windows (Armonk, New York, NY, USA). Data were tested for normal distribution using the Kolmogorov-Smirnov test. Data were described using mean and standard deviation for continuous normal distributions and frequency for categorical variables. Comparisons between groups were performed using Kruskal-Wallis test for nonparametric variables with more than two groups. Chi-square test was performed for categorical variables. Spearman's correlation analysis was used for the analysis of the correlations among parameters. Statistical significance was defined as $p<0.05$.

Table 1. Vascular contact patterns of the facial nerve.

Type I	Absence of a vascular contact
Type II	Presence of a single vascular contact in any of the three anatomical locations of the facial nerve including the root entry/exit zone (REZ), the cisternal and the intracanalicular segments
Type III	Presence of multiple vascular contacts (contacts with more than one vessel in the same anatomic location and/or contacts in more than one anatomic location)

Results

Subjects

After patients with a history of facial palsy on the opposite side (n=1), history of bilateral facial palsy (n=1), vestibular schwannoma (n=3), stroke (n=2), middle ear and mastoid inflammation (n=4), and Ramsay Hunt syndrome (n=3) were excluded, 52 patients [29 (55.8%) women; mean age 45.7±18)] with acute onset of idiopathic unilateral facial palsy and 25 controls with 50 facial nerves [27 (54%) women; mean age 44.8±18.5] without a history of facial palsy were included in the study. There was no significant difference between

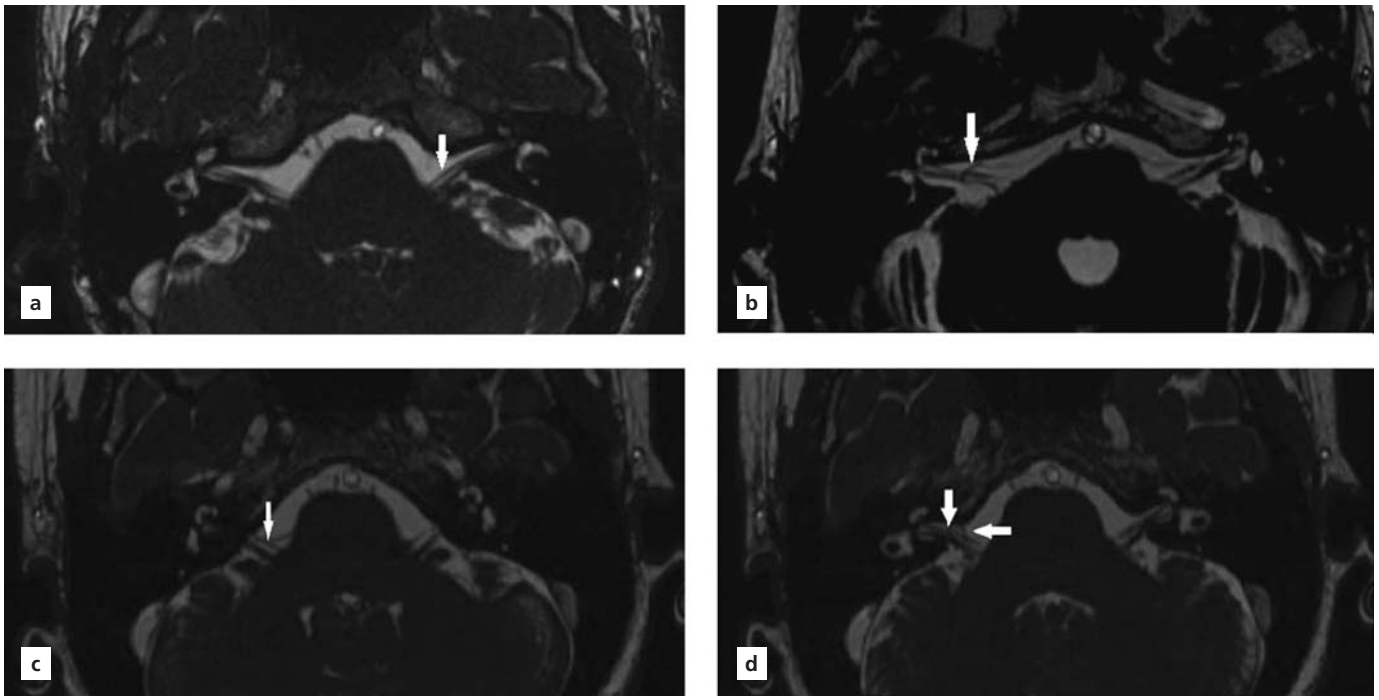

Fig. 1. Examples of vascular contact patterns on axial 3D-FIESTA images. (**a**) Type I, absence of a vascular contact of the left facial nerve is seen (**arrow**). (**b**) Type II, presence of a single vascular contact in the proximal intracanalicular segment of right facial nerve is seen (**arrow**). (**c**, **d**) Type III, presence of multiple vascular contacts in more than one anatomic location (cisternal and intracanalicular segments) of the right facial nerve is seen (**arrows**).

the study and the control group in terms of gender and age (p=0.97 and p=0.95, respectively). Besides the facial palsy and control groups, a third group was formed by the asymptomatic sides of the patients with facial palsy. A total of 154 sides including 52 symptomatic sides and 52 asymptomatic sides of the patients with facial palsy and 50 (both sides of 25 patients) sides in the control group were evaluated on 3D-FIESTA MRI.

MRI results

The vascular contact patterns of the facial nerve in the symptomatic sides of the study group, asymptomatic sides of the study group and in the control group were as follows, respectively: 5 (9.6%), 28 (53.8%) and 29 (58%) were classified as type I; 13 (25%), 14 (26.9%) and 16 (32%) were classified as type II; and 34 (65.4 %), 10 (19.2 %) and 5 (10 %) were classified as type III. A significant difference was found between groups in terms of vascular contact patterns of the facial nerve (p<0.001). Presence of multiple vascular contacts (contacts with more than one vessel in the same anatomic location and/or contacts in more than one anatomic location) (type III vascular contact pattern) was more prominent in the symptomatic sides of the study group, while absence of a vascular contact (type I vascular contact pattern) was more prominent in the asymptomatic sides of the study group and in the control group.

HB facial nerve grading score results

According to the HB facial nerve grading system, 12 patients were grade V, 23 patients were grade IV, 11 patients were grade III, and 6 patients were grade II at presentation. Two patients were grade V, 9 patients were grade IV, 21 patients were grade III, 13 patients were grade II, and 7 patients were grade I at the 3rd week from the initial symptom onset. Complete recovery was achieved in 29 patients after 3 months of treatment with corticosteroids. Regarding the remainder of the patients, 16 were grade II, 6 were grade III and one was grade V. There was a positive statistical correlation between vascular contact patterns of the facial nerve and HB grades of the patients at presentation, at the 3rd week and at the 3rd month follow-up (r=0.335; p=0.015, r=0.587; p<0.001 and r=0.493; p<0.001). Therefore, patients who had vascular contacts of the facial nerve on the symptomatic sides had higher HB grades both at presentation and in the follow-up period in comparison to patients who had no vascular contacts.

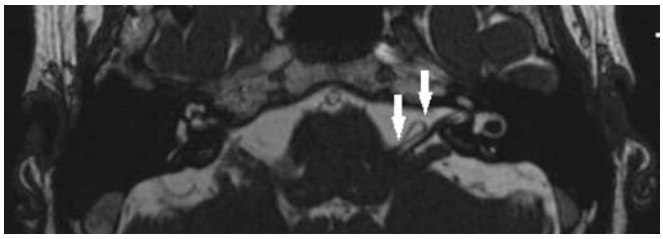

Fig. 2. A 52-year-old woman with recurrent left facial palsy (recurrent case no. 2). Axial 3D-FIESTA image shows multiple vascular contacts (**arrows**) in cisternal segment of the left facial nerve (Type III contact pattern).

Four patients had recurrent disease on the same side and all of them had type III vascular contact patterns of the facial nerve on the symptomatic side, while 2 patients had type I, and 2 patients had type III pattern on the asymptomatic side. One of these patients, who was HB grade V at the 3rd month follow-up, did not recover after 4 months of standard treatment and reconstructive procedures were performed to improve the appearance of the paralyzed facial side (Fig. 2). The vascular contact patterns, HB grades and outcomes of these recurrent cases are shown in Table 2. Three of the patients in the study group (one of them had recurrent disease) had higher HB grades at the 3rd week than at presentation and all of them had type III vascular contact patterns of the facial nerve on

Table 2. Vascular contact patterns on the affected sides, House-Brackmann grades and outcomes of the recurrent cases.

Case	Vascular contact pattern	House-Brackmann grade			Outcome
		Presentation	3rd week	3rd month	
No. 1	Type III	IV	II	I	Complete recovery at 5th month
No. 2	Type III	III	V	V	Progression during follow-up, reconstructive procedure at 4th month
No. 3	Type III	V	III	II	Complete recovery at 5th month
No. 4	Type III	V	IV	II	Complete recovery at 5th month

the symptomatic side. Complete recovery was achieved after 6 months of standard treatment in two of them, while in one who had recurrent disease the recovery was not achieved after 4 months of standard treatment and reconstructive procedures were performed. One patient with a history of bilateral facial palsy who was excluded from the study also had type III vascular contact patterns on both sides (Fig. 3).

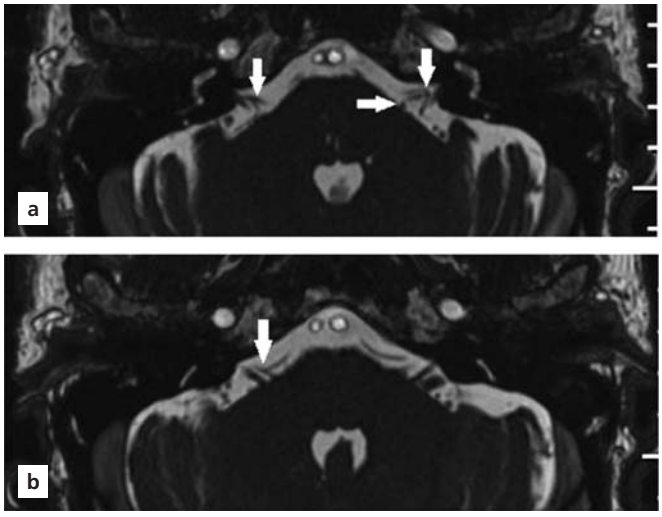

Fig. 3. A 43-year-old man with bilateral facial palsy. (**a**, **b**) Axial 3D-FIESTA images show multiple vascular contacts (**arrows**) in cisternal segments of the left and right facial nerves (Type III contact pattern on both sides).

Discussion

BP is an acute unilateral facial nerve paresis or paralysis that appears in less than 72 hours without any identifiable cause.[1] Although the precise cause remains unclear, numerous etiologies have been proposed, such as ischemic neuropathy, autoimmune diseases and viral inflammation of the facial nerve.[6,7] The most commonly accepted etiology, however, is HSV-1 infection that induces edema within the facial nerve as an inflammatory response.[8] Some risk factors for the development of BP have been identified, including pregnancy, severe preeclampsia, diabetes, hypertension, obesity, and upper respiratory tract infections.[1,9] On the other hand, HSV-1 infection is relatively common in comparison to BP, thus, the presence of contributing factors such as vascular contacts along the course of the facial nerve is a factor to explain why some patients develop palsy and others do not.

In this study, we have demonstrated that vascular contact patterns of the facial nerve on 3D-FIESTA MRI differ in patients with facial palsy. The type III contact pattern was found to be more common on the affected side in patients with facial palsy. Furthermore, it was shown that patients with multiple vascular contacts had higher HB grades both at presentation and at control in comparison to patients with no vascular contacts of the facial nerve.

Hemifacial spasm is a neurovascular compression syndrome (NVCS) of the facial nerve that is characterized by unilateral, intermittent contractions of the muscles of facial expression. NVCS refers to direct contact of cranial nerves by blood vessels that results in mechanical irritation.[10,11] This mechanical irritation has been proposed to cause demyelination, compression-induced conduction block, edema, and gliosis.[11,12] In idiopathic peripheral facial palsy, inflammation and edema associated with HSV-1 infection have been implicated as the cause of the entrapment of the facial nerve that initiates the ischemic neuropathy. Nevertheless, the exact cause of inflammation, the location of entrapment and anatomical differences or contributing factors in peripheral facial palsy still remains unknown. On the other hand, vascular pathologies of the cisternal and intracanalicular segments of the facial nerve, such as vertebrobasilar dolichoectasia, vertebrobasilar and PICA or AICA aneurysms and loops are considered in the etiology of facial nerve palsy.[13,14] Given that multiple vascular contacts were found to be more common on the affected sides in facial palsy cases versus the unaffected sides and controls in our study, we propose that these vascular contacts, though unlikely to be the main predisposing factor in the development of BP, may nevertheless contribute to the risk. The underlying mechanism may be similar to that in NVCS. Vascular contacts that lead to mechanical irritation of the facial nerve and microcirculatory failure of the vasa nervorum may promote the edema associated with HSV-1 infection.

MRI provides optimal soft tissue resolution and has greater accuracy for detecting nervous system lesions compared to other imaging modalities. However, some controversy exists in the literature regarding the value of MRI in cases of idiopathic facial palsy. While MRI, particularly obtained after intravenous administration of gadolinium-chelate, was considered to be of limited value in some studies, others reported that facial nerve enhancement on MRI is valuable in the diagnosis and is associated with a poor prognosis.[13,15–17] Furthermore, clinicians are discouraged from routinely performing diagnostic imaging for patients with new onset Bell's palsy.[1] On the other hand, 3D-FIESTA MRI provides much higher spatial resolution than rou-

tine MRI sequences and accurate visualization of the cisternal portion of the cranial nerves without the need for intravenous administration of gadolinium-chelate. In the previous studies, direct contact of cranial nerves by blood vessels depicted on MRI has been proposed as a cause of trigeminal neuralgia, hemifacial spasm, vestibulocochlear paroxysmia, and glossopharyngeal neuralgia.[11,18–20] In our study, we found that multiple vascular contacts of the facial nerve were more common in patients with Bell's palsy and the presence of these vascular contacts was associated with poor recovery after standard treatment. While most patients with Bell's palsy show complete recovery within 3 to 4 months, 30% of patients do not recover completely and have poor outcomes.[1] These patients may experience dramatic effects of the facial palsy on their appearance, quality of life and psychological status. Thus, we may assume that 3D-FIESTA MRI may be valuable in predicting the prognosis in patients with Bell's palsy, particularly in those with recurrent disease and/or progression in HB grades during follow-up. In this way, patients who will require emergency facial nerve surgical decompression and appropriate rehabilitation can be determined beforehand.

In our study, we have demonstrated and classified the vascular contact patterns of the facial nerve on 3D-FIESTA MRI in patients with Bell's palsy. The classification system used in the current study is primarily based on the presence of neurovascular contacts. As loop formation of a vessel is not essential to cause neurovascular contact, using the "vascular loops" definition was consciously avoided in order to determine the actual contacts that have the highest possibility to contribute to neurovascular compression. Second, we have considered the number of contacts. We classified multiple contacts (contacts with more than one vessel or contacts within more than one anatomic location) as a separate group. We believe that this classification may help in standardization of MRI reports in the relationship between the branches of AICA/PICA and cranial nerves along their courses from the brain stem to the IAC in future studies.

Our study has several limitations. The study design was single center and retrospective. The classification system used to define vascular contacts of the facial nerve on 3D-FIESTA MRI was based on the consensus of two radiologists. However, this classification system needs to be validated in future studies. Some risk factors for the development of Bell's palsy including diabetes, hypertension and obesity could be excluded; however, only four patients had these risk factors and this did not change the results of the study significantly. Also we did not determine whether the contact vessel is an artery or vein. Probably contact of an artery may cause more microcirculatory failure of the vasa nervorum than a vein. However, this initial study on this subject may serve as a starting point for conducting a prospective study involving a larger patient cohort where clinical variables could be controlled in order to draw useful conclusions.

Conclusion

We have demonstrated that multiple vascular contacts of the facial nerve on 3D-FIESTA MRI were more common in patients with Bell's palsy. The mechanical irritation associated with these vascular contacts may contribute to the risk by promoting edema associated with HSV-1 infection. Furthermore, presence of these vascular contacts was associated with poor recovery after standard treatment. Thus, 3D-FIESTA MRI may provide valuable prognostic information in patients with Bell's palsy and would be most beneficial in those with recurrent disease and/or progression in HB grades during follow-up.

Conflict of Interest: No conflicts declared.

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Pediatric deep neck infections: efficacy of conservative treatment versus immediate surgical intervention

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Abstract

Objective: The objective of this study was to review the management of deep neck space infections in pediatric patients and to evaluate the efficacy of intravenous antibiotic treatment alone before surgical drainage, and also to point out the indications for the drainage.

Methods: We reviewed sixty pediatric cases who were treated in our clinic because of deep neck space infections. The details of demographic data, medical history, initial complaints and physical examination, radiological examination, microbiology and laboratory results (C-reactive protein level and leukocyte count), treatment modality and follow-up findings were collected. The bacteriological results, management, complications, follow-up data and outcomes were also noted. A basic treatment algorithm for the management of the pediatric deep neck space infections was constituted.

Results: In 47 (78.3%) of the children, infection did not require any surgical intervention or puncture – in other words, needle aspiration – and it was successfully treated with antibiotic therapy alone. Fifty-six patients (93%) were initially treated with sulbactam-ampicillin.

Conclusion: We advise surgical drainage in cases of fluctuating large abscesses and infections without clinical improvement despite antibiotic treatment, and in complicated or life-threatening cases such as retropharyngeal abscess and mediastinitis. An otolaryngologist should be patient before any surgical intervention.

Keywords: Deep neck infection, children, antibiotic treatment, surgery.

Özet: Pediyatrik derin boyun enfeksiyonları: Acil cerrahi girişime karşılık konservatif tedavinin etkinliği

Amaç: Bu çalışmanın amacı pediyatrik hastalarda derin boyun enfeksiyonlarının yönetimini gözden geçirmek, cerrahi drenajdan önce yalnızca intravenöz antibiyotik tedavisinin etkinliğini değerlendirmek ve drenaj endikasyonlarına dikkati çekmekti.

Yöntem: Kliniğimizde derin boyun enfeksiyonu nedeniyle tedavi edilmiş 60 pediyatrik olguyu gözden geçirdik. Demografik veriler, tıbbi öykü, başlangıç yakınmaları ve fizik muayene, radyolojik inceleme, mikrobiyoloji ve laboratuvar sonuçları (C-reaktif protein düzeyi ve lökosit sayımı), tedavi yöntemi ve izlem bulgularının ayrıntıları toplandı. Bakteriyolojik sonuçlar, tedavi komplikasyonları, takip verileri ve sonuçlar da kaydedildi. Pediyatrik derin boyun enfeksiyonları için bir temel tedavi algoritması oluşturuldu.

Bulgular: Çocukların 47'sinde (%78.3) enfeksiyon cerrahi girişim veya ponksiyon, başka bir deyişle iğne aspirasyonu gerektirmemiş yalnızca antibiyotiklerle başarılı bir şekilde tedavi edilmişlerdi. Elli altı hasta (%93) başlangıçta sulbaktam-ampisilinle tedavi edilmişti.

Sonuç: Fluktuasyon veren büyük apselerde ve antibiyotik tedavisine rağmen klinik iyileşme olmayanlarda, retrofarengeal apse ve mediastinit benzeri komplike ve yaşamı tehdit edici olgularda cerrahi drenajı önermekteyiz. Bir KBB uzmanı herhangi bir cerrahi girişimden önce sabırlı olmalıdır.

Anahtar sözcükler: Derin boyun enfeksiyonu, çocuklar, antibiyotik tedavisi, cerrahi.

Deep neck space infection in the pediatric age group is a common and morbidity-causing disease. These infections may involve the parapharyngeal, submandibular, and retropharyngeal spaces. Symptoms may differ from mild fever to life-threatening airway obstructions. Occasionally, patients present with fever, neck mass, sore throat, and limited neck movements.[1,2]

The most common pathogens are *S. aureus*, including the methicillin-resistant *Staphylococcus aureus* (MRSA) subtype, Group A beta-hemolytic Streptococcus, and anaer-

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obes, often as a polymicrobial flora.[3] For diagnosis, cultures and antibiograms must be taken to identify the microorganism and the appropriate antibiotic therapy. Ultrasonography (USG) is a useful diagnostic technique in case of a liquefactive abscess. In deeply situated infections and complicated patients, computerized tomography (CT) is advised.[4]

Treatment options are intravenous (IV) antibiotics alone, or with surgical drainage if necessary. Despite the numerous studies, there is a lack of consensus about the treatment algorithm.[4,5] Early surgical drainage versus conservative medical treatment as the primary treatment modality is a subject of ongoing debate.

Our objective was to review the management of deep neck abscesses in pediatric patients and to evaluate the efficacy of IV antibiotic treatment before considering surgical drainage, and also to point out the indications for the drainage.

Materials and Methods

Institutional ethics committee approval was obtained with a number of GO 14/278. All the procedures followed were in accordance with the ethical standards of Helsinki Declaration of 1964, as revised in 2000.

A retrospective chart review of children diagnosed with deep neck infection in Otolaryngology Department of Faculty of Medicine at Hacettepe University between January 2010 and December 2014 was performed. Patients from 0–16 years of age were included in the study. The diagnosis of deep neck infection was based on clinical features, radiological investigation (ultrasonography or computerized tomography), surgical and microbiological findings. Children who had neck swelling due to malignant diseases, tuberculosis, chronic granulomatous infections or immune deficiency were excluded. The details of demographic data, medical history, initial complaints and physical examination, radiological examination, microbiology and laboratory results (C-reactive protein level and leukocyte count), treatment modality and follow-up findings were collected. The bacteriological results, management, complications, follow-up data, and outcomes were also noted.

The microbiological investigation was done via aerobic and anaerobic pus culture which was taken from the fluctuating abscesses. Specimens are placed onto blood agar in the microbiology laboratory. Culture and puncture were not performed if the patient has no fluctuating lesion.

Results

A total of 60 cases that met the criteria were identified. The mean age of the patients was 5 years, ranging from 10 days to 16 years.

Initial complaints were reviewed. Among 60 patients, 55 (91.6%) were admitted with neck swelling. Other initial symptoms were presented as restricted neck movements in two children and dysphagia in three children. Fifty-three children (88.3%) had a fever (above 37.5°C) initially. Additional signs and symptoms were sore throat (12 patients), dental abscess (2 patients) and tachypnea (1 patient). The most common symptoms upon admission are shown in Table 1.

Laboratory results were reviewed. All children were tested for C-reactive protein (CRP) and complete blood count. Twenty-two of them (36.6%) had elevated CRP levels. Leukocyte counts were ranged from 2300 to 23,900 microliter. Fifty-seven patients (95%) had elevated leukocyte counts (above 10,000 microliter).

All patients underwent radiological investigations. Ultrasonography was preferred in 54 non-complicated children who had no evidence of prominent complicated and fluctuating neck mass. USG was the most commonly preferred radiologic study for 90%, because there was no evidence of complication. In five children, CT scan was required as the initial radiological assessment. These patients were thought to have complicated deep neck space infections such as retropharyngeal or parapharyngeal space involvements. Magnetic resonance imaging (MRI) was used in only one child who had mediastinitis. Ultrasonographic measurement of the abscess, if any, was performed and the patients who had an abscess ≥3 cm in diameter were evaluated and followed up for possible puncture or drainage.

In 47 (78.3%) of the children, infection did not require any surgical intervention or puncture and it was success-

Table 1. Most common symptoms upon admission day.

Symptom	Number of cases (%)
Neck mass	55 (91.6)
Fever	53 (88.3)
Sore throat	12 (20)
Dental abscess	2 (3.3)
Tachypnea	1 (1.6)
Limited neck motion	2 (3.3)
Dysphagia	3 (5.0)

fully treated with antibiotic therapy alone. Thirteen of the patients (21.7%) required puncture or drainage. In 8 of those 13 children, puncture was performed and the pus was aspired. Nine of the cases required minimal incision and drainage upon admission because of large fluctuating abscess. One patient was complicated with mediastinitis and had a huge fluctuating abscess on the neck. She was treated with immediate surgical drainage and intravenous antibiotics for three weeks and healed without any problem. After discharge from the hospital, oral antibiotics (amoxicillin clavulanate) were prescribed to all of the patients for 10 days and they were recalled for a control examination. Surgical complications such as neurovascular injury or extensive scar formation were not observed in the study group. Mean duration of hospital stay was 8 days, ranging from 1 to 21 days. Mean hospitalization period in the surgically drained group was 12 days, slightly longer than the non-drained group, with 10 days.

Cultures from the abscess were taken in 13 patients who required puncture or drainage. The most common microorganism isolated in the cultures was *S. aureus* in 9 patients. Other microorganisms were *S. epidermidis* in 2 patients, *Streptococcus agalactia* and *Bacteroides fragilis* each in 1 patient. Microorganisms isolated by drainage are shown in Table 2. None of the patients were immunocompromised.

The most commonly used antibiotic regime was a 40 mg/kg/day sulbactam+ampicillin (SAM) combination divided into 4 doses. Fifty-six patients (93%) were initially treated with SAM. Vancomycin in 3 patients and ceftriaxone in 1 patient were the antibiotherapies of choice because of the complicated clinical course. The mean duration of antibiotherapy was 8.07 days. For 4 patients, ornidazole was added to SAM because of their underlying odontogenic infections and the increased possibility of polymicrobial flora with anaerobic microorganisms. Clindamycin was added in 3 cases who had anaerobic microorganisms, proven by culture. The patient treated with ceftriaxone had previously received unsuccessful amoxicillin + clavulanic acid treatments and the patients treated with vancomycin had history of hospitalization at a hospital known for MRSA colonization. This is mostly because patients referred to our clinic had been already received antibiotics before bacterial culture. Antibiotics were adjusted according to culture results and susceptibility results. Antibiotic regimens were ordered according to the consultation of pediatric infectious diseases department.

Table 2. Most commonly isolated microorganisms.

Microorganism	Number of patients (%)
Staphlococcus aureus	9 (69.2)
Staphylococcus epidermidis	2 (15.4)
Streptococcus agalactia	1 (7.7)
Bacteroides fragilis	1 (7.7)

Discussion

Deep neck space infections (DNSIs) are infections in the potential spaces and fascial planes of the neck, which could be related to lymphadenitis, cellulitis, necrotic node or abscess. DNSIs are common diseases in childhood. Infections of the ears, nose, throat, and teeth can produce DNSI by lymphatic drainage or direct spread.[5]

The disease often presents with upper respiratory tract symptoms, fever, neck pain, swelling of the cervical lymph nodes, neck mass, dysphagia, odynophagia, torticollis, trismus and limitations of neck movements. Neurologic symptoms may arise if cranial nerves or sympathetic chain are involved.[6] Among our 40 patients, 87.5% presented with neck mass and fever as the most frequently encountered symptoms on admission day. Complications of deep space neck infections include airway obstruction, jugular vein thrombosis, mediastinitis, and carotid rupture.[7] Life-threatening complications such as airway obstruction and dissemination of infection to potentially dangerous spaces like the mediastinum can develop in hours. A rapidly progressive course with fatal outcome may be seen, especially in infants and immunocompromised patients.[8] Children with congenital immune deficiencies or oncologic patients under chemotherapy may develop complications very rapidly and dramatically. One of our patients presented with a mediastinal involvement of a huge fluctuating neck abscess that needed immediate surgical drainage and IV antibiotics in order to save her life.

A wide spectrum of pathogens is involved in deep neck infections. The most common pathogens are *S. aureus*, incuding MRSA, beta hemolytic streptococcus, Group A *Streptococcus* and anaerobes. The increasing isolation of community-acquired MRSA in pediatric head and neck abscesses has been a major focus of the current literature.[9] In our study, the most commonly isolated pathogen in the pus culture was *S. aures* in 9 patients (69.2%). Because of different causative microorganisms often found as polymicrobial floras, broad spectrum parenteral antibiotics are advocated for DNSIs.

In the present study, it should also be noted that a majority of the cases (78.3%) received empirical antibiotic

treatments because it is not possible to take cultures unless there is a fluctuant collection to be punctured, and early recognition and treatment prevent DNSIs from forming abscesses. For the rest of the cases, antibiotic treatments had been started empirically before the culture results became available, and were tailored if necessary.

Rozovsky et al. stated that ultrasonography is sufficient to provide information about the nature, size and extent of inflammatory neck masses.[10] Meyer et al. suggest CT upon presentation in all patients with deep neck abscesses.[11]

In our study, 54 patients (90%) were evaluated by ultrasonography. In 6 patients, cross-sectional studies like CT or MRI were required. Although CT is accurate in differential diagnosis of cellulitis, phlegmon or abscess, radiation exposure and possible sedation or anesthesia requirements must be considered. Ultrasonography is useful as an initial imaging modality, especially for the identification of abscesses. It evaluates whether the abscess is liquefied enough to be drained and may also be used in ultrasonography-assisted drainage procedures. However, in deeply situated infections which may not be visible by ultrasonography, CT or MRI may be required.

Abscesses within the lymph nodes are formed by liquefactive necrosis, a process that may require a long time if the infection is left untreated. Some clinicians advocate initial antibiotic therapy, especially for patients with early admissions to hospital.[12,13] They suggest surgical intervention in case of a failure of improvement. They state that an initial trial of IV antibiotics may reduce the need for surgical intervention, which has potential complications. The urgency of the surgical drainage for children is not clearly stated in the current literature. The study of Cramer et al. found that delay in surgical drainage was significantly associated with greater morbidity and mortality in adults, whereas in children they found no difference between the early and late drainage groups.[13] Bolton et al. examined 130 patients in their clinic and point out the requirement of surgical drainage if the diameter of the abscess is more than 2 cm. They also showed the efficacy of antimicrobial therapy alone.[14] Our institutional experience and clinical practice is also similar. Puncture/drainage was performed to the patients who had ≥3 cm fluctuating abscess and majority of the cases were treated solely antibiotics.

Some researchers also claim that medical treatment alone is not enough to entirely cure deep neck abscesses and consider surgical drainage as the gold standard.[15,16] On the other hand, the morbidity of surgery (such as the need for anesthesia, scar formation and complications) should be taken into account. Advantages of initial medical treatment include avoidance of iatrogenic injury to great vessels or cranial nerves. Treatment algorithm for pediatric DNSI is summarized in Fig. 1.

Main limitations of this study are its retrospective design, small sample size, and lack of pus staining prior to antibiotherapy. Thus, a properly-designed prospective study should be performed to identify the results of successful non-operative management.

Otolaryngologists must be aware of such infections, microbiology of this disease and should not underestimate the potential risks of any surgical intervention especially in pediatric population. This study confirms that the medical treatment with appropriate doses of intravenous antibiotics could be a tolerable and safe option for the treatment of patients with uncomplicated small deep neck space infections.

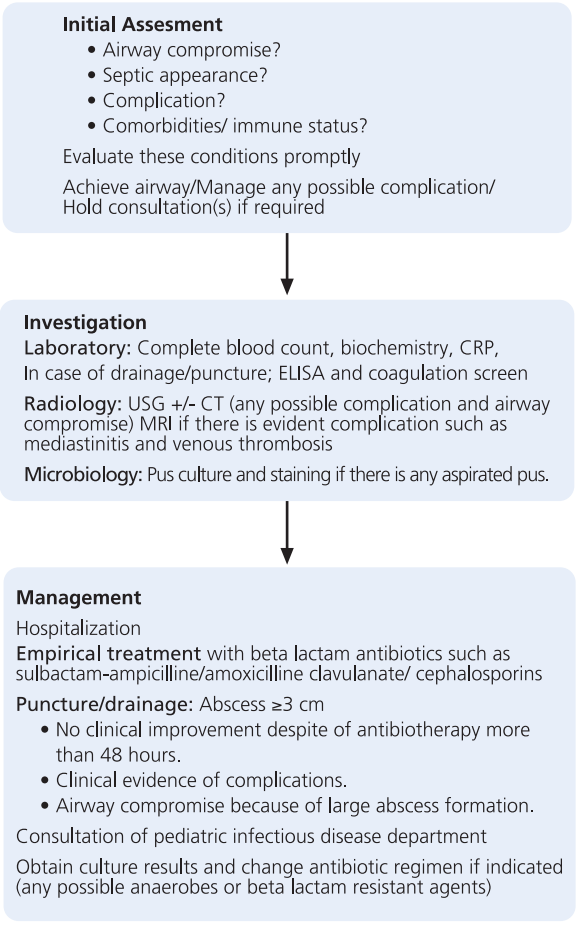

Fig. 1. Management algorithm for pediatric deep neck space infections.

Conclusion

In conclusion, most children with uncomplicated DSNIs can be successfully managed medically and initial surgery is not obligatory. In order to have surgical access to the deep neck spaces, the superficial tissues must be crossed with the risk of injury to the neurovascular structures in the neck. Fluctuating abscesses larger than 3 mm should be drained and pus culture should be obtained for the diagnosis of causative microorganism.

Conflict of Interest: No conflicts declared.

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The investigation of neutrophil to lymphocyte ratio and platelet to lymphocyte ratio in children with pathological cervical lymphadenopathy

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Abstract

Objective: To reveal whether if neutrophil to lymphocyte ratio (NLR) and platelet to lymphocyte ratio (PLR) rates are useful or not in children followed-up due to pathological cervical lymphadenopathy (LAP) of unknown etiology who have a normal hematologic examination.

Methods: A total of 100 children admitted to the otorhinolaryngology clinic between 2014 and 2017 with the complaint of swelling in the neck without any etiology revealed on examination and established with the diagnosis of idiopathic pathological LAP were retrospectively included in the study. The control group consisted of 100 children who did not have any infectious condition and could be considered healthy in terms of examination and laboratory findings. Patients' and the control group's age, gender, clinical history, disease course and examination findings were screened from the patients' records in the clinic.

Results: Mean white blood cell and lymphocyte count parameters in the patient group were higher than the control group, and the difference was statistically significant (p=0.008 and p=0.001, respectively). In the patient group, mean NLR and PLR values were significantly lower than the control group (p=0.009 and p=0.020, respectively).

Conclusion: NLR and PLR rates may be well correlated with inflammation in children followed-up due to pathologic cervical LAP with unknown etiology.

Keywords: Neutrophil to lymphocyte ratio, platelet to lymphocyte ratio, lymphadenopathy.

Özet: Patolojik servikal lenfadenopatili çocuklarda nötrofil/lenfosit ve trombosit/lenfosit orantılarının araştırılması

Amaç: Bu çalışmada, bilinmeyen etiyolojili patolojik lenfadenopati (LAP) nedeniyle takip edilen, hematolojik muayeneleri normal çocuklarda nötrofil/lenfosit (NLO) ve trombosit/lenfosit orantılarının (TLO) yararlı olup olmadığının açıklığa kavuşturulması amaçlanmıştır.

Yöntem: Muayene sırasında saptanan herhangi bir neden olmaksızın boyunda şişme şikayetiyle 2014 ile 2017 yılları arasında KBB kliniğine kabul edilen ve idiyopatik patolojik LAP tanısı konulan toplam 100 çocuk retrospektif çalışmaya dahil edildi. Kontrol grubu herhangi bir enfeksiyonu olmayan ve muayene ve laboratuvar tahlillerine göre sağlıklı olduğu düşünülen 100 çocuktan oluşmaktaydı. Hastalar ve kontrol grubu klinikteki hasta kayıtlarına bakılarak yaş, cinsiyet, klinik öykü, hastalık süreci ve muayene bulguları açısından tarandı.

Bulgular: Hasta grubunda ortalama lökosit ve lenfosit sayıları kontrol grubundan daha yüksek olup farklılık istatistiksel olarak anlamlıydı (sırasıyla p=0.008 ve p=0.001). Hasta grubunda ortalama NLO ve TLO değerleri kontrol grubuna göre anlamlı derecede daha düşüktü (sırasıyla p=0.009 ve p=0.020).

Sonuç: Bilinmeyen etiyolojili patolojik servikal LAP nedeniyle takip edilen çocuklarda NLO ve TLO enflamasyonla iyi bir korelasyon gösterebilir.

Anahtar sözcükler: Nötrofil/lenfosit orantısı, trombosit/lenfosit orantısı, lenfadenopati.

Lymphadenopathies constitute most of the neck masses of the children. Lymph nodes are arranged along the lymphatic canal. They are rich in lymphocytes and antigen-presenting cells and surrounded by a fibrous capsule. Lymph node enlargement in local and systemic infectious cases is seen as lymphadenomegaly or lymphadenopathy

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(LAP). Due to the antigenic state caused by any infection or other reasons, lymphocytes and macrophages migrate to lymph nodules and cause to grow.[1,2] In childhood period, the most common causes leading to LAP are viral and bacterial followed by autoimmune diseases and malignancies.[1–3]

White blood cell, lymphocyte and neutrophil counts that could routinely be performed in every clinic and used in hemogram data are laboratory tests showing the existence of infection and they do not have high financial load. Parameters such as procalcitonin, pro-adrenomedullin, serum amyloid A, fibrinogen and CD-14 binding protein, which are used following some infections, are extremely expensive tests.[4,5] Recently, neutrophil to lymphocyte ratio (NLR) and platelet to lymphocyte ratio (PLR) rates calculated according to hemogram data in patients with a white blood cell count within the normal range can be used to evaluate systemic inflammation.[6,7]

In this study, we aimed to reveal whether if NLR and PLR rates are useful or not in children followed-up due to pathological cervical LAP of unknown etiology who have a normal hematologic examination.

Materials and Methods

Study design

A total of 100 children admitted to the otorhinolaryngology clinic between 2014 and 2017 with the complaint of swelling in the neck without any etiology revealed on examination and established with the diagnosis of idiopathic pathological LAP were retrospectively included in the study.

One hundred subjects were included as the control group. The control group consisted of children who did not have any infectious condition and could be considered healthy in terms of examination and laboratory findings. The patients' and the control group's age, gender, clinical history, disease course and examination findings were screened from the patients' records in the clinic.

The patients who have hypertension, diabetes mellitus, metabolic diseases, coronary artery disease, thyroid dysfunction, kidney and liver disease, epilepsy, malignancy and anemia, those operated within the last 3 months, and the patients having systemic infections, chronic inflammation and other chronic diseases were excluded from the study.

Patients had multiple LAPs about 1 to 3 cm in size detected with ultrasonography who were followed-up for about 6 months. Most of the patients were followed by the pediatric hematology clinic. Most of these patients which revealed reactive LAP were made incisional biopsy according to the proposal of hematology department.

Patient files and data on white blood cell (WBC) count, erythrocyte count (RBC), platelet count (PC), mean platelet volume (MPV), neutrophil count, lymphocyte count were obtained from the archives of the hospital computer automation program for analysis. NLR value was calculated by dividing neutrophil count to lymphocyte count. PLR value was obtained by dividing platelet count to lymphocyte count. The age, gender, WBC, RBC, PC, MPV, PLR and NLR values were recorded, and the data were statistically analyzed.

Statistics analysis

All statistical analyses were done with using SPSS software. Normal distribution suitability of groups were tested Kolmogorov-Smirnov. The difference meaningful between groups were tested with chi-square, Student's t-test, and for comparison of non-uniform distribution, groups were tested with Mann-Whitney U test. Less than $p<0.05$ values were considered statistically significant.

Results

The patient group included 71 (52.6%) boys and 29 (44.6%) girls whose median age was 8 (range: 2 to 15) years. Also, the control group had 64 boys (47.4%) and 36 (55.4%) girls whose median age was 9 (range: 2 to 15) years. There was no difference between the two groups in terms of the age. Comparison of gender and age between patient and control groups is shown in Table 1.

Comparison of hemogram parameters between patient and control groups is shown in Table 2. Mean WBC and lymphocyte count parameters in the patient group were higher than the control group, and the difference was statistically significant ($p=0.008$ and $p=0.001$, respectively).

Table 1. Comparison of gender and age between patient and control groups.

		Patient (n=100)	Control (n=100)	p-value
Age		8 (min=2, max=15)	9 (min=2, max=15)	0.272*
Gender	Male	71 (52.6%)	64 (47.4%)	0.291†
	Female	29 (44.6%)	36 (55.4%)	

*Mann-Whitney U test, †Chi-square test.

Table 2. Comparison of hemogram parameter values between patient and control groups.

	Patient (n=100)	Control (n=100)	p-value
WBC	7.91±1.79	7.28±1.48	**0.008***
RBC	4.86±0.32	4.85±0.39	0.813*
Platelet	327±75.18	313±67.91	0.169*
MPV	8.68±1.57	8.60±1.35	0.690*
Neutrophil	3.66±1.49	3.69±1.19	0.873*
Lymphocyte	3.22±0.96	2.77±0.79	**0.001***
NLR	1.22±0.59	1.55±1.08	**0.009***
PLR	107.0 (min=53.2, max=344.9)	118.7 (min=46.3, max=265.9)	**0.020†**

*Student's t-test, †Mann-Whitney U test. **NLR:** neutrophil to lymphocyte ratio, **PLR:** platelet to lymphocyte ratio, **SD:** Standard deviation.

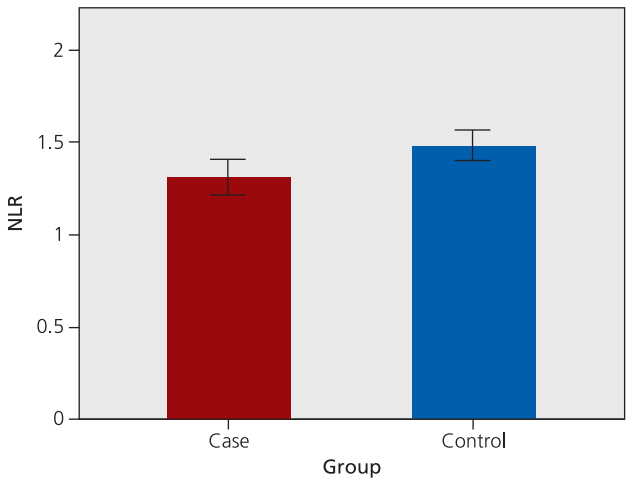

Fig. 1. Neutrophil to lymphocyte ratio values in the patient and the control groups.

In the patient group, mean NLR and PLR values were significantly lower than the control group (p=0.009 and p=0.020, respectively) (Figs. 1 and 2).

Discussion

Neck masses are most commonly seen in pediatric age group and require a careful differential diagnosis because of the variability of etiology. Although children's neck masses are easier to diagnose with physical examination and radiological imaging than adults, perfect medical history should be taken.[8,9] Children usually applied to the outpatient clinic due to malignancy when the size of the neck reaches pathological size. So, in most cases surgical excision is required for definitive diagnosis. Some of the patients cannot be diagnosed despite follow-up and examination.

The size of lymph nodes that are undistinguished in newborn period varies by age, localization of the node and immunological status of individuals. Lymph nodes reach to the maximum size around the age of 8 to 12 and lymph node atrophy begins after adolescence. Lymph nodes of 1 cm in the cervical region in childhood period are usually not considered pathologic.[1,2] Therefore, the patients who had cervical LAP in pathological sizes between 1 and 3 cm participated in this study.

Etiological factors in neck masses differ by countries. While inflammatory lesions are the most common cause of neck masses in developing countries, congenital and neoplastic masses are more prominent in developed countries.[9,10] In our patient group in which we ruled out neoplastic and congenital masses, lymphocyte count was increased as viral infections increase (p=0.001). Thus, we think that an inflammation without a certain cause may exist with the increase in lymphocyte count in children with cervical LAP.

In recent years, among the novel markers used in the measurement of inflammatory status, NLR is used for the evaluation of systemic inflammatory response against several diseases including cardiovascular diseases, diabetes melli-

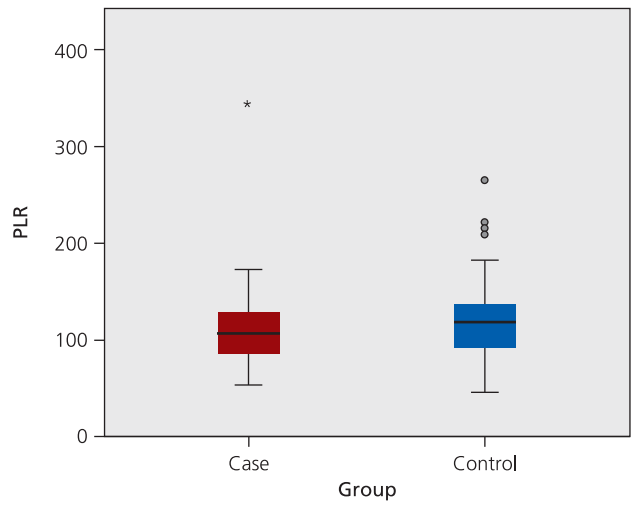

Fig. 2. Platelet to lymphocyte ratio values in the patient and the control groups.

tus, metabolic syndrome, local and systemic infections and cancer (lung, ovarian and colorectal).[6–11] Wolfswinkel et al.[12] argued that evaluation of NLR together with lymphocytopenia is more effective than studying CRP and total leukocyte count. Again, numerous studies suggested that NLR is an important criterion in making diagnostic and prognostic decisions in psoriasis, infective endocarditis, pneumonia, bacteremia and acute appendicitis.[13–17] In our study, we found that lymphocyte was higher in the patient group than the control group, and as a result, NLR was significant. This result supports the cause of chronic inflammation which plays an etiologic role in children with LAP.

PLR as another novel marker is a poor prognosis in some cancers and cardiovascular diseases reported.[18] Another study by Sula et al. reported that PLR and PDW values were higher in patients with leishmaniasis compared to the control subjects.[19] In our study, we found that lymphocyte was higher and PLR values were significantly lower in the patient group. This finding suggests that PLR value can be used as a criterion indicating subclinical inflammation in children with pathological cervical LAP.

There are many studies in the literature demonstrating that mean platelet volume (MPV), which is one of the parameters used in the evaluation of platelet size, is used for the evaluation of both systemic inflammatory activity and response to treatment.[19–22] In a study, platelet count was measured at high levels and MPV at low levels in the active period of inflammation and infection, and they were suggested as reliable markers.[22] However, Sula et al.[19] found no significant difference in MPV level in patients with leishmaniasis. Similarly, we could not obtain any significant results at the levels of MPV in our patient group. In our study, we found that the platelet counts did not change much.

Conclusion

In the present study, we attempted to demonstrate inflammation using NLR and PLR rates in children with LAP. As a result, we think that these descriptive parameters may be well correlated with inflammation in children followed-up due to pathologic cervical LAP with unknown etiology.

Conflict of Interest: No conflicts declared.

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Review

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Effects of pregnancy on olfaction

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Abstract

In this review, we aimed to report the effects of pregnancy on olfaction function of the women. Since estrogen and progesterone levels change in specific physiological conditions, pregnancy and postmenopausal period exert an effect on the capability to sense and identify smells. Nasal stuffiness increased during pregnancy. 66.6% of the pregnant women were suffering olfactory dysfunction in the second trimester; while 95.8% in the first and third trimesters. Olfactory function was lessened following birth and throughout the first 6–12 weeks; however, it seemed to improve entirely. In pregnant women, olfactory dysfunction was observed in all trimesters; while it was less in the second trimester and high in the first and third trimesters. The smell abnormalities were almost absent at postpartum period. As olfactory functions improved after delivery of the baby, olfactory changes during pregnancy may be accepted as physiological changes which were observed in many pregnant women.

Keywords: Olfaction, pregnancy, olfactory dysfunction.

Özet: Hamileliğin koku alma üzerindeki etkileri

Bu derlemede, gebeliğin kadınların koku alma fonksiyonuna etkilerinin araştırılması amaçlanmıştır. Gebelik ve postmenopozal dönemde, östrojen ve progesteron seviyeleri spesifik fizyolojik koşullarda değiştiğinden, koku algılama ve tanımlama yeteneği üzerinde etkili olmaktadırlar. Hamilelik sırasında burun tıkanıklığı artmaktadır. Hamilelerin %66.6'sı 2. trimesterde olfaktör bozukluktan rahatsızken; %95.8'i birinci ve üçüncü trimesterde rahatsızdır. Koku alma fonksiyonu doğumdan sonra azalmakta ve ilk 6–12 hafta içinde tamamen düzeldiği görünmektedir. İkinci trimesterde daha az, birinci ve üçüncü trimesterde daha yüksek olmak üzere, hamile kadınlarda tüm trimesterlerde koku alma bozukluğu gözlenmektedir. Postpartum dönemde koku anormallikleri neredeyse tamamen kaybolmaktadır. Koku alma fonksiyonları bebeğin doğumundan sonra iyileştiği için, hamilelik süresince birçok gebede görülen olfaktör değişiklikler fizyolojik değişiklikler olarak kabul edilebilir.

Anahtar sözcükler: Gebelik, koku alma, koku alma bozuklukları.

Olfaction is the capability to distinguish and identify smells. The olfactory sense influences management of somatic and visceral functions, and sexual activities associated with the limbic system. Since estrogen and progesterone levels change in specific physical conditions, pregnancy and postmenopausal period exert an effect on the capacity to sense and identify smells. Also, it connects higher cortical functions and the endocrine system.[1] Substances must fulfill two requirements for an odor to be perceived. Firstly, it must be volatile at ambient temperature, and secondly, it must be soluble in fat solvents. Once a molecule reaches the receptors located in the upper portion of the superior nasal cavity, it binds to and depolarizes the olfactory nerve receptors. The bipolar cells are grouped in bundles that infiltrate the ethmoid bone cribriform plate. They form a synapse with the olfactory bulb neurons. From the olfactory bulb, projections of secondary neurons bind to the primitive cortex, hippocampal formation and the pyriform lobe.[2]

The smell sense leads to minimum three distinctive mechanisms: (i) odor threshold, (ii) odor discrimination, and (iii) odor identification. Testing of the different components of olfaction as well as threshold assessment postulates the utmost noteworthy method to the identification of smell loss.[3]

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Olfactory Loss

The absence of the sense of smell is called anosmia. Hyposmia refers to diminished sensitivity to smell. Dysosmia refers to a distortion of smell. Phantosmia refers smell of an odor for which there is no stimulus. Presbyosmia refers hyposmia associated with aging. Due to gender, smoking status or age, normal individuals may have some degree of olfactory loss. Women's olfactory acuity is higher than men at all ages.[2]

The olfactory dysfunction may well be triggered by nasal obstruction or olfactory epithelium inflammation. Management of olfactory loss associated with sinonasal disease is possible with surgical procedures and/or management with antibiotics or steroids. Mostly, enhancement of olfactory function seems to be associated with the anti-inflammatory properties of steroids. It seems possible that minor nasal congestion occurs in pregnancy which is not relevant to nasal airflow. However, it adequately narrows the olfactory cleft to influence olfactory thresholds. This condition is similar to the existence of nasal polyposis.[4]

Assessment of Olfactory Performance

"Sniffin' sticks" is based on pen-like odor-dispensing devices to test nasal chemosensory performance. For repetitive and inexpensive screening of odor identification, this portable test is sufficient. The test includes a forced odor-identification task for seven odor types. Sniffin' sticks may be useful in the standard clinical evaluation of olfactory function.[5]

Nose and Pregnancy

Nasal symptoms in pregnancy

The incidence of nasal obstruction improved during pregnancy. It occurred in 27% of the pregnant women at 12 weeks of gestation, in 37% at 20 weeks of gestation, in 40% at 30 weeks of gestation, and in 42% at 36 weeks of gestation. It was common in multiparous women. Self-reported nasal obstruction for three or more weeks was frequent during pregnancy in two-thirds of the women.[6]

Pregnant women manifest an odor intolerance compared to non-pregnant women. It disturbs their everyday actions, with mainly sensory/somatic symptoms. Embryo and maternal protective functions may affect this behavior[7]

Significant fluctuations were also noted for body temperature, nasal airflow across the cycle phases of the women with normal cycling for all the hormones examined. Fluctuations reported in some sensory systems during the menstrual cycle.[8] Increasing levels of beta-estradiol that occur in vitro fertilization treatment cause no significant effect on nasal physiology.[9] The menstrual cycle does not significantly influence olfactory sensitivity.[10]

Nausea-vomiting and olfaction

Though the trigger of nausea and vomiting during pregnancy is not identified, there is convincing evidence relating to estrogens or human chorionic gonadotropin.[11] Olfaction is a well-known cause for nausea and vomiting during pregnancy.[12] The exact etiology of hyperemesis gravidarum is unidentified, but hyperolfaction may be a causative feature. Hyperolfaction in pregnancy may cause the pregnant woman to search for a fresher, noiseless, and comfortable environment.[13]

The Effects of Pregnancy to Olfaction

66.6% of the pregnant women were suffering olfactory dysfunction in the second trimester; while 95.8% in the first and third trimesters. Of the schizophrenics, 81% were dominated by partial anosmia. Moreover, 5% of the patients in this condition either exhibited parosmia or phantosmia.[14]

Variations in the discernment of odors in pregnancy are a renowned phenomenon. Researchers have reported a general improvement in sensitivity. The highest impact diverges from the first trimester to the second and third trimesters.[15] Other investigators revealed reduced sensitivity in late pregnancy. The variations in olfactory sensation were examined in pregnant women during each trimester of pregnancy, in non-pregnant women and in women between postpartum 2 and 3 months. The differences in odor evaluation were greatest in the third trimester. Olfactory function was evaluated through each trimester of pregnancy and postpartum. In this report, no constant variances in olfactory sensitivity were revealed between two groups.[15]

Kuga et al. revealed that non-pregnant women had lower gustatory thresholds than pregnant women. Apparent reduction in the gustatory function was observed in the first trimester of pregnancy. During the first trimester, gustatory sense is reduced and the reduction is considered to be due to the hormonal changes in pregnancy.[16]

It is hypothesized that olfactory function is decreased obviously after birth and postpartum 6–12 weeks; however, it appears to be improved totally. Although pregnancy is characteristically along with variations in olfactory show, olfaction does not diminish as a function of the number of pregnancies.[17]

Zwaardemaker stated that, especially in the first trimester, pregnancy is related with hyperacuity.[18] Early pregnancy can be associated with a bizarre sense of smell instead of hyperosmia. The misperception of certain odors during early pregnancy was revealed.[19]

Savoviç et al. reported that all variations of the olfactory sense in pregnancy are clarified by mental fluctuations of pregnant women. The reduction of olfactory capacity in postmenopause is described by the weakening sexual hormone levels.[1] In another study, 31 healthy pregnant women in the first trimester, 30 in the second trimester, 31 in the third trimester, and 30 non-pregnant healthy controls were investigated. This study showed that early pregnancy may possibly be associated with significant changes in olfactory performance. They analyzed that the misrepresentation of odor recognition in the first trimester might be a contributing factor for the occurrence of pregnancy-specific conditions, such as morning sickness and hyperemesis gravidarum, which are both joint complaints throughout the initial stage of parturition.[19] Others revealed that, during early pregnancy, olfactory dysfunction has an insignificant effect on nausea and vomiting.[20] In another study, the pregnant women rated their particular smell sense truncated.[21] 76% of the pregnant women reported unusual smell and/or taste sensitivity. Increased smell sensitivity was found in 67% of all pregnant respondents at early pregnancy and occasionally 17% of them associated with qualitative smell alterations, and 14% of them with phantom smells. The smell anomalies were found less common at late pregnancy and nearly absent during the postpartum stage.[22] 90% of pregnant women stated that some odors were sensed less pleasing. These and earlier results may reveal that the pregnancy's effect on olfaction is minor and varying.[23]

In a research, pregnant women had significantly lower gustatory sensitivity scores. Besides, pregnant women rated the odors 'rum', 'cigarette' and 'coffee' as extra aversive than non-pregnant women. Kölble et al. reported that pregnant women had a reduced odor threshold when compared to non-pregnant women. Six weeks after birth, this variance was still present. The link between olfactory and limbic systems during pregnancy may trigger this effect.[24]

Ochsenbein-Kölble evaluated the olfactory function of pregnant women at about 12, 21, and 36 weeks of gestation and postpartum7 weeks. There was no difference in olfactory function between the control cases and the pregnant women in the first trimester. Nevertheless, the pregnant women suffered a reduced odor threshold compared to the non-pregnant controls at about 36 weeks of gestation. Pregnant women have evaluated olfactory sense higher than the control cases. Hormonal, cognitive, and metabolic factors may cause transform in the discernment of odors throughout the pregnancy. Pregnant women have cardiovascular, respiratory, renal, hematologic, and endocrine variations. These variations affect olfactory perception in different ways. The olfactory threshold is reduced during pregnancy.[25]

The Embryo Protective Hypothesis

Numerous pregnant women remark changes in taste and smell which may be called as "morning sickness".[26] Bitter perceptions and strong odors are frequently signals of advanced toxic resistances in florae. These may be detoxified or processed without injury in the adults. However, they are harmful for the embryo in even insignificant quantities. Variations in olfactory discernment would take action as a mechanism to amplify maternal prevention of toxins. Pregnancy sickness occurs in early pregnancy just when the embryo is utmost defenseless to maternally consumed toxins.[21]

Conclusion

In pregnant women, olfactory dysfunction was observed in all trimesters. It was low in the second trimester and higher in the first and third trimesters. The smell abnormalities were almost absent at postpartum period. As olfactory functions improved after delivery of the baby, olfactory chances during pregnancy may be accepted as physiological changes which were observed in many pregnant women.

Conflict of Interest: No conflicts declared.

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Case Report

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Ethmoidal meningoencephalocele and cerebrospinal fluid leak after septoplasty: a rare complication

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Abstract

A 24-year-old man referred to our clinic with complaint of intermittent right-sided watery rhinorrhea. Patient underwent nasal septoplasty one year ago and rhinorrhea occurred two weeks after the surgery. Rhinorrhea was ignored and then patient developed meningitis two months after the surgery. Subsequently, meningoencephalocele formation developed. In this case report, we present a case of meningoencephalocele associated with cerebrospinal fluid leak diagnosed one year after the septoplasty. Septoplasty is usually regarded as a relatively safe operation. However, forceful maneuvers to perpendicular lamina of the ethmoid bone may cause breakdown of the skull base structures, particularly the horizontal lamella of the cribriform plate. When this occur, immediate management is necessary to prevent intracranial complications including meningitis, intracranial abscess, and pneumocephalus. Delay in the diagnosis of such injury may cause erosion of the bone and gradual herniation of the intracranial contents through the skull base defect.

Keywords: Cerebrospinal fluid leak, complication, endoscopic repair, meningoencephalocele, septoplasty.

Özet: Septoplasti sonrasında etmoidal meningoensefalosel ve serebrospinal sıvı kaçağı: Nadir görülen bir septoplasti komplikasyonu

Yirmi dört yaşında erkek hasta aralıklarla olan sağ taraflı su gibi burun akıntısı şikayeti ile kliniğimize refere edildi. Hasta 1 yıl önce septoplasti operasyonu olmuş ve operasyondan 2 hafta sonra rinore ortaya çıkmıştır. Rinore şikayeti ihmal edilen hastada ameliyattan 2 ay sonra da menenjit gelişmiştir. Bunu takiben de meningoensefalosel formasyonu oluşmuştur. Bu olgu sunumunda, septoplasti operasyonundan bir yıl sonra tanı konan meningoensefalosel ve eşlik eden serebrospinal sıvı kaçağı olgusunu sunduk. Septoplasti genellikle güvenli bir operasyon olarak kabul edilmektedir. Bununla birlikte, etmoid kemiğin perpendiküler laminasına zorlayıcı kuvvetli manevralar uygulanması kafa kaidesi yapılarında özellikle de kribriform plakanın horizontal laminasında fraktüre neden olabilmektedir. Böyle bir durumda, menenjit, intrakraniyal apse ve pnömosefalus gibi intrakraniyal komplikasyonların gelişmesini önlemek için hemen tamir edilmesi gerekmektedir. Böyle bir hasarda tanıda gecikme kafa kaidesindeki kemikte erozyona ve zamanla bu defektten intrakraniyal içeriğin herniye olmasına neden olabilmektedir.

Anahtar sözcükler: Endoskopik onarım, komplikasyon, meningoensefalosel, septoplasti, serebrospinal sıvı kaçağı.

Meningoencephalocele and cerebrospinal fluid (CSF) rhinorrhea of the anterior cranial fossa is a well known entity resulting from iatrogenic and non-iatrogenic causes including congenital malformations and skull base erosion from intracranial tumors. Iatrogenic CSF leaks frequently occur during endonasal transsphenoidal pituitary surgery and functional endoscopic sinus surgery.[1,2]

Septoplasty, one of the most common operations performed in otolaryngology, is usually regarded as a relatively safe operation. However, various complications including CSF leak following septoplasty are reported previously.[3,4] Meningoencephalocele formation associated with CSF leak following septoplasty is very rare.[5]

In this case report, we present a case of meningoencephalocele associated with CSF leak diagnosed one year after nasal surgery. The probable pathological mechanism and endonasal endoscopic management of this complication were discussed.

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Case Report

A 24-year-old man was referred to our tertiary clinic with complaint of profuse, intermittent right-sided watery rhinorrhea. His medical history revealed that the patient underwent nasal septoplasty at his local hospital one year ago. As noted in the perioperative records, deviated perpendicular lamina of the ethmoid bone was taken out after fracturing with Brunings nasal forceps. On the postoperative 14th day control, watery right-sided rhinorrhea occurred but was initially ignored. Eight weeks later, patient developed meningitis with complaint of headache and clouding of consciousness. Lumbar puncture revealed purulent (1000 leucocyte/mm^3) and highly viscous CSF. Patient was successfully treated and discharged from the hospital. However, intermittent rhinorrhea has continued since patient was discharged. Nasal endoscopy revealed a small polypoid lesion between nasal septum and middle turbinate (Fig. 1a). Valsalva maneuver elicited profuse right-sided watery rhinorrhea. Paranasal sinus computed tomography (CT) revealed an asymmetrical anterior skull base height which was fairly suspicious for a small right cribriform encephalocele and bony defect of the right olfactory cleft base. Subsequent fast imaging employing steady-state acquisition (FIESTA) magnetic resonance (MR) imaging confirmed the cribriform lamina defect (5×5 mm) and meningoencephalocele sac in which a part of gyrus rectus herniated throughout the defect (Fig. 1b). The patient underwent endonasal endoscopic repair. The meningoencephalocele was cauterized using a bipolar device. The skull base around the defect site was circumferentially demucosalized and cauterized to prevent postoperative mucocele formation. The skull base defect was repaired using underlay septal cartilage graft, followed by an overlay septal mucosa graft (Fig. 2). The overlay graft was bolstered with pieces of Gelfoam. Bed rest was recommended and diuretics were prescribed. The patient's postoperative course was uneventful. At his first-year follow-up, no evidence of rhinorrhea was present.

Discussion

CSF leak and meningitis is a dreaded complication of rhinologic and neurosurgical procedures. Rhinorrhea is caused by a breakdown of the skull base and closely adherent dura causing connection between subarachnoid space and nose. Therefore, any case of rhinorrhea associated with a recent history of endonasal surgery warrants further investigation.[6] Particularly, endoscopic sinus surgery and skull base surgery are due to potential for iatrogenic CSF leak. However, uncontrolled twisting manipulations of the perpendicular

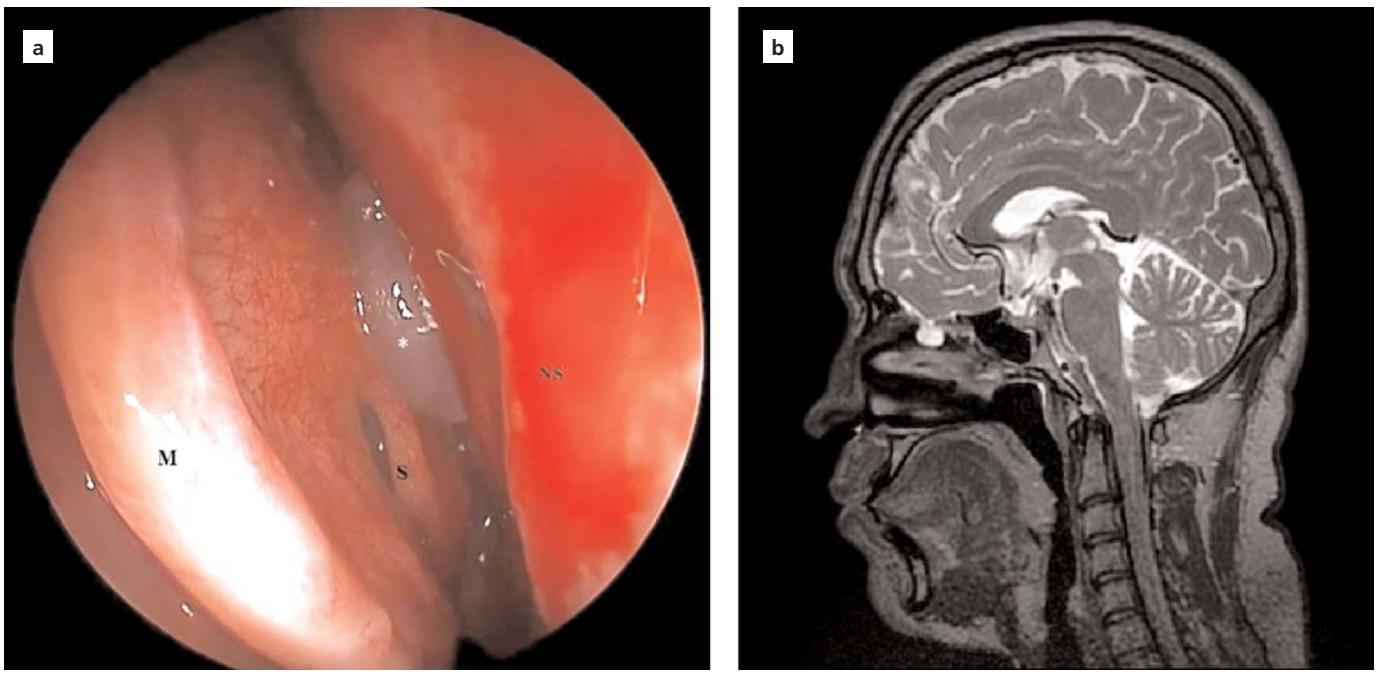

Fig. 1. (**a**) Endoscopic view of nasal polypoid lesion (meningoencephalocele sac) between middle turbinate and nasal septum. **M:** middle turbinate, **S:** superior turbinate, **NS:** nasal septum. *Meningoencephalocele sac. (**b**) Meningoencephalocele sac was shown in FIESTA T2-weighted MR sagittal section.

lamina of the ethmoid bone during septoplasty may elicit skull base injury leading life-threatening complications.

Anterior skull base is extremely vulnerable to trauma because of the thin bone and attachment of dura to the bone. The perpendicuar crista galli, comparatively strong and thick bone complex, forms the midline structure. The ethmoid labyrinth and cribriform plate supports the olfactory bulbus and is punched by various foramina for the passing of the olfactory filaments and small arachnoid pouches. Fractures of the ethmoid bone related with damages to the arachnoid and olfactory ligaments. A few authors have reported CSF leakage after septoplasty.[3,7,8] They proposed that these slit-shaped dehiscences at the horizontal lamella of the cribriform plate or perforation of the cribriform plate likely resulted from forceful operative technique applied for removal of the perpendicular plate of the ethmoid bone.

Thakar et al.[9] reported two patients with delayed CSF leak which occurred three months after the septoplasty operation. They attributed this delayed leaks to following dural pulses at the injury site, leads to bone resorption and resultant dural herniation and rupture. Previously, Taveras and Ransohoff[10] suggested a similar system for the disposition of a leptomeningeal cyst: iatrogenic trauma produces a skull fracture; meninges herniate through the defect and pulsation gradually pushes more meninges through the defect; growing sac subsequently corrodes the bone. In our current patient, at first year after the septal surgery, meningoencephalocele sac was observed in nasal cavity between the middle turbinate and nasal septum. This theory may explain the acquired meningoencephalocele in our patient.

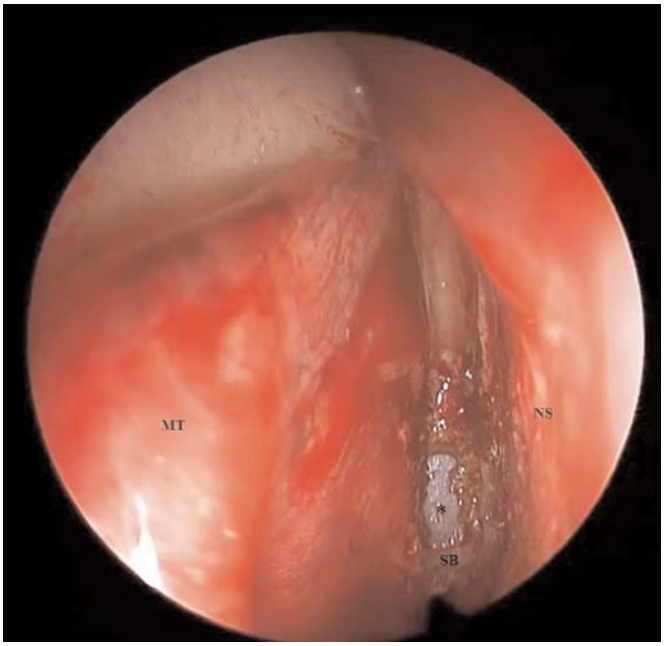

Fig. 2. Intraoperative endoscopic view after skull base repair with underlay septal cartilage. **MT:** middle turbinate, **NS:** nasal septum, **SB:** demucosalized skull base bone. *Underlay septal cartilage.

Removing the deviated posterior bony septum by applying forceful maneuvers to perpendicular lamina of the ethmoid bone remains common practice in septoplasty. We agree with Thakar et al[9] who proposed that sharp instruments such as bone scissors may be much safer than grasping forceps to fracture bony septum. Small amounts of the CSF leak might not be recognized. In addition, neurologic findings are not present straightway postoperatively, if there is a noteworthy rapidly growing hematoma or pneuomcephalus. When skull base injury occur, immediate management is necessary to prevent intracranial complications. The current management of CSF leak and meningoencephalocele are endoscopic endonasal repair which has evolved significantly during the past decade.[11] Safety and efficacy of this approach have surpassed the traditional open approaches. In the current case we also performed a successful endonasal endoscopic repair with uneventful postoperative course.

In conclusion, although the CSF leak following nasal septoplasty is rare, forceful maneuvers to perpendicular lamina of the ethmoid bone may cause breakdown of the skull base. Delay in the diagnosis of such injury may cause gradual herniation of the intracranial contents through the skull base defect and encephalocele formation and, life threatening complications including ascending meningitis, intracranial abscess and pneumocephalus. Therefore, surgeon should consider the possibility of such injury and seek for its findings.

Conflict of Interest: No conflicts declared.

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