Formerly Journal of Medical Updates

ISSN 2149-7109

ENT updates

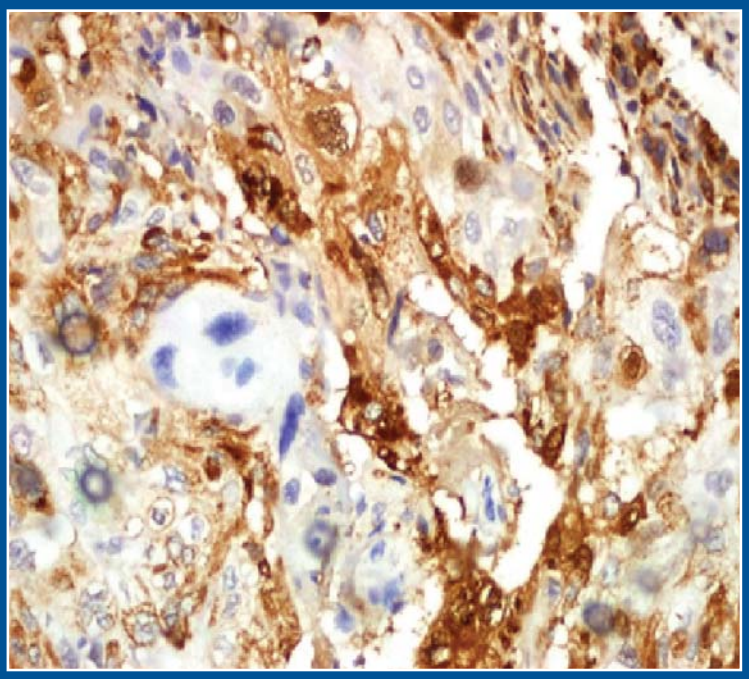
An International Journal of ENT and Related Subjects

Editor / Cemal Cingi, MD

Official Journal of Continuous Education and Scientific Research Association (CESRA), Turkey

Volume **7** / Issue **1** / April **2017**

Published three times a year



2017 1

www.entupdates.org

deomed®

ENT updates
www.entupdates.org
(formerly Journal of Medical Updates)

Volume 7 | Issue 1 | April 2017
Published three times a year

Official Journal of Continuous Education and Scientific Research Association (CESRA), Turkey

ENT updates
www.entupdates.org

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.

Copyright

Subscription

Annaul rates: Individual 60 EUR, institutional 100 EUR (for 3 printed issues include postage and local VAT). Supplements are not included in the subscription rates. Single issue price is 20 EUR. For subscription requests please refer to www.entupdates.org

Publication Info

Owner: On behalf of Continuous Education and Scientific Research Association (CESRA), Turkey, Prof. Cemal Cingi, MD, President

Responsible Manager: Mustafa Bedel

Bibliographical Advising: Beyhan Karpuz

Prepublishing & Technical Coordinator: Can Cemal Cingi

Administrative Office: Sümer Mah. Sapmaz Sok. No: 4 Eskişehir, Turkey

Due the Press Law of Turkish Republic dated as June 26, 2004 and numbered as 5187, this publication is classified as local periodical in Turkish or English.

Printing and Binding

Birmat Press: Yüzyıl Mahallesi MASSİT 1. Cad. No: 131, Bağcılar, İstanbul

Phone: +90 (0)212 629 05 59-60

Printed in Turkey on acid-free paper (April 2017).

ENT Updates is available online at www.entupdates.org

Deomed Publishing

Gur Sokak, No: 7B

34720 Kadıkoy, İstanbul

Phone: +90 216 414 83 43 (Pbx)

Fax: +90 216 414 83 42

e-mail: medya@deomed.com

www.deomed.com

deomed®

ENT updates
www.entupdates.org

Table of Contents

Volume 7 | Issue 1 | April 2017

On the Front Cover: Fig. 2. Moderately keratinizing squamous cell carcinoma. H&E ×20 (Keratinization in 25–75% tumor cells, and moderate p16 staining). Aslan H, Özkul Y, Pınar E, Işık E, Aladağ İ, İmre A, Songu M, Etit D. Effect of p16 positivity in oral cavity and oropharyngeal squamous cell carcinoma. ENT Updates 2017;7(1):17–21.

ENT updates
www.entupdates.org

Editorial

ENT Updates 2017;7(1):iv
doi:10.2399/jmu.2017001000

ScholarOne

Cemal Cingi
www.entupdates.org

Dear Colleagues,

I would like to thank you all for your support as authors, reviewers and readers for our journal to improve its scientific level. As we stepped up to the seventh year of our publication, it is my great pleasure and excitement to announce to you that **"ENT Updates"** has been included in **ScholarOne Manuscripts,** which is the premier journal and peer review tool. I hope it will be easier for you to upload your papers and review reports.

We tried to do our best for our journal and hope and expect to be upgraded by Thomson Reuters to Science Citation Index – Expanded (SCI-E) by the end of this year.

There is a great movement from printed copies to online versions in many journals and newspapers. I believe that everything will be online in future. But for the sake of colleagues who are still fond of holding their books or journals in their hands, we have decided to continue our publication with both printed and online versions for one more year. We will see together what the future will bring us.

Please do not hesitate to contact me if you have any questions about the journal or to volunteer to be a reviewer.

Best regards,
Cemal Cingi, MD
Editor-in-Chief

Experimental Study

ENT Updates 2017;7(1):1–8
doi:10.2399/jmu.2017001011

ENT updates
www.entupdates.org

The effect of nimodipine and prednisolone on traumatic facial nerve injury treatment

Tolga Dölen[1], İrfan Kaygusuz[1], Nusret Akpolat[2], Hayrettin Cengiz Alpay[3], Erol Keleş[1], Turgut Karlıdağ[1], Şinasi Yalçın[1], Koray Yüksel[1]

[1]Department of ORL, Faculty of Medicine, Fırat University, Elazığ, Turkey
[2]Department of Pathology, Faculty of Medicine, İnönü University, Malatya, Turkey
[3]Department of ORL, Faculty of Medicine, Istanbul Kemerburgaz University, Istanbul, Turkey

Abstract

Objective: To investigate the histopathological effect of nimodipine and prednisolone treatment on an animal model with peripheral facial nerve paralysis generated by clamping.

Methods: Twenty-eight New Zealand originated rabbits with facial nerve paralysis of the buccal branches generated by clamping were divided into four groups of seven each, administered with nimodipine, methylprednisolone and nimodipine-methylprednisolone combination throughout 21 days. The injured neural tissues were investigated histopathologically after treatment regarding perineural fibrosis, collagen degeneration, axonal degeneration, myelin degeneration, Schwann cell proliferation, normal myelin structure, and edema. The groups were compared with each other and with the control group.

Results: Statistically significant difference was determined between nimodipine and control groups regarding increased number of collagen fibers, myelin degeneration, axonal degeneration and myelin structure; between nimodipine and methylprednisolone groups, and between nimodipine and nimodipine-methylprednisolone combination groups regarding edema ($p<0.05$). Statistically significant data were also found between methylprednisolone and control groups in terms of increased number of collagen fibers, myelin degeneration, axonal degeneration and edema; between nimodipine-methylprednisolone combination and the control groups in terms of increased number of collagen fibers, myelin degeneration, axonal degeneration, normal myelin structure and edema ($p<0.05$).

Conclusion: Nimodipine and methylprednisolone both have positive effects on traumatic peripheral nerve paralysis with nerve integrity preserved whereas advantage of nimodipine over methylprednisolone cannot be suggested.

Keywords: Facial nerve paralysis, nimodipine, methylprednisolone.

Özet: Nimodipin ve prednizolonun travmatik fasiyal sinir hasarı üzerine etkisi

Amaç: Çalışmanın amacı klempleme ile periferik fasiyal paralizi oluşturulmuş hayvan modelinde nimodipin ve prednizolon tedavisinin histopatolojik etkisini araştırmaktır.

Yöntem: Bukkal sinir dalları klemplenerek fasiyal sinir felci oluşturulmuş 28 Yeni Zelanda orijinli tavşan, yedişerlik 4 gruba ayrıldı ve her bir gruba 21 gün boyunca nimodipin, metilprednizolon ve nimodipin-metilprednizolon kombinasyonu uygulandı. Tedavi sonrasında hasarlı nöral dokular histopatolojik olarak perinöral fibrozis, kollajen dejenerasyonu, aksonal dejenerasyon, miyelin dejenerasyonu, Schwann hücre proliferasyonu, normal miyelin yapısı ve ödem açısından incelendi. Gruplar birbirleriyle ve kontrol grubuyla karşılaştırıldı.

Bulgular: Kollajen liflerde artış, miyelin dejenerasyonu, aksonal dejenerasyon ve miyelin yapısı açısından nimodipin grubu ile kontrol grubu arasında; nimodipin grubu ile metilprednizolon grubu arasında ve nimodipin grubu ile nimodipin-metilprednizolon kombinasyon grubu arasında ise ödem oluşumu açısından istatistiksel olarak anlamlı farklılık belirlendi ($p<0.05$). Metilprednizolon grubu ile kontrol grubu arasında kollajen liflerde artış, miyelin dejenerasyonu, aksonal dejenerasyon ve ödem, nimodipin-metilprednizolon kombinasyonu ile kontrol grubu arasında da kollajen liflerde artış, miyelin dejenerasyonu, aksonal dejenerasyon ve normal miyelin yapısı ve ödem açısından istatistiksel açıdan anlamlı veriler saptandı ($p<0.05$).

Sonuç: Hem nimodipin hem de metilprednizolon sinir bütünlüğü korunmuş travmatik sinir paralizisi üzerine olumlu etkilere sahiptir. Ancak nimodipinin metilprednizolona göre daha avantajlı olduğu ileri sürülemez.

Anahtar sözcükler: Fasiyal paralizi, nimodipin, metilprednizolon.

Correspondence: Hayrettin Cengiz Alpay, MD. Department of ORL, Faculty of Medicine, Istanbul Kemerburgaz University, Istanbul, Turkey.
e-mail: hayrettincengizalpay@gmail.com

Received: Received: March 12, 2017; **Accepted:** April 15, 2017

Online available at:
www.entupdates.org
doi:10.2399/jmu.2017001011
QR code:

deomed

The mimic muscles on our face reflect not only our genetic and physical properties but also our mood expression, therefore, helping other people to understand our feelings. Patients with facial nerve dysfunction suffer from some functional and emotional problems.[1] In order to prevent these issues and regain facial nerve functions, alternative methods of nerve recovery are needed to be developed in addition to surgical treatment.

Recently, there has been a remarkable achievement in the treatment of peripheral nerve lesions and constructing related defects after increased anatomic and histopathological knowledge together with the improvement of surgical techniques to overcome nerve injury due to trauma, surgical intervention, tumors, compression and inflammatory processes.[2] Markedly increased microsurgical techniques and improved histological and immunohistochemical methods have contributed to success in peripheral nerve injury treatment.[3] In the treatment of traumatic peripheral facial nerve paralysis, substances such as neurotrophic factors, steroids, hormones and varying chemicals are also used for the purpose of nerve recovery in addition to many surgical techniques depending on the type of tissue damage.[4–6]

One of the chemical agents under investigation today is a 1,4 dihydropyridine derivative L-type voltage-dependent calcium channel antagonist, known as nimodipine. Calcium ions have key roles in depolarization, growth, excitability, aging, learning and cell proliferation, therefore, maintaining neural plasticity.[7] During peripheral nerve injury, permeability dysfunction of plasma membrane results in intracellular calcium accumulation due to electrochemical gradient difference.[8] This intracellular calcium triggers a chain of periodic chemical reactions leading to cell death.[9]

In this study, we have developed a hypothesis of a chemical agent which prevents excessive calcium transition into the cell, with an assumption of having a role in diminishing mechanically induced nerve injury, therefore improving tissue recovery. For this purpose, we investigated the effects of nimodipine and methylprednisolone treatments in an animal model of peripheral facial nerve paralysis.

Materials and Methods

This study is performed on 28 New Zealand originated rabbits weighing 1200–1300 grams each, with the approval of Animal Experiments Ethic Committee, and the materials are supplied by Scientific Search Project Unit of our University (Project No. TF05.11) All of the subjects were evaluated in terms of facial functions and those with no abnormalities were included. Symmetrical movements of mustache during chewing and presence of blinking reflex of the eyes during positive air pressure applied to the face by using a syringe were accepted as criteria of normal function.

All subjects underwent same surgical procedures by the same surgeon. They were given anesthesia by administering 10 mg/kg xylazine hydrochloride (Rompun®, Bayer AG, Leverkusen, Germany) and 50 mg/kg ketamine hydrochloride (Ketalar®, Eczacıbaşı Drug, Istanbul, Turkey) and the area over facial nerve route on their faces were shaved before the intervention. A 2 cm long horizontal incision was made infraorbital parallel to the mandible. The skin and subcutaneous tissue were dissected, and the buccal branch of the facial nerve was identified with the help of nerve stimulator in each case. Marked area of the nerve was clipped by Yaşargil-Phynox Aneurysm Clips (Aesculap AG, Tuttlingen, Germany) with a standard closure pressure of 188 g/cm^2 and tolerance pressure of 162–198 g/cm^2 lasting for one-minute compression (Fig. 1). Clipped area was pointed out by a suture applied to the underlying muscle tissue 5-0 silk (Ethicon Deutschland, Norderstedt, Germany) and the incision is closed at the end of clipping time by using 4-0 silk suture (Ethicon Deutschland, Norderstedt, Germany). 20–40 mg/kg of cefazoline sodium (Sefazol Flk®, Mustafa Nevzat, Istanbul, Turkey) was administered to each subject prophylactically through intramuscular route, 1 hour before and after the surgical procedure.

Fig. 1. Clamping the buccal branch of facial nerve with aneurysm clips.

28 subjects were divided into four randomized groups including seven of each and given medical treatment specified below for 21 days:

- **Group I (Nimodipine group):** 0.5 mg/kg/day nimodipine (Nimotop®, Bayer AG, Leverkusen, Germany), intraperitoneally
- **Group II (Methylprednisolone group):** 1 mg/kg/day methylprednisolone (Prednol-L®, Mustafa Nevzat, Istanbul, Turkey), intramuscularly
- **Group III (Nimodipine-methylprednisolone group):** 0.5 mg/kg/day nimodipine intraperitoneally and 1 mg/kg/day methylprednisolone intramuscularly
- **Group IV (Control group):** 1 cc of saline solution intramuscularly

A re-incision was made over preexisting incision site on 21st day postoperatively. The destroyed segment of the buccal branch of the nerve was found as it was pointed out before, dissected from surrounding tissue and excised 5 mm proximally and 5 mm distally.

Excised specimens were fixed in 10% glutaraldehyde and cross-sectioned into vertical and horizontal slices with a 1.5 µ thickness of each by ultratome III glass knives (Shandon Finesse, Fisher Scientific, Leicester, UK). Slices were stained with Masson trichrome and hematoxylin-eosin (HE) and examined under the light microscope under ×40, 100, 200 and 1000 magnifications (Olympus, BX51, Tokyo, Japan).

Perineural fibrosis, increased number of collagen fibers, myelin degeneration, axonal degeneration, Schwann cell proliferation, normal structure of myelin and edema were studied on half thin tissue sections and graded as; none: - (0), mild: + (1), moderate: ++ (2), severe: +++ (3). Eyepiece graticule (ocular micrometer, 1x1 mm sized with 100 equal squares) attached to Olympus light microscope was used for counting. 4 areas of 4 cross-sections of each subject (×40, 100, 200, 1000 magnification) were counted and the averages of 4 areas for each group were calculated.

Histopathological data were collected by subject follow-up forms, SPSS 11.5 (SPSS Inc., Chicago, IL, USA) program was used for statistical analysis and Mann-Whitney U test was used for group comparison. The statistical significance level was determined as 0.05.

Results

Histopathological grading of parameters for each group is shown in Table 1. As given in details, perineural fibrosis was not detected in any group except for 1 subject of the control group. Therefore, no statistically significant difference was found ($p>0.05$) (Table 2).

Increased number of collagen fibers was mostly seen in the control group (Group IV) followed by Groups I, II and III, respectively. Statistically significant data were found between Groups I, II, III, and the control group ($p<0.05$) whereas no significant data was found when Groups I, II and III were compared with each other ($p>0.05$) (Table 2; Fig. 2).

Myelin and axonal degeneration were found mostly in control group and less in Group III. Statistically significant data were found between the control group (Group IV) and Groups I, II, III ($p<0.05$) and no significance detected when Groups I, II and III were compared between each other ($p>0.05$) (Table 2; Figs. 3 and 4).

In terms of Schwann cell proliferation, despite higher histopathological scores were detected in Groups I, II and III when compared with the control group (Group IV), no significance was found between the control group and Groups I, II, III and between Groups I, II and III when compared with each other ($p>0.05$) (Table 2; Fig. 5).

The normal myelin structure was mostly seen in Group III followed by Groups I, II and IV, respectively. Significant data were found between Groups I and III ($p<0.05$), whereas no significant data were found between Group II and the control group (Group IV) and between Groups I, II and III when compared with each other ($p>0.05$) (Table 2; Fig. 6).

Edema was found at least in Group III, followed by Groups II, I and IV, respectively. No statistically significant data were found between Groups II and III ($p>0.05$), whereas the data collected from comparisons between Groups II–III (together) and I and between Groups II–III (together) and IV were found to be significant ($p<0.05$). Also, no significance was found between Groups I and IV ($p>0.05$) (Table 2; Fig. 7).

Discussion

Facial paralysis is a clinical issue, which occurs due to a partial or complete dysfunction of the facial nerve, mostly seen as a result of trauma, surgical intervention, tumors, compression, inflammation or infection.[10]

Trauma is the second most common cause of peripheral facial nerve paralysis, following Bell's palsy.[2,11] Facial nerve can be traumatized by temporal bone fractures, gunshots, surgery (tympanomastoid surgery, acoustic neuroma surgery, parotid surgery) and penetrating laceration of the face.[12,13]

Table 1. Grading of histopathological findings of the groups.

	Subject number	Perineural fibrosis	Increase in the number of collagen fibers	Myelin degeneration	Axonal degeneration	Schwann cell proliferation	Normal myelin structure	Edema
Nimodipine group	1	-	++	++	++	++	+	++
	2	-	++	++	+	++	+	++
	3	-	+	+	+	++	++	+++
	4	-	+	+	+	+++	+	+
	5	-	+	+	+	+	++	+++
	6	-	++	+	++	+	++	++
	7	-	++	++	++	+	++	+++
Methylprednisolone group	1	-	++	++	+	+	+	++
	2	-	++	+	++	+	+	+
	3	-	+	++	++	++	+	++
	4	-	+	+	+	++	+	+
	5	-	+	+	++	+++	+	+
	6	-	+	++	+	+	++	++
	7	-	+	++	++	++	++	+
Nimodipine – methylprednisolone group	1	-	-	++	+	++	++	++
	2	-	+	+	+	++	+	+
	3	-	++	+	++	++	++	+
	4	-	++	++	+	+++	++	++
	5	-	+	+	+	++	++	+
	6	-	+	+	+	+	++	+
	7	-	+	+	++	+	+	+
Control group	1	-	+++	+++	+++	+	-	+++
	2	-	++	+++	+++	+	+	+++
	3	+	++	+++	++	++	+	++
	4	-	++	++	+++	+	+	+++
	5	-	+++	+++	+++	++	+	+++
	6	-	++	+++	+++	++	-	+++
	7	-	++	+++	+++	++	+	+++

None: - (0), mild: + (1), moderate: ++ (2), severe: +++ (3)

The treatment varies according to the type of the injury and clinical manifestation.[14] Many medical treatments have been suggested for years to improve neural function and shorten recovery period, and investigations still go on. Today, steroids are the most preferred agents as their anti-inflammatory and immunosuppressive effects are known to play a key role in the treatment of nerve injury, particularly in Bell's palsy.[15] Lieberman et al.[16] demonstrated a significant effect of low-dose steroids on the recovery of neural function by studying on rats with clamping induced nerve injury. Sekiya et al.[17] investigated the effect of methylprednisolone on cochlear nerve degeneration created by clamping and suggested that it might prevent neural damage. Edema reducing the effect of methylprednisolone is believed to play an important role. In concordance with the literature, we observed remarkable antiedema effect in groups of which methylprednisolone was administered.

Vita et al.[18] investigated neural regeneration rate in subjects with sciatic nerves clamped, examined from the point of injury to tibialis anterior and concluded that the group which received steroid had shown slightly significant improvement as compared to the control group. In our study, we observed less increase in the number of collagen fibers, less axonal and myelin degeneration and also less edema in the groups which were administered methylprednisolone (Groups II and III). In addition to those parameters, we found significant increment in a normal myelin structure in the nimodipine-methylprednisolone group (Group III). All these results suggest that steroids have a positive effect on traumatic nerve injury in those

Table 2. The comparison of groups in terms of investigated parameters.

Groups compared		Perineural fibrosis	Increase in the number of collagens fibers	Myelin degeneration	Axonal degeneration	Schwann cell proliferation	Normal myelin structure	Edema
Nimodipine group	Control group	.317	**.030**	**.002**	**.002**	.775	**.015**	.096
Nimodipine group	Methylprednisolone group	1.000	.298	.606	.606	1.000	.298	**.040**
Nimodipine group	Nimodipine-methylprednisolone group	1.000	.225	.591	.591	.674	.591	**.020**
Methylprednisolone group	Control group	.317	**.006**	**.002**	**.002**	.775	.054	**.002**
Methylprednisolone group	Nimodipine-methylprednisolone group	1.000	.705	.298	.298	.674	.122	,591
Nimodipine-methylprednisolone group	Control group	.317	**.007**	**.001**	**.001**	.424	**.006**	**.001**

Mann-Whitney U test

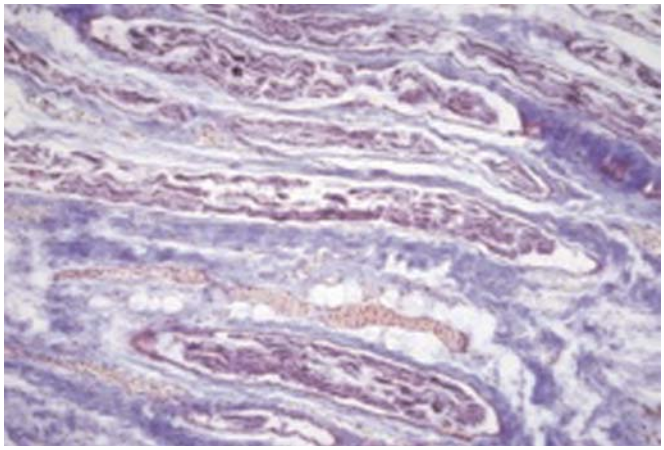


Fig. 2. The increase in the number of collagen fibers in nimodipine group (×200 HE).

with nerve integrity preserved, as in concordance with the literature.

Despite these facts, the effect of corticosteroids on traumatic nerve injury recovery could not be thoroughly revealed. On the other hand, there are some reports about corticosteroids which emphasize their worsening effects on wound healing.[19–21] Karlıdağ et al.[22] found no effect of methylprednisolone on recovery after cutting and suturing of the facial nerve. In our study, we observed no Schwann cell proliferation and no increase in the number of the normal myelin structure, whereas we noticed an increase in myelin when administered in combination with nimodipine.

For the first time, Van der Zee et al. investigated the effect of nimodipine on peripheral nerve injury and

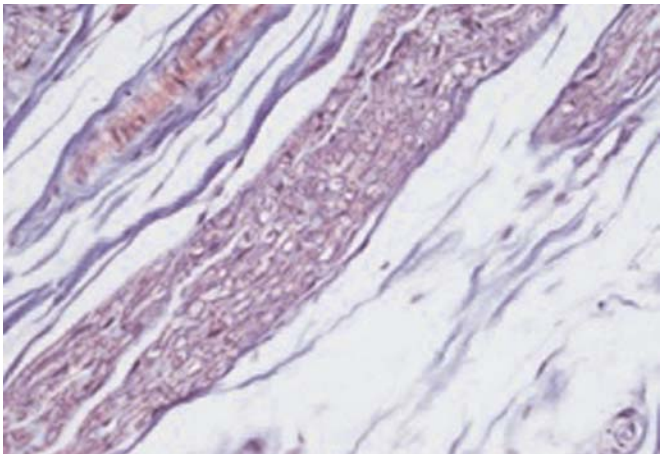


Fig. 3. Myelin degeneration in methylprednisolone group (×200 HE).

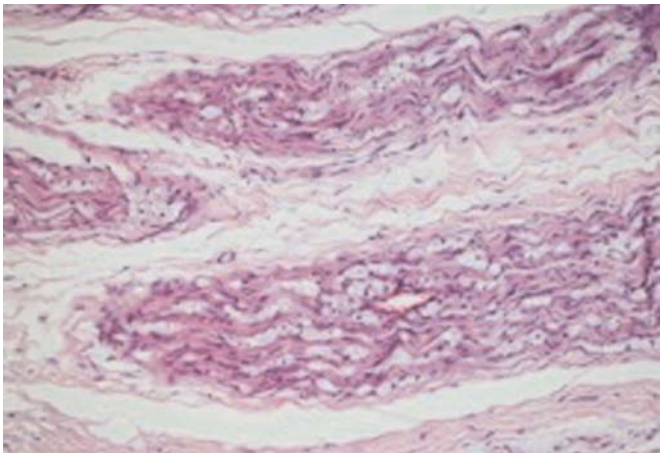


Fig. 4. Axonal degeneration in the control group (×200 HE).

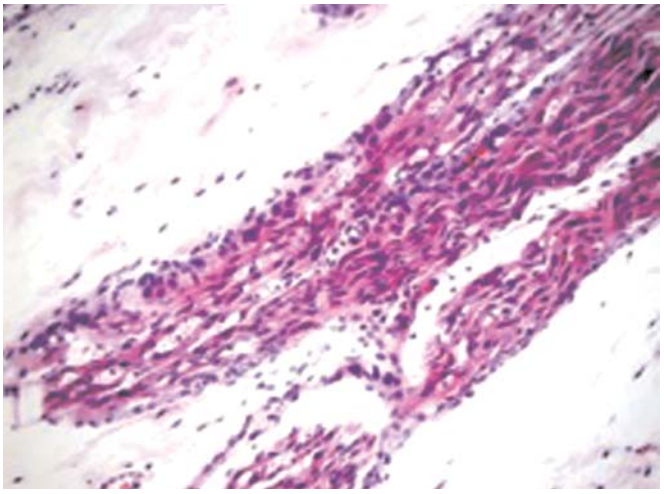


Fig. 5. Schwann cell proliferation in nimodipine group (×200 HE).

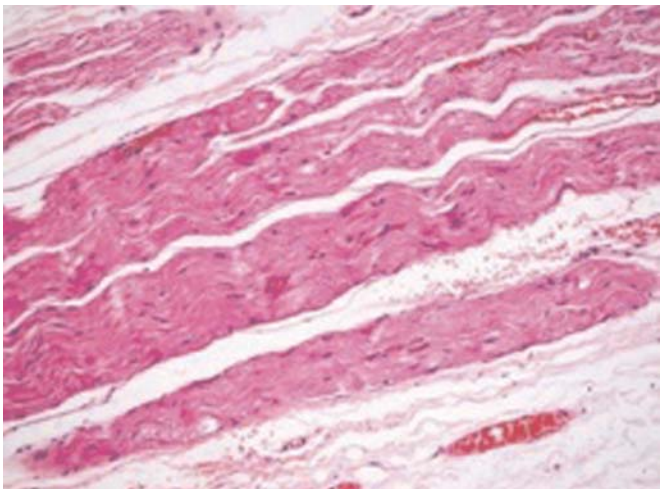


Fig. 6. Normal myelin structure in nimodipine-methylprednisolone group (×200 HE).

reported a corrective effect on neuromuscular functions of rat sciatic nerve.[23] Angelov et al.[24] reported that nimodipine administration after cutting and suturing of facial nerve had improved the axonal regeneration, had stimulated nerve healing and had reduced the hyper-innervation possibility. Our study supported the idea of reducing the effect of nimodipine on axonal and myelin degeneration.

Mattsson et al.[25] underlined the importance of nerve surveillance on functional recovery after neural injury. For this purpose, they created facial nerve injury by cutting down subjects at the level of the middle cranial fossa and repaired them immediately, administered nimodipine and noticed that the number of surviving neurons in facial nerve motor nuclei was significantly high at the first month. In another study, Mattsson et al. created the intracranial nerve injury by crushing this time and reported that nimodipine had not much effect on motor nucleus cell loss (%13), but had stimulated axonal and myelin growth and improved functional recovery.[26] In our study, we made a crushing type injury by compressing the nerve, and we detected decreased rates of axonal and myelin degeneration and increased normal myelin structure in nimodipine and nimodipine-methylprednisolone groups. Despite the fact that the increase in normal myelin structure in nimodipine group compared to the control group suggests the efficacy of nimodipine on nerve regeneration, it has no superiority over methylprednisolone regarding statistically significant difference.

Scheller et al.[27] administered oral nimodipine in a group of patients with facial paralysis after maxillofacial surgery and graded the clinical manifestation by House-Brackmann scale. They indicated a lower duration of recovery period compared to the control group. In various studies, nimodipine used in the treatment of laryngeal nerve injury is shown to accelerate recovery period, and this is supported by objective measurements (EMG).[28–30]

Pointillart et al.[31] defined the therapeutic effect of 1-week nimodipine administration on spinal cord injury by increasing blood flow. He stated significant improvement in neurologic signs after administering methylprednisolone and nimodipine to 100 patients with spinal cord injury in

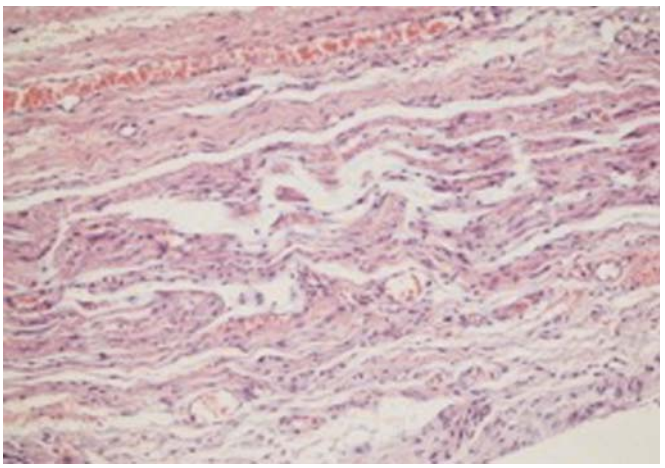


Fig. 7. Edema in nimodipine group (×200 HE).

acute phase but found no difference between two groups.[32] Our study showed that nimodipine and methylprednisolone improved nerve regeneration, methylprednisolone had a superior effect on edema, and there was no significant difference in other parameters. Regarding normal myelin structure, we found remarkable increment in nimodipine group, but there was no evidence on the superiority over methylprednisolone.

Conclusion

As a conclusion, evidence obtained from clinical trials suggests that nimodipine, a calcium-channel blocker, improves functional recovery after nerve injury. Our study also demonstrated the accelerating effect of nimodipine on neural tissue healing, but we could not prove any superior effect of nimodipine over methylprednisolone. This result correlates with previous studies in the literature. Further studies should be performed to reinforce these results by using other objective methods such as EMG together with histopathological examination.

Conflict of Interest: No conflicts declared.

References

1. Proctor B, Nager GT. The facial canal: normal anatomy, variations and anomalies. I. Normal anatomy of the facial canal. Ann Otol Rhinol Laryngol Suppl 1982;97:33–44.
2. Davis RE, Telischi FF. Traumatic facial nerve injuries: review of diagnosis and treatment. J Craniomaxillofac Trauma 1995;1:30–41.
3. Frostick SP, Yin Q, Kemp GJ. Schwann cells, neurotrophic factors, and peripheral nerve regeneration. Microsurgery 1998;18:397–405.
4. Makwana M, Raivich G. Molecular mechanisms in successful peripheral regeneration. FEBS J 2005;272:2628–38.
5. Gordon T, Sulaiman O, Boyd GJ. Experimental strategies to promote functional recovery after peripheral nerve injuries. J Peripher Nerv Syst 2003;8:236–50.
6. Mendonça AC, Barbieri HC, Mazzer N. Directly applied low intensity direct electric current enhances peripheral nerve regeneration in rat. J Neurosci Methods 2003;129:183–90.
7. Gispen WH, Schuurman T, Traber J. Nimodipine and neural plasticity in the peripheral nervous system of adult and aged rats. In: Morad M, Nayler W, Kazda S, Schramm M, editors. The Ca2+ channel: structure, function and implications. Berlin: Springer; 1988. p. 491–502.
8. Borgens RB. Voltage gradients and ionic currents in injured and regenerating axons. Adv Neurol 1988;47:51–66.
9. Schanne F, Kant AB, Young EE, Farber JL. Calcium dependence of toxic cell death: a final common pathway. Science 1979;206: 700–2.
10. Gates GA. Facial paralysis. Otolaryngol Clin North Am 1987;20: 113–31.
11. Roob G, Fazekas F, Hartung HP. Peripheral facial palsy: etiology, diagnosis and treatment. Eur Neurol 1999;41:3–9.
12. Akyıldız N. Kulak Hastalıkları ve mikrocerrahisi. Ankara: Bilimsel Tıp Yayınevi; 2002. p. 215–332.
13. May M. Trauma to the facial nerve. In. May M, editor. The facial nerve. New York, NY: Thieme; 1986. p. 192–224.
14. May M. Surgical rehabilitation of facial palsy: Total approach. In. May M, editor. The facial nerve. New York, NY: Thieme; 1986. p. 695–777.
15. Şenel A, Kaya AH. Omurilik yaralanmasında farmakolojik tedavi. In: Kofralı E, Zileli M, editors. Temel nöroşirürji. Vol. 2. Ankara: Buluş Tasarım ve Matbaacılık; 2010. p. 1637–41.
16. Lieberman DM, Jan TA, Ahmad SO, Most SP. Effects of corticosteroids on functional recovery and neuron survival after facial nerve injury in mice. Arch Facial Plast Surg 2011;13:117–24.
17. Sekiya T, Shimamura N, Suzuki S, Hatayama T. Methylprednisolone ameliorates coclear nerve degeneration following mechanical injury. Hear Res 2001;151:125–32.
18. Vita G, Dattola R, Girlanda P, Oteri G, Lo Presti F, Messina C. Effects of steroid hormones on muscle reinnervation after nerve crush in rabbit. Exp Neurol 1983;80:279–87.
19. Wicke C, Halliday B, Allen D, et al. Effects of steroids and retinoids on wound healing. Arch Surg 2000;135:1265–70.
20. Pessoa ESI, Melhado RM, Theodoro LH, Garcia VG. A histologic assessment of the influence of low-intensity laser therapy on wound healing in steroid-treated animals. Photomed Laser Surg 2004;22:199–204.
21. Sharma N, Moeller CW, Marzo SJ, Jones KJ, Foecking EM. Combinatorial treatments enhance recovery following facial nerve crush. Laryngoscope 2010;120:1523–30.
22. Karlidag T, Yildiz M, Yalcin S, Colakoglu N, Kaygusuz I, Sapmaz E. Evaluation of the effect methylprednisolone and N-acetylcysteine on anastomotic degeneration and regeneration of the facial nerve. Auris Nasus Larynx 2012;39:145–50.
23. van der Zee CE, Schuurman T, Traber J, Gispen WH. Oral administration of nimodipine accelerates functional recovery following peripheral nerve damage in the rat. Neurosci Lett 1987;83:143–8.
24. Angelov DN, Neiss WF, Streppel M, Andermahr J, Mader K, Stennert E. Nimodipine accelerates axonal sprouting after surgical repair of rat facial nerve. J Neurosci 1996;16:1041–8.
25. Mattsson P, Aldskogius H, Svensson M. Nimodipine-induced improved survival rate of facial motor neurons following intracranial transection of the facial nerve in the adult rat. J Neurosurg 1999;90:760–5.
26. Mattsson P, Janson AM, Aldskogius H, Svensson M. Nimodipine promotes regeneration and functional recovery after intracranial facial nerve crush. J Comp Neurol 2001;437:106–17.
27. Scheller K, Scheller C. Nimodipine promotes regeneration of peripheral facial nerve function after traumatic injury following maxillofacial surgery: An off label pilot-study. J Craniomaxillofac Surg 2012;40:427–34.
28. Mattsson P, Björck G, Remahl S, et al. Nimodipine and microsurgery induced recovery of the vocal cord after recurrent laryngeal nerve resection. Laryngoscope 2005;115:1863–5.

29. Nishimoto K, Kumai Y, Minoda R, Yumoto E. Nimodipine accelerates reinnervation of denervated rat thyroarytenoid muscle following nerve-muscle pedicle implantation. Laryngoscope 2012;122:606–13.
30. Hydman J, Björck G, Persson JKE, Zedenius J, Mattsson P. Diagnosis and prognosis of iatrogenic injury of the recurrent laryngeal nerve. Ann Otol Rhinol Laryngol 2009;118:506–11.
31. Pointillart V, Gense D, Gross C, et al. Effect of nimodipine on posttraumatic spinal cord ischemia in baboons. J Neurotrauma 1993;10:201–13.
32. Pointillart V, Petitjean ME, Wiart L, et al. Pharmacological therapy of spinal cord injury during the acute phase. Spinal Cord 2000; 38:71–6.

Please cite this article as: Dölen T, Kaygusuz İ, Akpolat N, Alpay HC, Keleş E, Karlıdağ T, Yalçın Ş, Yüksel K. The effect of nimodipine and prednisolone on traumatic facial nerve injury treatment. ENT Updates 2017;7(1):1–8.

Clinical Research

ENT Updates 2017;7(1):9–16
doi:10.2399/jmu.2017001010

ENT updates
www.entupdates.org

Psychiatric analysis of treatment-resistant allergic rhinitis and evaluation of the effects of antidepressant use

Yusuf Orhan Uçal[1], Hasan Deniz Tansuker[2], Bahadır Bakım[3], Ömürsen Yıldırım[4], Esra Sözen[5], Berna Uslu Coşkun[5]

[1]*Department of Otolaryngology-Head and Neck Surgery, Sur Hospital, Istanbul, Turkey*
[2]*Department of Otolaryngology-Head and Neck Surgery, Bağcılar Training and Research Hospital, Istanbul, Turkey*
[3]*Department of Psychiatry, Faculty of Medicine, Yeni Yüzyıl University, Istanbul, Turkey*
[4]*Department of Otolaryngology-Head and Neck Surgery, Florance Nightingale Hospital, Istanbul, Turkey*
[5]*Department of Otolaryngology-Head and Neck Surgery, Şişli Hamidiye Etfal Training and Research Hospital, Istanbul, Turkey*

Abstract

Objective: We evaluated the incidence of psychiatric disorders in patients with allergic rhinitis (AR) and assessed the effects of the use of antidepressants on symptoms when they are included in the treatment regimen of patients with AR who are resistant to AR treatment.

Methods: A total of 49 patients who were resistant to the treatment for AR and who did not accept the option of immunotherapy were included in the study. Thirty-eight of the 40 patients were advised to take the antidepressant sertraline; however, only 21 of them agreed to use the medication while 17 of them refused. The 21 patients who agreed to begin the antidepressant were also advised to undergo AR treatment with desloratadine once per day and intranasal mometasone furoate once per day (Group 1). The patients who refused to use the antidepressant were advised to begin the AR treatment (Group 2). Symptom scoring for AR was again performed for all patients 6 weeks after treatment. The Psychological Symptom Checklist-90 (SCL-90), Beck Depression Inventory (BDI), and State-Trait Anxiety Inventory (STAI TX I and TX II) were performed on the patients in the company of a psychiatrist.

Results: The post-treatment nasal and non-nasal symptom scores in Group 1 were significantly better than the pretreatment scores for any of the seven symptoms (p=0.000). No significant correlation was found between the AR symptom scores and the average SCL-90 general symptom score, the SCL-90 subscale scores, the total BDI scores, and the STAI scores (p>0.05).

Conclusion: This study suggests that the use of antidepressants diminishes the allergic symptoms in patients with treatment-resistant AR since psychosomatic factor is of great importance in the patient population of AR.

Keywords: Psychiatric disorders, allergic rhinitis, antidepressant.

Özet: Tedaviye dirençli alerjik rinitin psikiyatrik analizi ve antidepresan kullanımı etkilerinin değerlendirilmesi

Amaç: Bu çalışmada alerjik rinit (AR) hastalarında psikiyatrik bozuklukların insidansı ve AR tedavisine dirençli AR hastalarının tedavi rejimine dahil edildiğinde antidepresanların etkilerini değerlendirmeyi amaçladık.

Yöntem: Çalışmaya AR tedavisine dirençli ve immünoterapi seçeneğini kabul etmeyen toplam 49 hasta alındı. Kırk hastanın 38'ine antidepresan sertralin alması önerildi. Ancak yalnızca 21'i ilacı kullanmayı kabul ederken 17'si reddetti. Antidepresana başlamayı kabul eden 21 hastaya ayrıca günde tek doz desloratadin ve intranazal mometazon furoat alması önerildi (Grup 1). Antidepresan kullanmayı reddeden hastalara AR tedavisine başlaması önerildi (Grup 2). Tedaviden 6 hafta sonra hastaların tümünde yeniden AR için semptom skorlaması yapıldı. Bir psikiyatrist nezaretinde hastalara Psikolojik Semptom Kontrol Listesi-90 (The Psychological Symptom Checklist-90; SCL-90), Beck Depresyon Envanteri (Beck Depression Inventory; BDI) ve Anksiyete Durum Envanteri (State-Trait Anxiety Inventory; STA-I TX I ve TX II) uygulandı.

Bulgular: Grup 1'de tedavi sonrası nazal ve nazal olmayan semptom skorları yedi semptomun her biri için tedavi öncesi skorlardan anlamlı derecede daha iyiydi (p=0.000). AR semptom skorlarıyla ortalama SCL-90 genel semptom skoru, SCL-90 altölçek skorları, total BDI skorları ve STAI skorları arasında anlamlı bir korelasyon bulunmadı (p>0.05).

Sonuç: AR popülasyonunda psikosomatik faktör büyük önem taşıdığından bu çalışma antidepresan kullanımının tedaviye dirençli AR'de alerjik semptomları azalttığını akla getirmektedir.

Anahtar sözcükler: Psikiyatrik bozukluklar, alerjik rinit, antidepresan.

Correspondence: Yusuf Orhan Uçal, MD. Department of Otolaryngology-Head and Neck Surgery, Sur Hospital, Istanbul, Turkey.
e-mail: orhanucal@gmail.com

Received: March 3, 2017; **Accepted:** April 10, 2017

Online available at:
www.entupdates.org
doi:10.2399/jmu.2017001010
QR code:

Allergic rhinitis (AR) is a highly prevalent chronic disease which is reported as 15% to 20% in industrial societies, and 42% in children.[1,2]

The nasal symptoms in patients with AR may cause sleep disorders at night and concentration difficulty during the day. Moreover, the resulting psychosocial symptoms, such as chronic fatigue, loss of appetite, a low degree of success at school, low self-image, unemployment, irritability, and pessimism, coincide with symptoms of depression and anxiety.[3,4] Despite the fact that AR affects the patient's quality of life in an extremely negative manner and that patients exhibiting severe symptoms regularly consult with specialists, clinicians do not tend to focus on the psychological effects of AR.[5] Psychosocial causes of allergic responses have long been of interest among physicians dealing with psychosomatics. After the clinical studies, a discussion has started on the role of psychological factors in allergic reactions, and individuals with AR were reported to be more anxious, obsessional, ambitious, and neurotic than were individuals without AR.[6,7] In subsequent studies, however, depression, hypochondriasis, psychasthenia, and avoidant personality traits were reported to be associated with allergy.[8,9] The role of psychological disorders, such as anxiety and depression, in patients with AR, is still being discussed. We believe that psychological disorders such as depression and anxiety trigger the allergic process by both affecting the hypothalamic-pituitary-adrenal (HPA) system and enhancing the immune response associated with Th2 cells and that AR, in turn, aggravates these symptoms and psychological disorders, resulting in a vicious circle.[10–12]

Given such information, some patients with AR state that their symptoms do not improve despite medical treatment. Therefore, we evaluated the incidence of psychiatric disorders in patients with AR and assessed the effects of the use of antidepressants on symptoms when they are included in the treatment regimen of patients with AR who are resistant to allergic rhinitis treatment.

Materials and Methods

This controlled, randomized, single-blind study was approved by the Research Ethics Committee of the Istanbul Faculty of Medicine, Istanbul University (9 December 2011; 2011/1996-864).

Of all patients who visited the Allergy and Immunology Clinic at Şişli Etfal Training and Research Hospital from January 2012 to July 2012, those clinically diagnosed with persistent, perennial AR according to ARIA and who reacted against at least one allergen with a score of 3+ in the skin-prick test were assessed (positive test correlated with symptoms). Among these patients, 49 who were resistant to the treatment for AR and who did not accept the option of immunotherapy were included in the study. Treatment-resistant patients were defined as those who experienced no symptom relief after at least 1 year of antihistaminic and intranasal steroid treatment.

None of these patients had any systemic diseases or diagnosed psychiatric disorders. The exclusion criteria were negative skin-prick tests, no history of AR treatment, inconsistency of positive test results with the symptoms, patient eligibility for and acceptance of immunotherapy, the presence of nasal pathology other than AR leading to nasal obstruction (e.g., non-allergic rhinitis with or without eosinophils, chronic sinusitis, septal deviation, conchal hypertrophy, and nasal polyposis), the presence of additional systemic disease, a history of antidepressant use, a known history of psychiatric disease, and conditions that did not allow for the use of antidepressant or antihistaminic medications. All patients underwent anterior rhinoscopy to establish nasal patency, and nasal endoscopy to look at possible polyps.

All patients were informed about the study details and signed a voluntary informed consent form. AR symptom scoring was performed on all patients with treatment-resistant AR. A score of 0 to 3 was given for each question (0, no complaint to 3, serious enough to affect daily life). The questions covered seven symptoms (rhinorrhea, nasal itching, nasal obstruction, sneezing, watery eyes, eye burning-itching, and ear or palatal itching); four of these symptoms were specific to nasal problems, and three were non-nasal symptoms. Each patient's symptom triggers, the timing of events that affected daily life and their relationships with the disease, symptom duration, hospitalization frequency, socioeconomic level, educational background, age, and sex were recorded. The Psychological Symptom Checklist-90 (SCL-90), Beck Depression Inventory (BDI), and State-Trait Anxiety Inventory (STAI TX I and TX II) were performed on the patients in the company of a psychiatrist.

At least one psychological problem was found in 44 of the 49 patients (89.7%). A psychiatric consultation involving detailed examination and the one-to-one interview was requested from the patients in whom pathology was assessed. Four patients refused to undergo a psychiatric consultation and were excluded from the study. After 40 patients had undergone their interview with the psychiatrist, they were called for a second check-up 6 weeks later.

At the end of the consultation, 38 of the 40 patients (95%) were advised to take the antidepressant sertraline (Lustral®; Pfizer Medications, Istanbul, Turkey); however, only 21 of them agreed to use the medication. The remaining two patients were not considered to be in need of antidepressants and were thus excluded from the study. As a result, the study involved 38 patients (25 female, 13 male; mean age: 33.3±11.3 years). Twenty-one of these patients began the antidepressant, and 17 refused. The 21 patients who agreed to begin the antidepressant were also advised to undergo AR treatment with desloratadine (Deloday® 5-mg tablets; Vitalis Med, Istanbul, Turkey) once per day and intranasal mometasone furoate (Nasonex Aqueous Nasal Spray®; Schering-Plough Med, Istanbul, Turkey) once per day (50-µg to both nasal cavities twice each morning). This population was defined as Group 1 (n=21). The patients who refused to use the antidepressant were advised to begin the AR treatment (desloratadine and intranasal mometasone furoate only); they were fully informed about this treatment, and its regular use was encouraged. This patient population was defined as Group 2 (n=17). Symptom scoring for AR was again performed for all patients 6 weeks after treatment. All patients in both groups were analyzed regarding the symptom scores, psychiatric analysis results, and psychiatric interview records, and the pretreatment and post-treatment AR symptom scores were compared within and between the groups. The two groups were analyzed separately regarding the symptom triggers and the timing of the events that affected daily life and their relationship with the disease.

The descriptive statistics concerned the frequency, correlation, average, and standard deviation values. The distribution of the variables was evaluated using the Kolmogorov–Smirnov test. ANOVA, the independent-samples t-test, and the Mann–Whitney U-test were used to analyze the quantitative data. Repeated-measures analysis was performed using the paired-sample t-test and Wilcoxon test. The chi-square test and Fischer's exact test were used to analyze the qualitative data. The SPSS ver. 20.0 (SPSS Inc., Chicago, IL, USA) was used for all analyses.

Table 1. Age and sex data.

		Group 1 Mean±SD	Group 2 Mean±SD	p*
Age (year)		31.5±11.5	35.1±11.0	0.343
		n (%)	n (%)	
Sex	Female	12 (57.1)	13 (76.5)	0.215
	Male	9 (42.9)	4 (23.5)	

*Independent samples t test/chi-square test. **SD:** standart deviation

Results

No statistically significant differences were seen in age, sex, symptom duration, hospitalization frequency, socioeconomic level, or educational status between the two groups (p>0.05) (Tables 1 and 2).

Patients in both Groups 1 and 2 who did not benefit from the AR treatment had high values on the SCL-90, indicating the presence of a psychological disorder. The BDI scores indicated moderate depressive symptoms in both groups, whereas the STAI TX I and II scores indicated anxiety disorders in both groups. No significant difference was found between the two groups (Table 3).

The post-treatment nasal and non-nasal symptom scores in Group 1 were significantly better than the pretreatment

Table 2. The distribution of socio-demographic data.

		Group 1 Mean±SD	Group 2 Mean±SD	p*
Duration of symptoms (year)		5.2±3.3	6.9±6.1	0.429
		n (%)	n (%)	
Hospitalization frequency	Rarely (<3 times/year)	8 (38.1)	11 (64.7)	0.103
	Frequently (>3 times/year)	13 (61.9)	6 (35.3)	
Socio-economic level	Low (<1000 TL)	8 (38.1)	5 (29.4)	0.575
	Moderate-high (>1000 TL)	13 (61.9)	12 (70.6)	
Educational status	Primary/High school	15 (71.4)	15 (88.2)	0.257
	University	6 (28.6)	2 (11.8)	

*Independent samples t test/chi-square test. **SD:** standart deviation, **TL:** Turkish Lira

Table 3. The evaluation of psychiatric analysis scales in Group 1 and Group 2.

		Group 1 Mean±SD	Group 2 Mean±SD	p*
SCL-90	Somatization	1.7±0.8	1.6±0.9	0.696
	Obsessive-compulsive	1.7±0.6	1.6±0.8	0.674
	Interpersonal sensitivity	1.7±0.7	1.7±0.8	0.799
	Depression	1.7±0.8	1.5±0.9	0.451
	Anxiety	1.4±0.6	1.3±0.9	0.505
	Anger-hostility	1.7±0.8	1.8±0.9	0.792
	Phobic anxiety	0.9±0.8	0.9±1.0	0.939
	Paranoid ideation	1.5±0.7	1.5±0.7	0.998
	Psychoticism	1.2±0.9	1.2±1.0	0.905
	Other scales**	1.6 ±0.7	1.6±0.8	0.835
	General symptom scores	1.5±0.5	1.5±0.8	0.769
Between 0.5–1.0: moderate psychological problem; ≥1.0: severe psychological problem.				
Beck depression jnventory	Total score	21.4±8.5	20.2±6.7	0.636
17–29 points: moderate depressive symptoms; 30–63 points: severe depressive symptoms				
State-trait anxiety inventory	State anxiety (STAI-S) scores	48.1±10.6	46.1±8.7	0.541
	Trait anxiety (STAI-T) scores	50.3±6.4	49.0±6.3	0.526
>40 points: anxiety disorder				

*Independent samples t test/chi-square test. **Other scales: appetite and sleep disorders, guiltiness. **SD:** standart deviation, **SCL:** Symptom check-list; **STAI:** state-trait anxiety inventory (**S:** state, **T:** trait).

scores for any of the seven symptoms (p=0.000). In Group 2, significant recovery was achieved in all of the non-nasal symptoms. Among the nasal symptoms, however, only rhinorrhea and sneezing exhibited significant recovery over pretreatment levels. Nasal itching and nasal obstruction symptoms did not demonstrate a significant change after the treatment. A significant difference in the post-treatment sneezing and nasal obstruction symptoms occurred between Groups 1 and 2. In contrast, the rates of change in all nasal and non-nasal symptoms before and after treatment were significantly higher in Group 1 (Tables 4 and 5).

The pretreatment total symptom scores were not significantly different between Groups 1 and 2. Post-treatment total symptom scores were significantly better than pretreatment scores in both Groups 1 and 2. The post-treatment total symptom score was significantly lower in Group 1 than in Group 2 (p<0.001). Again, the rates of change in the total symptom score before and after treatment were higher in Group 1 (p<0.001) (Table 6).

On the correlation between the hospitalization frequency and symptom scores, the total AR symptom scores of patients who were rarely hospitalized were significantly lower than those frequently hospitalized (p=0.001). There was no correlation between another socio-demographic data and symptom scores (sex, socio-economical status, and educational status). No significant correlation was found between the AR symptom scores and the average SCL-90 general symptom score, the SCL-90 subscale scores, the total BDI scores, and the STAI scores (p>0.05).

Discussion

Many authors have investigated the relationship between atopic or allergic diseases and psychological disorders such as depression and anxiety, and many have reported that a psychoneuroimmunologic mechanism might play a role in the pathophysiology of AR.[13–16] Psychological stress, particularly in obsessive people, may alter the release of mediators by affecting the IgE-allergen cross-linking on the mast cell surface and create allergic symptoms secondary to mast cell activation regulated by the central nervous system through the peripheral nerves.[17–19] The limbic system may also be associated with allergic reactions; during allergic reactions, psychological changes occur in the central nervous system due to mediators such as serotonin, which has neurotransmitter functions, and vasoactive intestinal peptide.[20] Some researchers advocate that depression directly affects the development of atopic diseases. Depression affects cortisol release and the function of the HPA cycle, which may contribute to the disorders seen during the development of an allergic immune response.[21,22]

Table 4. Allergic rhinitis symptom scoring (nasal symptoms).

		Group 1 Mean±SD	Group 2 Mean±SD	p*
Rninorrhea	Pre-treatment	2.2±0.8	2.2±0.9	0.992
	Post-treatment	1.1±0.8	1.5±0.7	0.083
	Difference (%)	49.2±35.1	22.5±54.0	**0.024**
	P	**0.000**	**0.013**	
Nasal itching	Pre-treatment	2.2±0.7	1.9±0.7	0.103
	Post-treatment	1.2±0.8	1.6±0.7	0.115
	Difference (%)	50.0±33.7	4.9±58.0	**0.005**
	P	**0.000**	0.172	
Sneezing	Pre-treatment	2.8±0.4	2.6±0.6	0.329
	Post-treatment	1.1±0.7	1.6±0.7	**0.038**
	Difference (%)	57.1±31.9	35.3±26.9	**0.031**
	P	**0.000**	**0.000**	
Nasal obstruction	Pre-treatment	2.2±0.7	2.4±0.9	0.555
	Post-treatment	1.2±0.8	2.0±0.9	**0.007**
	Difference (%)	40.5±48.8	12.7±41.5	**0.015**
	P	**0.000**	0.111	
Nasal symptoms total scores	Pre-treatment	9.8±1.8	9.2±1.8	0.321
	Post-treatment	4.7±2.2	6.8±2.0	**0.004**
	Difference (%)	50.4±27.0	23.1±25.6	**0.003**
	P	**0.000**	**0.001**	

*Independent samples t test/Paired samples t test. **SD:** standart deviation

Patients who experience increases in their allergic symptoms and restrictions in their daily activities secondary to the above-described mechanisms experience far more psychological stress in coping with this chronic disease and complain more about allergic symptoms as a result of the stress experienced. Thus, a vicious circle develops. Either the allergic symptoms must be controlled, or the psychological stress must be suppressed to

Table 5. Allergic rhinitis symptom scoring (Non-nasal symptoms).

		Group 1 Mean±SD	Group 2 Mean±SD	p*
Eye burning-itching	Pre-treatment	2.1±0.8	2.4±0.7	0.293
	Post-treatment	0.8±0.8	1.7±0.7	**0.001**
	Difference (%)	63.5±38.6	22.5±38.6	**0.002**
	P	**0.000**	**0.002**	
Watery eyes	Pre-treatment	2.1±0.7	2.4±0.6	0.322
	Post-treatment	1.0±0.7	1.8±1.0	**0.005**
	Difference (%)	54.0±36.1	22.6±33.4	**0.009**
	P	**0.000**	**0.021**	
Ear/Palatal itching	Pre-treatment	2.6±0.7	2.5±0.8	0.591
	Post-treatment	1.2±0.9	1.7±0.8	0.101
	Difference (%)	57.2±33.7	25.4±46.8	**0.020**
	P	**0.000**	**0.007**	
Non nasal symptoms total scores	Pre-treatment	6.9±1.3	7.2±1.4	0.464
	Post-treatment	3.0±2.0	5.2±1.6	**0.000**
	Difference (%)	57.2±27.7	26.8±16.9	**0.000**
	P	**0.000**	**0.000**	

*Independent samples t test/Paired samples t test/Mann-Whitney U test/ Wilcoxon test. **SD:** standart deviation

Table 6. Allergic shinitis symptom scoring (nasal and non-nasal symptoms total scores)

		Group 1 Mean±SD	Group 2 Mean±SD	p*
Total symptom scores	Pre-treatment	16.6±2.4	16.4±2.8	0.753
	Post-treatment	7.6±3.7	12.1±2.7	**0.000**
	Difference (%)	53.2±23.7	25.2±15.8	**0.000**
	P	**0.000**	**0.002**	

*Independent samples t test/Paired samples t test. **SD:** standart deviation

break this vicious circle. In the present study, we evaluated whether antidepressants administered to suppress the stress in patients with treatment-resistant allergic symptoms could break this vicious circle or not. Marshall et al. determined that cognitive impairment, mental fatigue, mood changes, and psychological states similar to depression were present when seasonal AR symptoms increased.[23,24] Tonelli et al. performed a multidisciplinary study involving the fields of molecular biology, psychoneuroimmunology, and pharmacogenetics to elucidate the relationship between AR and psychological disorders.[25] They advocated that the allergic condition could directly affect the biochemical response in the central nervous system, giving rise to psychological disorders. Moreover, Kiecolt-Glaser et al. demonstrated that stress not only altered allergic symptoms but also changed the laboratory parameters.[26] Cuffel et al. evaluated more than 600,000 individuals. Depression was present in 85,298 patients with AR and it was 1.7 times more likely to develop in those with than without AR; moreover, anxiety was 1.41 times more likely to develop in those with than without AR.[27] In a study by Patten and Williams, depression, panic disorder, and social phobia were found to be more prevalent in 12,171 allergic patients than in nonallergic patients.[28] Similar studies have also shown a relationship between anxiety/depression and allergic diseases.[29–34] In our study, at least one psychological problem was found in 89.7% of the patients with treatment-resistant AR.

In this study, the SCL-90 was administered as a screening test; its reliability, validity, and effectiveness have been demonstrated previously.[15,33,35] Bavbek et al. found significant differences in all subscales of the SCL-90, including somatization, depression, and average general symptom scores, between patients with and without allergy.[33] Lv et al. reported higher SCL-90 scores for somatization, depression, anxiety, anger-hostility, and psychosis in patients with than without seasonal AR. In our study, high scores consistent with those reported in the literature were observed for all subscales of the SCL-90 and the average general symptoms.[15]

Comparison of anxiety scores among allergic patients has revealed high State Anxiety Scores (STAI-S) in patients with asthma, AR, and sinusitis and high Trait Anxiety Scores (STAI-T) in patients with asthma and nasal polyposis.[36] Stauder and Kovacs evaluated 646 allergic patients and found an average STAI-S score of 40.6 and average STAI-T score of 42.9; these high scores were found to be associated with anxiety.[37] The average STAI-S and STAI-T scores in the two groups in our study were 47.1 and 49.7, respectively. These anxiety scores in patients with AR are higher than those reported previously, supporting the notion of a relationship between AR and anxiety.

BDI is commonly used to measure and assess depressive symptoms with high validity and reliability. Huurre et al. found that the total BDI score was high in allergic patients and identified a relationship between AR and depression.[32] Bell et al. confirmed a history of allergies in 71% of patients diagnosed with depression.[38] In our study, the average BDI total score among all patients in both groups was 20.8, indicating the presence of moderate depressive symptoms. This finding suggests that depressive symptoms are present in many patients with treatment-resistant AR. The symptom score for AR is a reliable scale frequently utilized to establish a diagnosis of AR based on the history of the patient.[15,39,40] Lv et al. suggested that nasal obstruction is associated with obsessive–compulsive disorder, interpersonal sensitivity, depression, anxiety, and psychosis and that nasal itching is associated with somatization, depression, and anxiety. They also argued that controlling the symptoms of nasal obstruction and nasal itching may contribute to psychological improvement.[15]

In this study, we saw improvements in all nasal and non-nasal symptoms and the total symptom score after antidepressant and AR treatment in Group 1. However, Group 2 undertook AR treatment only, and improvements were

present only in rhinorrhea and sneezing. In contrast, we noted improvement in all non-nasal symptoms. These outcomes may indicate that when psychiatric improvement occurs, the symptoms of nasal itching and obstruction also regress, but that when psychological stress continues, no changes occur in these symptoms. In other words, despite the fact that we observed no correlation between the AR symptom scores and the psychiatric scores in our study, the severity of nasal itching and nasal obstruction may be affected by psychological improvements. In this study, we found a positive relationship between hospitalization frequency and the total symptom score. This suggests that patients with severe AR symptoms desire to alleviate the symptoms or the disease itself and thus visit hospitals more frequently. However, this increases the costs associated with AR.

In a survey, Özmen et al.[7] assessed 32 patients with AR who were considered to have a possible psychiatric disorder and 32.9% of the patients stated that they had survived a major event in their lives that had upset them immediately before their allergic symptoms developed. In 44.4% of the patients, the allergic symptoms developed after the psychiatric symptoms had started, while the allergic symptoms were extant in 37.3% of them before the onset of the psychiatric disorder. In our study, 47.3% of the patients stated that their allergic symptoms emerged in the wake of a major event in their lives, such as dismissal from work, the death of a family member, marriage, divorce, pregnancy, or a traffic accident. These findings support the theory that individuals with psychiatric disorders have increased sensitivity to allergens.

As a result, patients must be approached with biopsychosocial integrity. This study suggests that psychiatric disorders may be present in patients with treatment-resistant AR and that the combination of AR treatment and antidepressants may improve both the AR and psychological symptoms. Breaking this vicious circle will reduce the frequency of affected patients to visit hospitals, enhance the response to medical treatment, and decrease the total cost associated with AR. The weaknesses of this study were the absence of a healthy control group, a control group suffering from nonallergic chronic rhinitis and lack of double-blindness.

Conclusion

This study suggests that the use of antidepressants diminishes the allergic symptoms in patients with treatment-resistant AR since psychosomatic factor is of great importance in the patient population of AR. However, additional placebo-controlled and double-blind studies are required to determine the role of antidepressants among the various AR treatment options.

Acknowledgement

The English in this document has been checked by at least two professional editors, both native speakers of English. For a certificate, please see: http://www.textcheck.com/certificate/FD79M2

Conflict of Interest: No conflicts declared.

References

1. Wright AL, Holberg CJ, Martinez FD, Halonen M, Morgan W, Taussig LM. Epidemiology of physician-diagnosed allergic rhinitis in childhood. Pediatrics 1994;94:895–901.
2. Ercan I, Cakir B, Başak T, et al. Effects of topical application of methotrexate on nasal mucosa in rats: a preclinical assessment study. Otolaryngol Head Neck Surg 2006;134:751-5.
3. Passàli D, Lauriello M, Mezzedimi C, Passàli GC, Bellussi L. Natural history of allergic rhinitis. A review. Clin Appl Immunol Rev 2001;1:207–16.
4. Bell IR, Jasnoski ML, Kagan J, King DS. Is allergic rhinitis more frequent in young adults with extreme shyness? A preliminary survey. Psychosom Med 1990;52:517–25.
5. Bousquet, J, Bullinger, M, Fayol, C, Marquis P, Valentin B, Burtin B. Assessment of quality of life in patients with perennial allergic rhinitis with the French version of the SF-36 Health Status Questionnaire. J Allergy Clin Immunol 1994;94:182–8.
6. Kremer B, Klimek L, Bullinger M, Mösges R. Generic or disease-specific quality of life scales to characterize health status in allergic rhinitis? Allergy 2001;56:957–63.
7. Ozmen M, Ozdemir A. Allergic rhinitis and psychological problems. Turkiye Klinikleri Journal of Internal Medical Sciences 2006;2:23–8.
8. Gauci M, King MG, Saxarra H, Tulloch BJ, Husband AJ. A Minnesota Multiphasic Personality Inventory profile of women with allergic rhinitis. Psychosom Med 1993;55:533–40.
9. Michel FB. Psychology of the allergic patients. Allergy 1994;49(18 Suppl):28–30.
10. Wright RJ, Cohen RT, Cohen S. The impact of stress on the development and expression of atopy. Curr Opin Allergy Clin Immunol 2005;5:23–9.
11. Cohen N. Norman Cousins Lecture. The uses and abuses of psychoneuroimmunology: a global overview. Brain Behav Immun 2006;20:99–112.
12. Hashizume H, Takigawa M. Anxiety in allergy and atopic dermatitis. Curr Opin Allergy Clin Immunol 2006,6:335–9.
13. Chida Y, Hamer M, Steptoe A. A bidirectional relationship between psychosocial factors and atopic disorders: a systematic review and meta-analysis. Psychosom Med 2008;70:102–16.
14. Slattery MJ, Essex MJ. Specificity in the association of anxiety, depression, and atopic disorders in a community sample of adolescents. J Psychiatr Res 2011;45:788–95.

15. Lv X, Xi L, Han D, Zhang L. Evaluation of the psychological status in seasonal allergic rhinitis patients. ORL J Otorhinolaryngol Relat Spec 2010;72:84–90.
16. Wamboldt MZ, Hewitt JK, Schmitz S, et al. Familial association between allergic disorders and depression in Finnish twins. Am J Med Genet 2000;96:146–53.
17. Sugarman AA, Southern L, Curran JF. A study of antibody levels in alcoholic, depressive and schizophrenic patients. Ann Allerg 1982; 48:16671.
18. Hurwitz EL, Morganstern H. Cross-sectional associations of asthma, hay fever, and other allergies with major depression and low-back pain among adults aged 20–39 years in the United States. Am J Epidemiol 1999;150:1107–16.
19. Williams K, Bienenstock J, Perdue MH. The role of psychological and neurological factors in allergic reactions. ACI News 1992;4: 77–85.
20. Tønnesen P, Hindberg I, Schaffalitzky de Muckadell OB, Mygind N. Effect of nasal allergen challenge on serotonin, substance P and vasoactive intestinal peptide in plasma and nasal secretions. Allergy 1988;43:310–7.
21. Maes M. A review of the acute phase response in major depression. Rev Neurosci 1993;4:407–16.
22. American Psychiatric Association. The dexamethasone suppression test: an overview of its current status in psychiatry. The APA Task Force on Laboratory Tests in Psychiatry. Am J Psychiatry 1987;144:1253–62.
23. Marshall PS, O'Hara C, Steinberg P. Effects of seasonal allergic rhinitis on selected cognitive abilities. Ann Allergy Asthma Immunol 2000;84:403–10.
24. Marshall PS, O'Hara C, Steinberg P. Effects of seasonal allergic rhinitis on fatigue levels and mood. Psychosom Med 2002;64:684–91.
25. Tonelli LH, Holmes A, Postolache TT. Intranasal immune challenge induces sex-dependent depressive-like behaviors and cytokine expression in the brain. Neuropsychopharmacology 2008;33:1038–48.
26. Kiecolt-Glaser JK, Heffner KL, Glaser R, et al. How stress and anxiety can alter immediate and late-phase skin test responses in allergic rhinitis. Psychoneuroendocrinology 2009;34:670–80.
27. Cuffel B, Wamboldt M, Borish L, Kennedy S, Crystal-Peters J. Economic consequences of comorbid depression, anxiety, and allergic rhinitis. Psychosomatics 1999;40:491–6.
28. Patten SB, Williams JV. Self-reported allergies and their relationship to several Axis I disorders in a community sample. Int J Psychiatry Med 2007;37:11–22.
29. Gauci M, King MG, Saxarra H, Tulloch BJ, Husband AJ. A Minnesota Multiphasic Personality Inventory profile of women with allergic rhinitis. Psychosom Med 1993;55:533–40.
30. Addolorato G, Ancona C, Capristo E, et al. State and trait anxiety in women affected by allergic and vasomotor rhinitis. J Psychosom Res 1999;46:283–89.
31. Derebery J, Meltzer E, Nathan RA, et al. Rhinitis symptoms and comorbidities in the United States: burden of rhinitis in America survey. Otolaryngol Head Neck Surg 2008;139:198–205.
32. Huurre TM, Aro HM. Long-term psychosocial effects of persistent chronic illness. A follow-up study of Finnish adolescents aged 16 to 32 years. Eur Child Adolesc Psychiatry 2002;11:85–91.
33. Bavbek S, Kumbasar H, Tuğcu H, Misirligil Z. Psychological status of patients with seasonal and perennial allergic rhinitis. J Investig Allergol Clin Immunol 2002;12:204–10.
34. Muluk NB, Oğuztürk O, Koç C, Ekici A. Minnesota Multiphasic Personality Inventory profile of patients with allergic rhinitis. J Otolaryngol 2003;32:198–202.
35. Xi L, Zhang Y, Han D, Zhang L. Effect of asthma, aeroallergen category, and gender on the psychological status of patients with allergic rhinitis. J Investig Allergol Clin Immunol 2012;22:264–9.
36. Annesi-Maesano I, Beyer A, Marmouz F, Mathelier-Fusade P, Vervloet D, Bauchau V. Do patients with skin allergies have higher levels of anxiety than patients with allergic respiratory diseases? Results of a large-scale cross-sectional study in a French population. Br J Dermatol 2006;154:1128–36.
37. Stauder A, Kovacs M. Anxiety symptoms in allergic patients: identification and risk factors. Psychosom Med 2003;65:816–23.
38. Bell IR, Jasnoski ML, Kagan J, King DS. Depression and allergies: survey of a nonclinical population. Psychother Psychosom 1991;55;1:24–31.
39. Simons FE, Prenner BM, Finn A Jr; Desloratadine Study Group. Efficacy and safety of desloratadine in the treatment of perennial allergic rhinitis. J Allergy Clin Immunol 2003;111:617–22.
40. Graif Y, Goldberg A, Tamir R, Vigiser D, Melamed S. Skin test results and self-reported symptom severity in allergic rhinitis: the role of psychological factors. Clin Exp Allergy 2006;36:1532–7.

Please cite this article as: Uçal YO, Tansuker HD, Bakım B, Yıldırım Ö, Sözen E, Uslu Coşkun B. Psychiatric analysis of treatment-resistant allergic rhinitis and evaluation of the effects of antidepressant use . ENT Updates 2017;7(1):9–16.

Clinical Research

ENT Updates 2017;7(1):17–21
doi:10.2399/jmu.2017001009

ENT updates
www.entupdates.org

Effect of p16 positivity in oral cavity and oropharyngeal squamous cell carcinoma

Hale Aslan[1], Yılmaz Özkul[2], Ercan Pınar[1], Elif Işık[2], İbrahim Aladağ[1], Abdülkadir İmre[2], Murat Songu[2], Demet Etit[3]

[1]*Department of Otorhinolaryngology, Faculty of Medicine, Izmir Katip Çelebi University, Izmir, Turkey*
[2]*Department of Otorhinolaryngology, Izmir Katip Çelebi University Atatürk Training and Research Hospital, Izmir, Turkey*
[3]*Department of Pathology, Izmir Katip Çelebi University Atatürk Training and Research Hospital, Izmir, Turkey*

Abstract

Objective: To determine the frequency of p16 positivity in oral cavity and oropharyngeal squamous cell carcinoma (OC/OP-SCC) and to reveal whether there is a difference between p16-positive and -negative cases according to clinicopathological parameters.

Methods: p16 antibody was retrospectively analyzed immunohistochemically in biopsies of 60 patients with OC/OP-SCC operated between 2007 to 2015. Comparison was performed for age, sex, smoking habit, alcohol consumption, site of the tumor, the level of keratinization, T stage, lymphovascular invasion, perineural invasion, recurrence of the tumor, and survival.

Results: Of the 60 patients (18 females, 42 males), the median was 58 (range: 27 to 75) years. Seventeen patients were p16-positive, and 43 patients were p16-negative. Comparison of p16-positive and p16-negative groups according to age, sex, T-stage, tumor subsite, tumor profundity, lymphovascular invasion, perineural invasion and survival was not statistically significant (p>0.05). We found statistical difference between two groups according to tumor recurrence, smoking habit, and the degree of keratinization.

Conclusion: In patients who underwent surgical treatment after the diagnosis of zOC/OP-SCC, p16 positivity may have a predictive role in terms of tumor recurrence.

Keywords: p16 positivity, oral cavity cancer, oropharyngeal cancer.

Özet: Oral kavite ve orofarengeal skuamöz hücreli kanserlerinde p16 pozitifliğinin etkisi

Amaç: Çalışmanın amacı oral kavite ve orofarengeal skuamöz hücreli karsinom (OK/OF SHK) hastalarında p-16 pozitifliğinin sıklığını belirlemek ve klinikopatolojik parametreler açısından p-16 pozitif ve p-16 negatif olgular arasındaki farklılığı ortaya koymaktır.

Yöntem: 2007 ila 2015 yılları arasında ameliyat edilmiş yassı epitel hücreli 60 OK/OF SHK hastasının biyopsilerinde immünohistokimyasal yöntemle p16 antikoru analiz edilmiştir. p16 pozitif ve p16 negatif hastalar yaş, cinsiyet, sigara içimi, alkol kullanımı, tümör yeri, keratinizasyon düzeyi, T evresi, lenfovasküler invazyon, perinöral invazyon, tümör nüksü ve retrospektif olarak sağkalım açısından karşılaştırılmışlardır.

Bulgular: Altmış hastanın (18 kadın, 42 erkek) ortanca yaşı 58 (aralık: 27–75) idi. On yedi hasta p16 pozitif ve 43 hasta p16 negatif idi. Yaş, cinsiyet, T evresi, tümör yerleşimi, tümör derinliği, lenfovasküler ve perinöral invazyon, ve sağkalım açısından gruplar arasında istatistiksel olarak anlamlı bir farklılık bulunmamaktaydı (p>0.05). Tümör nüksü, sigara içimi, ve keratinizasyonun derecesi açısından iki grup arasında istatistiksel farklılık mevcuttu.

Sonuç: Oral kavite ve orofarengeal skuamöz hücreli karsinom tanısı alarak cerrahi olarak tedavi edilen hastalarda p16 pozitifliği tümör nüksü açısından prediktif bir parametredir.

Anahtar sözcükler: p16 pozitifliği, oral kavite kanseri, orofarengeal kanser.

Head and neck squamous cell carcinoma is a frequent and global problem and oropharyngeal squamous cell carcinoma comprises about half of these tumors. The main predisposing factors linked with oral cavity and oropharyngeal squamous cell carcinoma (OC/OP-SCC) are alcohol consumption, tobacco use, and human papillomavirus (HPV) infection.[1]

In relevant publications, it has been suggested that molecular biomarkers such as p16, epidermal growth factor

Correspondence: Hale Aslan, MD. Department of Otorhinolaryngology, Faculty of Medicine, Izmir Katip Çelebi University, Izmir, Turkey.
e-mail: drhaleaslan@gmail.com

Received: January 16, 2017; **Accepted:** February 5, 2017

Online available at:
www.entupdates.org
doi:10.2399/jmu.2017001009
QR code:

receptor (EGFR), B-cell lymphoma extra-large (Bcl-xL), p53, and Ki67 may have prognostic importance in OC/OP-SCC.[2]

The purpose of this study is to determine the frequency of p16 positivity in OC/OP-SCC and to investigate whether there is a difference between p16-positive and p16-negative cases with respect to prognostic factors and clinicopathologic parameters.

Materials and Methods

Study design

The study has been conducted in accordance with the principles of the Helsinki Declaration and approved by the local Institutional Review Board (05/02/2015, no:19).

A total of 60 patients with OC/OP cancer operated between 2007 to 2015 were analyzed.

p16 antibody was analyzed with immunohistochemistry. The histopathological classification and assessment of the tumors were conducted using light microscopy by one author. The patients with p16 positivity and negativity were retrospectively compared for age, sex, tobocco use, alcohol consumption, site of the tumor, the degree of keratinization, stage of the tumor, the profundity of the tumor, lymphovascular invasion, perineural invasion, tumor recurrence and survival.

Tumor tissue resected with negative margins and modified node dissection (level I–V) were performed in the patients with clinically positive for lymph node disease. Supraomohyoid node dissection (level I–III) were performed in clinically node-negative patients.

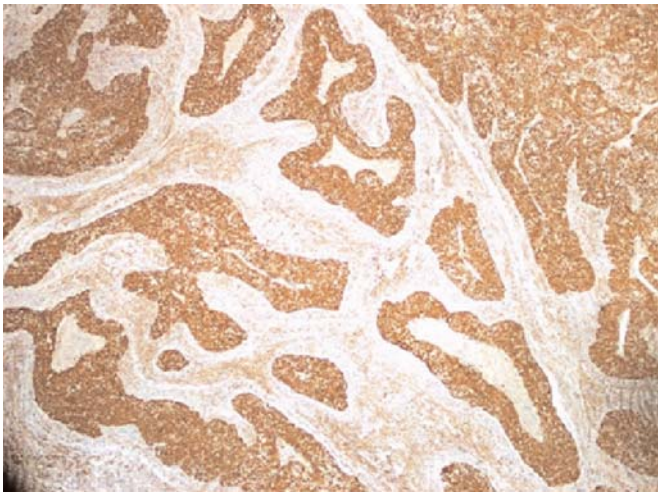


Fig. 1. Non-keratinizing squamous cell carcinoma. H&E ×10. (Keratinization in <25% tumor cells, and diffuse p16 staining).

Formalin-fixed paraffin-embedded samples were cut into 4-µm sections and stained with hematoxylin and eosin (H&E). Histological classification was made as non-keratinizing, moderate, and severely keratinizing squamous cell cancer (Figs. 1–3).

Sites of tumor were categorized as to tongue, tonsil and soft palate, the base of tongue and other regions. The

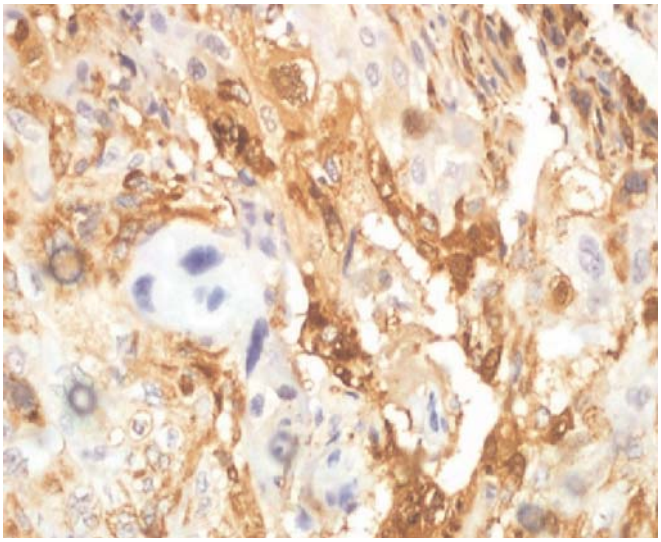


Fig. 2. Moderately keratinizing squamous cell carcinoma. H&E ×20 (Keratinization in 25–75% tumor cells, and moderate p16 staining).

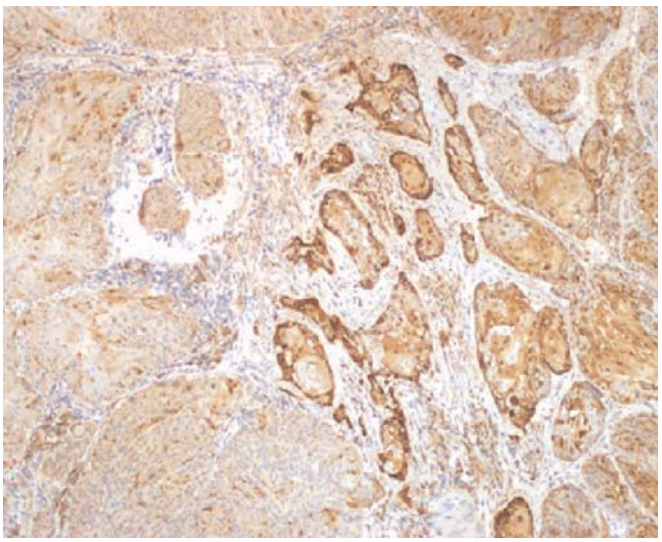


Fig. 3. Keratinizing squamous cell carcinoma. H&E x20 (Keratinization in >75% tumor cells, and weak p16 staining).

stages of tumor were T1 to T4. The profundity of tumor was classified as 0–10 mm, 10–20 mm, 20–30 mm.

Statistical analysis was carried out using Statistical Package for Social Sciences 21.0 (SPSS Inc., Chicago, IL, USA). Pearson's chi-square test was used to compare variables within groups. P<0.05 was considered significant.

Results

The median age of 60 patients (42 males, 18 females) was 58 (range: 27 to 75) years. Seventeen patients (28%) were p16-positive, while 43 patients (72%) were p16-negative.

Tumors were localized mostly in the tongue (n=23), followed by the tonsil and soft palate (n=10), base of the tongue (n=12), and other regions (n=15). At the time of admission, 38 patients were at early (T1 or T2) stage, and 22 patients were at late (T3 or T4) stage. Tumor profundity was 0–10 mm in 48 patients, 10–20 mm in 10 patients, 20–30 mm in two patients. Lymphovascular invasion was identified in 10 patients, perineural invasion in 14 patients and both in 5 patients. Median follow-up time was 24 months, and 25 (41%) patients died during follow-up.

Comparison of p16-positive and p16-negative groups according to clinicopathological parameters are presented in Table 1. Comparison of two groups according to age, sex, T-stage, tumor subsite, tumor profundity, lymphovascular invasion, perineural invasion and survival was not statistically significant (p>0.05). Among the study group, 31 (54%) patients were smokers and 11 (18%) were alcohol consumers. Four patients (23%) were smokers in p16-positive group, and 27 (62%) were smokers in p16-negative group. This result was statistically significant (p=0.03). Eleven patients showed local recurrence and all patients were in p16-negative group. This result was statistically significant (p=0.001). According to the degree of keratinization, histologic classification was non-keratinizing in 17 patients, moderately keratinizing in 17 patients, and severely keratinizing in 26 patients. In severely keratinizing group, 4 patients (23%) were p16-positive and 22 patients (41%) were p16-negative. This result was statistically significant (p=0.02). In moderately keratinizing group, eight patients (47%) were p16-positive and nine patients (20%) were p16-negative. This result was statistically significant (p=0.02).

Table 1. Comparison of p16-positive and p16-negative groups according to clinicopathological parameters.

		p16-positive group (n=17) n (%)	p16-negative group (n=43) n (%)	*p* value
Smokers (n=31)		4 (23%)	27 (62%)	0.03
Alcohol consumers (n=11)		2 (11%)	9 (20%)	-
Clinical T stage	T1-T2 (n=38)	10 (58%)	28 (65%)	>0.05
	T3-T4 (n=22)	7 (42%)	15 (35%)	>0.05
Tumor profundity	0-10 mm (n=48)	13 (76%)	35 (81%)	>0.05
	10-20mm (n=10)	4 (23%)	6 (13%)	>0.05
	20-30 mm (n=2)	0	2 (4%)	
Lymphovascular invasion		3 (17%)	7 (16%)	>0.05
Perineural invasion		5 (29%)	9 (20%)	>0.05
Site of tumor	Tongue (n=23)	7 (41%)	16 (37%)	>0.05
	Tonsil and soft palate (n=10)	4 (23%)	6 (13%)	>0.05
	Base of tongue (n=12)	4 (23%)	8 (18%)	>0.05
	Other (n=15)	2 (11%)	13 (30%)	>0.05
Keratinization	Non-keratinizing (n=17)	5 (29%)	12 (27%)	>0.05
	Moderately keratinizing (n=17)	8 (47%)	9 (20%)	0.03
	Severely keratinizing (n=26)	4 (23%)	22 (41%)	0.02
Survey (n=25)		8 (47%)	17 (39%)	>0.05
Recurrence	Local (n=11)	0	11 (25%)	
	Regional (n=8)	3 (17%)	5 (11%)	>0.05

Discussion

The human p16 protein, which is composed of 156 amino acids, was initially discovered in an in-vitro system to detect proteins that interact with human cyclin-dependent kinase 4.[3] The tumor suppressor function of p16 is associated with its capability to inhibit the catalytic activity of the cyclin-dependent kinase 4–6/cyclin D complex which is required for phosphorylation of retinoblastoma protein.[4]

In head and neck squamous cell carcinomas, three major mechanisms responsible for inactivation of p16 gene have been determined. These mechanisms are homozygous deletions, inactivation of mutation, and aberrant promoter methylation.[5] The frequency of absence of p16 protein expression in head and neck squamous cell carcinoma was found to be 74% (range: 55% to 90%) by immunohistochemical staining method.[6] In the present study, 17 patients (28%) were p16-positive, and 43 patients (72%) were p16-negative. These results are consistent with the relevant literature.

Ralli et al. reported that there was no significant difference between p16-positive and p16-negative groups according to age.[7] In the present study, we did not found any difference between groups with respect to age. Median age was 58 years in p16-negative group and 55 years in p16-positive group.

Smith et al. showed a statistically significant relationship between p16 expression, alcohol consumption, and tobacco use.[8] However, similar to our data, Lazarus et al. reported that there was no statistically significant association between p16 expression and tobacco use.[9] We found that four patients (23%) were smokers in p16-positive group, 27 patients (62%) were smokers in p16-negative group in our study. We did not compare two groups for alcohol consumption as the number of patients in groups was low for statistical comparison.

The most common tumor site was oropharynx in 63 cases (84%), especially from tonsils and base of the tongue. The highest incidence of p16 positivity was observed in tonsil tumors. However, no remarkable relationship was noted between p16-positivity and tumor site.[8] The most favorite site of the tumor was tongue in 23 patients in our study. There was no significant difference between 2 groups in terms of tumor site.

Ralli et al. reported that p16 over expression was more likely to occur in patients with higher histopathological grades.[7] The present study showed that non-keratinizing squamous cell carcinoma (NKSCC) is more likely to be in p16-positive group and these results are similar with the literature. Recent publications have demonstrated that HPV-positive oropharyngeal cancers occur at late stages (involvement of regional lymph nodes and distant metastasis) than HPV-negative cancers.[10] In the present study, contrary to the literature, we did not find any difference between p16-positive and p16-negative groups for tumor stage (early vs. late). In p16-positive group, 10 patients (58%) were at early stage (T1 and T2) and 7 patients (42%) were at late stage (T3 and T4); while in p16-negative group, 28 patients (65%) were at early stage and 15 patients (35%) were at late stage at the time of diagnosis.

Iyer et al. reported similar incidences for positivity of margins, lymphovascular invasion, and extracapsular spread in patients positive or negative for HPV.[11] In the current study, we found that lymphovascular invasion was present in 10 patients, perineural invasion was present in 14 patients, and both were present in five patients. We did not find any difference between two groups.

Advanced OPSCC patients with a solitary HPV-16 infection were 3 times more likely to develop distant metastases and were 2-3 times more likely to die earlier compared with HPV-negative patients.[12] In the present study, all patients with local recurrence were in p16-negative group. HPV-positive OC/OP cancers seem to be more sensitive to chemo-radiotherapy than HPV-negative tumors. This phenomenon is thought to result in improvement of progression-free and overall survival rates.[13] In contrast with the literature, our results on survival rate were not significant between p16-positive and p16-negative groups.

Conclusion

Our results indicated that p16 positivity was associated with tumor recurrence for patients with OC/OP-SCC and this finding supports the predictive role of p16 positivity, particularly in surgically treated patients.

Conflict of Interest: No conflicts declared.

References

1. Chandarana S, Lee J, Chanowski E, et al. Prevalence and predictive role of p16 and epidermal growth factor receptor in surgically treated oropharyngeal and oral cavity cancer. Head Neck 2013; 35:1083–90.
2. Lewis J, Thorstad W, Chernock R, Haughey B, Yip J, Zhang Q, et al. p16 positive oropharyngeal squamous cell carcinoma:an entity with a favorable prognosis regardless of tumor HPV status. Am J Surg Pathol 2010;34:1088–96.

3. Frisch M, Hjalgrim H, Jaeger AB, Biggar RJ. Changing patterns of tonsillar squamous cell carcinoma in the United States. Cancer Causes Control 2000;11:489–95.
4. Serrano M, Hannon GJ, Beach D. A new regulatory motif in cell-cycle control causing specific inhibition of cyclin D/CDK4. Nature 1993;366:704–7.
5. Rocco JW, Sidransky D. p16 (MTS-1/CDKN2/INK4a) in cancer progression. Exp Cell Res 2001;264:42–55.
6. Reed AL, Califano J, Cairns P, Westra WH, Jones RM, Koch W, et al. High frequency of p16 (CDKN2/MTS-1/INK4A) inactivation in head and neck squamous cell carcinoma. Cancer Res 1996;56:3630–3.
7. Ralli M, Singh S, Yadav S, Sharma N, Verma R, Sen R. Assessment and clinicopathological correlation of p16 expression in head and neck squamous cell carcinoma. J Cancer Res Ther 2016;12:232–7.
8. Smith EM, Rubenstein LM, Hoffman H, Haugen TH, Turek LP. Human papillomavirus, p16 and p53 expression associated with survival of head and neck cancer. Infect Agent Cancer 2010; 5:4.
9. Lazarus P, Sheikh SN, Ren Q, Schantz SP, Sten JC, Richie JP, et al. p53, but not p16 mutations in oral squamous cell carcinomas are associated with specific CYP1A1, and GSTM1 polymorphic genotypes and patient tobacco use. Carcinogenesis 1998;19:509–14.
10. Pintos J, Black MJ, Sadeghi N, Ghadirian P, Zeitoini AG, Viscidi RP et al. Human papillomavirus infection and oral cancer: a case control study in Montreal, Canada. Oral Oncol 2008;44:242–50.
11. Iyer N, Dogan S, Palmer F, Rahmati R, Nixon I, Lee N, et al. Detailed analysis of clinicopathologic factors demonstrate distinct difference in outcome and prognostic factors between surgically treated HPV-positive and negative oropharyngeal cancer. Ann Surg Oncol 2015;22:4411–21.
12. Lee LA, Huang C, Liao C, Lee LY, Hsueh C, Chen TC, et al. Human papillomavirus-16 infection in advanced oral cavity cancer patients is related to an increased risk of distant metastases and poor survival. Plos One 2012;7:1–11.
13. Chaturvedi AK, Engels EA, Anderson WF, Gillison ML. Incidence trends for human papillomavirus-related and -unrelated oral squamous cell carcinomas in the United States. J Clin Oncol 2008;26:612–9.

Please cite this article as: Aslan H, Özkul Y, Pınar E, Işık E, Aladağ İ, İmre A, Songu M, Etit D. Effect of p16 positivity in oral cavity and oropharyngeal squamous cell carcinoma. ENT Updates 2017;7(1):17–21.

ENT updates
www.entupdates.org

Clinical Research

ENT Updates 2017;7(1):22–27
doi:10.2399/jmu.2017001004

Speech and language delay in childhood: a retrospective chart review*

Ahmet Yasin[1], Hatice Aksu[1], Erdoğan Özgür[2], Börte Gürbüz Özgür[1]

[1]*Department of Child and Adolescent Psychiatry, Faculty of Medicine, Adnan Menderes University, Aydın, Turkey*
[2]*Otorhinolaryngology Clinic, Bigadiç State Hospital, Balıkesir, Turkey*

Abstract

Objective: Speech delay should be considered in a child in case of not demonstrating the stages of language development in accordance with general developmental period or compared to the peers. Speech delay often may be a sign of a variety of mental and somatic diseases rather than a diagnosis. In this study, we aimed to investigate the demographic characteristics, psychiatric diagnoses and factors that play a role in speech delay in patients admitted to a child psychiatry outpatient clinic with a complaint of speech delay.

Methods: Medical records of the patients who were admitted to the child and adolescent psychiatry outpatient clinic with complaints of "not talking", "speech delay", "language delay", "not forming a sentence" between November 1, 2014 and October 31, 2015 were retrospectively evaluated.

Results: Of a total of 127 cases, 22.8% were female and 77.2% were male. The mean age was determined as 3.1±1.1. Average duration of TV, tablet and smart phone exposure was 5.3±3.4 hours per day. Only 14.1% of cases were going to preschool education, primary school or special education. It was found that 38.2% were not presence in an environment where allows peer relationship; bilingualism history was present in 3.1%; 23.6% had a family history of speech delay, and 21.6% of cases had no meaningful words. Developmental language delay (28.18%) as a clinical finding and pervasive developmental disorders (PDD) as a psychiatric disorder (23.64%) were the most frequent diagnoses. There were no statistically significant differences between PDD and other patients when compared in terms of TV and other virtual media exposure duration [t(55)=1.58, p=0.12].

Conclusion: Different diagnoses lie under the complaint of speech delay. We emphasize that it is important to evaluate these patients multidisciplinary and refer to child and adolescent mental health experts for detection of probable psychopathology and establishing the appropriate treatment plan at an early stage.

Keywords: Child development disorders, pervasive, language development disorders, child psychiatry, mental disorders diagnosed in childhood, television.

Özet: Çocukluk çağında konuşma ve dil gecikmesi: Geriye dönük dosya taraması

Amaç: Çocuğun gelişim dönemine paralel bir şekilde dil gelişim safhalarını göstermemesi ya da konuşmasının yaşıtlarına göre geride kalması durumunda konuşma gecikmesi düşünülmelidir. Konuşma gecikmesi bir tanıdan ziyade sıklıkla çeşitli mental ve somatik hastalıkların bir belirtisi olabilir. Bu çalışmada konuşma gecikmesi şikayeti ile çocuk psikiyatrisi polikliniğine başvuran olguların sosyodemografik özellikleri, psikiyatrik tanıları ve konuşma gecikmesinde rolü olan faktörlerin incelenmesi amaçlandı.

Yöntem: 1 Kasım 2014 – 31 Ekim 2015 tarihleri arasındaki bir yıllık dönemde Çocuk ve Ergen Ruh Sağlığı ve Hastalıkları Polikliniğine "konuşmama", "konuşma gecikmesi", "konuşmada gecikme", "cümle kuramama" şikayetleri ile başvuran olguların dosyası geriye dönük olarak değerlendirildi.

Bulgular: Toplam 127 olgunun %22.8'i kız, %77.2'si erkek, olguların ortalama yaşı 3.1±1.1 idi. Ortalama TV, tablet ve telefona maruziyet süresi günde 5.3±3.4 saatti. Okul öncesi eğitime, ilkokula ya da özel eğitime yalnızca %14.1 olgu gidiyordu. Yaşıt ilişkileri sağlayabileceği ortamlarda %38.2 olgunun bulunmadığı, %3.1 olguda çift dillilik olduğu, %23.6 olgunun aile öyküsünde geç konuşmanın olduğu ve %21.6'sının hiç anlamlı kelimesinin olmadığı saptandı. En sık saptanan klinik bulgunun gelişimsel konuşma gecikmesi (%28.18); en sık saptanan psikiyatrik tanının ise yaygın gelişimsel bozukluk (%23.64) olduğu tespit edildi. Yaygın gelişimsel bozukluk tanısı olan olgular ile diğer tüm olgular karşılaştırıldığında TV ve diğer görsel medya türlerine maruziyet açısından gruplar aralarında istatistiksel olarak anlamlı fark saptanmadı [t(55)= 1.58, p=0.12].

Sonuç: Konuşma gecikmesi şikayetinin altından farklı tanılar çıkabilmektedir. Bu olguların erken dönemde multidisipliner olarak değerlendirilip olası psikopatolojilerin saptanması ve uygun tedavi planının oluşturulması için çocuk ve ergen ruh sağlığı ve hastalıkları uzmanları tarafından değerlendirilmesinin önemli olacağını vurgulamaktayız.

Anahtar sözcükler: Çocuk gelişimi bozuklukları, yaygın, dil yeteneğinde gelişim kusurları, çocuk psikiyatrisi, çocukluk çağında tanısı konulan akıl hastalıkları, televizyon.

Correspondence: Erdoğan Özgür. Çavuş Gazi Bulvarı, No: 4, 10440 Bigadiç, Balıkesir, Turkey.
e-mail: drerdoganozgur@gmail.com

Received: September 11, 2016; **Accepted:** October 19, 2016

*This study was presented as an oral presentation at 26th National Child and Adolescent Mental Health Congress, April 13–16, 2016, Izmir, Turkey.

Online available at:
www.entupdates.org
doi:10.2399/jmu.2017001004
QR code:

deomed

Speech is a valid conventional communication method, an action in which language is expressed with verbal symbols of the language.[1] In parallel with the developmental stage of the child, when he/she is unable to demonstrate phases of language development when compared with his/her peers we speak of speech delay. Detailed evaluation should be performed if the baby (a) does not babble till the first 12 months after birth, (b) does not understand simple directions till 18 months of his/her life; (c) does not speak up to 2 years after birth; (d) does not construct sentences till 3 years of age, and (e) feels very hard to narrate simple stories at 4–5 years of age.[2]

Speech delay can frequently be a manifestation of mental and somatic diseases rather than a diagnosis. In children, it is difficult to estimate the exact prevalence of speech delay because of methodologic differences. In investigations performed in preschool children, speech disorders have been reported at an incidence of 3–15 percent.[3–6] In an incidence study performed in the United States of America, speech delay among children aged six years was indicated at 3.8%, being 1.5-fold more frequently observed in male children. However, comorbidities as speech disorder and speech delay were reported in 1.3% of children.[7] In the literature, mental retardation, hearing loss, language development delay, verbal incoherency, autism spectrum disorder (OSD), bilingualism, and deficiency of psychosocial stimuli have frequently been held responsible for speech delay.[2] Harrison et al. indicated that risk factors for speech and language disorder among children aged between four and five years include male gender, hearing loss, and having a more reactive mood. On the other hand, stubborn and assertive mood and good nature of the mother were reported as protective factors.[8] A study which investigated the impact of exposures to virtual technologies (television, computer, tablet, smart phone, etc.) on speech, and communication skills during early childhood revealed the presence of a correlation between speech delay and watching TV for more than two hours in children aged one to three years.[9]

In the present study, we investigated the psychiatric diagnosis associated with complaints of speech delay in children and potential etiologies involved.

Materials and Methods

Approval of the Adnan Menderes University Ethics Committee of Non-invasive Interventions was obtained for the study (2016/828). Hundred and twenty-seven children who were referred to the Department of Mental Health and Diseases of Children and Adolescents during the time interval between November 1, 2014 and October 31, 2015 with the complaints of "inability to talk", "speech delay", inability to form sentences" were retrospectively evaluated. During evaluation process of the children, consultation from a pediatric neurologist, ENT specialist, and head and neck surgery was requested when other routine possible causes of speech delay, and phonologic disorder were suspected (hearing loss, lingual frenulum, cerebral palsy, genetic diseases etc.). Psychiatric diagnoses were made based on the diagnostic criteria of DSM-IV-TR (Diagnostic and Statistical Manual of Mental Disorders, 4th ed.).[10] Sociodemographic data of the cases, factors affecting speech delay, and distribution of psychiatric diagnoses were analyzed. Variables investigated included mean daily exposures to television, tablet, computer and smartphone, spending time with peers, attendance to preschool education, bilingualism, and the number of siblings at home.

Statistical analysis

SPSS 17.00 software package for Windows (SPSS Inc., Chicago, IL, USA) was used for the analysis of data.[11] Descriptive data were expressed as mean, standard deviation, and percentage (%). Fitness for normal distribution was evaluated using Kolmogorov-Smirnov test. Student t test was used as a parametric test. For the comparison of categorical variables chi-square test was used.

Results

Hundred and twenty-seven cases (female: n=29, 22.8%, and male: n=98, 77.2%) were enrolled in the study. The mean age of the cases was 3.1±1.1 (range: 1 to 7) years. Mean ages of the girls and boys were 3.2±1.1 and 3.1±1.1 years, respectively. Mean age of girls and boys did not differ [t(125)=0.40, p=0.68]. The patients had an average of 1.1±0.9 siblings. Mean ages of the mothers and fathers were 30.6±5.3 and 35.4±5.7 years, respectively. Analysis of sociodemographic characteristics of the parents demonstrated that mothers were primary school (31.7%), secondary school (17.5%), high school (24.6%), and university (17.5%) graduates. However, fathers were primary school (34.7%), secondary school (15.3%), high school (27.4%), and university (21%) graduates. Most (80.3%) of the mothers were jobless/housewives, while 91.3% of fathers had a job. Parents of some (14.3%) patients' were consanguineously married.

Mean daily exposure time to TV, tablet and phone which might be related to speech delay was estimated as

5.3±3.4 hours. Only 14.1% of the cases had received preschool, primary or private education. Based on the data obtained, 23.6% of the cases with speech delay had a family history of speech delay, besides it was learned that 38.2% of the children had not engaged in activities where they could develop a relationship with their peers. Bilingualism was detected in 3.1% of the cases.

It has been found that 21.6% of all cases (mean age 34.8±12 months) with speech delay could utter only meaningless words, and diagnosis of pervasive developmental disorder (PDD) was established in 40.7% of the cases. The etiology of speech delay was still being evaluated in 31.5% (n=17) of the cases. Distribution of psychiatric diagnoses of 110 patients whose evaluation process was completed as follows: PDD, 23.64%; phonologic disorder, 10%, mental retardation, 5.5%, and normal psychomotor development, 9.1% (Fig. 1). In addition, as clinical findings, developmental speech delay was found in 28.18% of the cases and deficient stimuli in 16.36% of the cases. A statistically significant difference was not detected between male and female patients (p>0.05, chi-square test) (Fig. 2). A statistically significant intergroup difference was not detected between cases with pervasive developmental disorder and all other cases as for television exposure [t(55)=1.58, p=0.12].

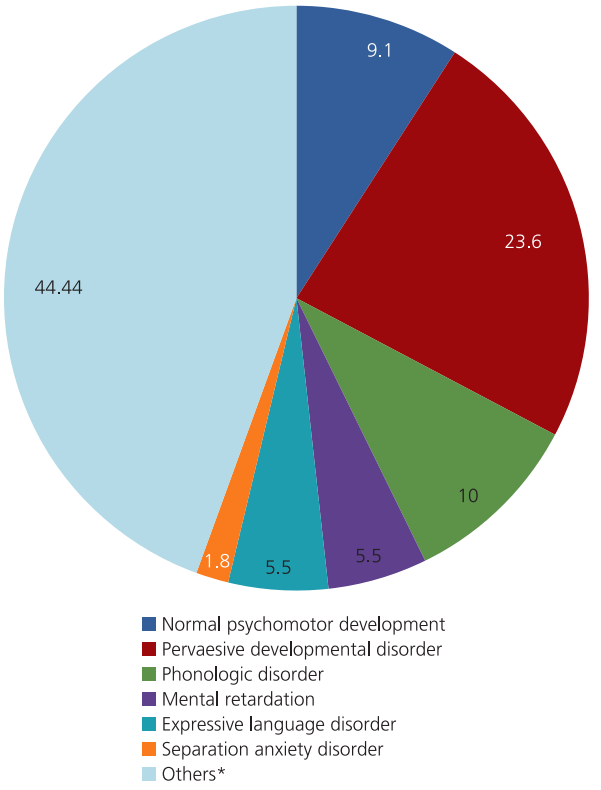


Fig. 1. Distribution of psychiatric diagnoses of the cases (%). *Language development delay, lack of stimuli.

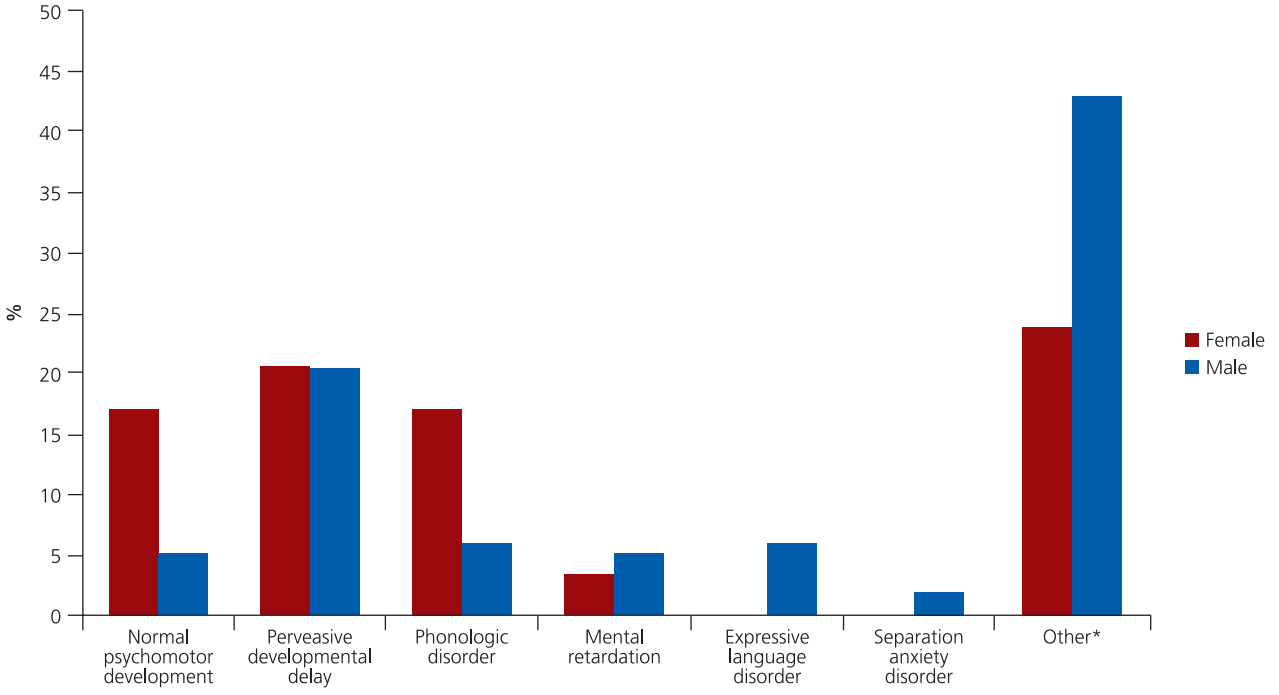


Fig. 2. Distortion of cases according to their diagnoses. *Developmental speech delay, lack of stimuli.

Discussion

It has been known that mental diseases seen during childhood are more frequently observed in male children.[12] Uçar et al. reported that 70.7% of the cases who presented with a complaint of speech delay constituted of male children.[13] Similarly, as reported in another study, most of the cases presented to the outpatient clinics with complaints of speech delay comprised of male patients.[14] Also in our study, 77.2 % of the patients who presented with a complaint of speech delay consisted of male, and 22.8% of them comprised of female patients. Since general opinions and beliefs which can be stated as "he/she speaks anyhow", "his/her father/uncle also had a speech delay" still prevail in our country, parents may seek medical help at a later stage when compared to developed countries. Thoughts favoring spontaneous resolution of speech delay may decrease the favorable effects of early treatment, and prolong the duration of treatment whereas mean ages of male, and female children at admission were comparable in our study.

In a study, 5-year-old children were followed up for 6 months without treatment, and 6 months later speech delay was still maintained in 54% of the cases,[15] while in another study speech disorder was found to remain in 22% of the cases at the end of 5 years of follow-up without treatment.[16] These outcomes may be considered as absolute indications of intervention. Besides in cases with observed speech delay, the risk of encountering speech disorders during school age also increases.[17,18] When cases presenting with speech, and language development delay were followed up for longer periods, and compared with their peers without speech and language development delay, the achievements of the first group were inferior to the healthy group as for vocabulary and forming grammatically correct sentences.[19,20] Speech delay encountered during early childhood may manifest at low levels of academic performance later on.[21] Literature information indicates that treatment of speech delay at an early stage and raising awareness of early referral are important for preventive mental health in the long-term.

Literature offers evidence indicating virtual exposure as one of the causative factors playing a role delay in stages of language and speech development. It has been reported that speech delay is more frequently encountered in children grown up by passing time with electronic media such as watching television, chatting on the phone, surfing on tablet, and internet because of limited time span they spent for interactive communication with their peers and families.[22] American Academy of Pediatrics does not recommend television watching for children younger than two years of age.[23] In a study performed by Akkuş et al. which was based on feedbacks of the parents of the children aged between 3, and 60 months, 21.2% of the children did not watch TV, while 31% and 47.7% of the children watched TV nearly 2 and more than 2 hours a day, respectively. Among children aged less than 2 years for whom television watching is more objectionable, daily television exposure time was reportedly nearly 1.05 hours, while for children aged 25–60 months it was approximately 2.9 hours. Besides, it was learned in the same study that even during play hours of more than half of the children, TVs were left open.[24] In a study performed by Öztürk et al. with families of the children aged 3–6 years, they reported more than 2 hours of television exposure in nearly half of their children.[25] In various studies performed in our country, weekly TV exposure times were indicated to range between 12.5 and 16 hours.[26–28] In a study performed abroad, similar results were reported.[29] However, in our study mean daily virtual exposure time was found as 5.3±3.4 hours. When compared with other studies, virtual exposure times were apparently 3–4-times longer in our study. Since our study did not contain a control group without speech delay, the impact of these data obtained on speech delay cannot be interpreted precisely. However, when compared with the rates reported in previous studies, detection of 3–4-fold longer exposure times is important complementary information. In addition to unfavorable effects of television, and virtual exposure, possibly children are adversely affected by TV programs and series not appropriately designed for them. It has been suggested that adverse outcomes can be encountered more frequently in line with longer periods of unfavorable virtual exposure.[30]

According to Piaget, maturation of the brain and cognitive processes are maintained in direct proportion to the individual's adaptation ability to environmental conditions.[31] When developmental stages of the children are taken into consideration, children cannot evaluate stimuli the same way as adults when they are exposed to TV or other areas of media. Since they cannot clearly differentiate fiction from fact, they are vulnerable to these adverse effects.[32] Besides, commercials and fragments passing swiftly in front of their eyes may encourage the children making rapid changes between images. Consequently, the children can not elaborate these images, and they form inaccurate, risky, and unstructured schematizations. Besides, their attention spans may not gain continuity, and their integrity may be broken in pieces. In all these times, the child will not be able to attach meaning to TV programs, and consequently, he/she cannot create something new, and surrender completely to TV programs. Therefore, the children will not

associate the things they have seen on TV with the real world, and remain in a passive mood.[33] False models, which adversely affect children who are vulnerable to these exposures, make them build their development on an unhealthy basis and constitute an open risk for a healthy adulthood in the forthcoming years.[34] Literature reviews have revealed that uncontrolled periods of TV watching in small children result in a risk for TV dependency when they reach school age. In addition, passing the stage of play which is one of the most important developmental stages of the childhood, in front of TV or using electronic instruments for longer periods of time increases the risk of encountering developmental delays in the years to come. These exposures increase the rate of observing adversities in personal and social communication-language skills.[23,26] In the light of all this information, we think that 3–4-fold longer exposure to TV, and virtual media during the preschool period is a matter of concern regarding the mental health of these cases during childhood and adolescence.

According to 2014–2015 data of The Turkish Statistical Institute, the rate of schooling in all over Turkey among children aged 3–5 years was 33%, while in Aydın province it was reported as nearly 40 percent.[35] Only 14.1% of the cases included in our study received preschool and/or private education which was nearly 3-fold below of the general statistical rates. Implementation of preschool education during early childhood is thought to exert favorable effects on the language and social development of the children. In our cases, schooling rate below our average provincial education level, limited play grounds or other recreational areas (only 38.2%) where the children can actively engage in interaction with their peers (38.2%) result in a vicious circle of virtual exposure.

Familial factors are thought to play important roles in speech delay. Tomblin et al. reported a 21% increase in the risk of the first-degree relatives.[36] Also in our study, in compliance with the literature in 23.6% of the cases presented with speech delay, relevant familial history was detected.

When literature data were reviewed, bilingualism was also found among causes of speech delay. In 3.1% of our study population, bilingualism was detected. In households where two languages are spoken simultaneously, the delay may occur in speaking two languages.[1] It has been suggested that bilingual children can use both languages effectively generally when they reach to 5 years of age.[37,38]

We could not encounter any descriptive study in the literature which analyzed distribution of psychiatric diagnoses, sociodemographic characteristics, and virtual (TV) exposure in children with speech delay in children in our country. Therefore, this study is the first of its kind. Only 23.64% of the cases included in our study were diagnosed as PDD. In a study performed by Akın Sarı, the authors indicated that 8.5% of the cases referred to the outpatient clinics of pediatric psychiatry because of speech delay was diagnosed as "not otherwise specified-Pervasive Developmental Disorder and Autism".[39] We think that higher rates in our region stemmed from the evaluation of the cases in a tertiary healthcare center. On the other hand, within the concept of Project of Early Diagnosis of Autism implemented by Ministry of Health, Directorate of Public Health in the Aydın Province, the awareness of primary care physicians has been raised about speech delay which might have an impact on families' referrals to our outpatient clinic.[40] Since only 9.1% of the patients presented with speech delay, and language development delay was detected in 28.18% of them, earlier diagnosis of underlying causes conveys importance.

Conclusion

In conclusion, different diagnoses can cause a complaint of speech delay. We emphasize that it is important to evaluate these cases by a multidisciplinary team including pediatric and adolescent psychiatrists at an early stage, so as to identify potential psychopathologies and formulate an appropriate treatment plan.

Conflict of Interest: No conflicts declared.

References

1. Çiyiltepe M, Türkbay T. Konuşmanın bileşenleri ve konuşma gecikmesi olan çocukların değerlendirilmesi: Gözden geçirme. Çocuk ve Gençlik Ruh Sağlığı Dergisi 2004;11:89–97.
2. Türkbay T. Konuşma ve dile özgü gelişimsel bozukluklar. In: Çuhadaroğlu Çetin F, Coşkun A, İşeri E, Miral S, Motavallı N, Pehlivantürk B, et al., editors. Çocuk ve ergen psikiyatrisi temel kitabı. Ankara: HYB Basım Yayın; 2008. p. 199–215.
3. Billeaud F. Communication disorders in infants and toddlers: assessment and intervention. 2 ed. Boston (MA): Butterworth-Heinemann; 1998.
4. Rescorla L, Hadicke-Wiley M, Escarce E. Epidemiological investigation of expressive language delay at age two. First Language 1993;13:5–22.
5. Silva PA, McGee R, Williams SM. Developmental language delay from three to seven years and its significance for low intelligence and reading difficulties at age seven. Dev Med Child Neurol 1983;25:783–93.
6. Wong V, Lee PW, Lieh-Mak F, et al. Language screening in preschool Chinese children. Eur J Disord Commun 1992;27:247–64.
7. Shriberg LD, Tomblin JB, McSweeny JL. Prevalence of speech delay in 6-year-old children and comorbidity with language impairment. J Speech Lang Hear Res 1999;42:1461–81.

8. Harrison LJ, McLeod S. Risk and protective factors associated with speech and language impairment in a nationally representative sample of 4- to 5-year-old children. J Speech Lang Hear Res 2010;53:508–29.
9. Byeon H, Hong S. Relationship between television viewing and language delay in toddlers: evidence from a Korea national cross-sectional survey. PLoS One 2015;10:e0120663.
10. American Psychiatric Association. Diagnostic criteria from DSM-IV-TR. Washington DC: American Psychiatric Association; 2000. p. xii, 370 p.
11. SPSS I. SPSS Statistics for Windows. Version 17.0 ed. Chicago (IL): SPSS Inc.: SPSS Inc.; 2008. Released 2008.
12. Rutter S, Bishop D, Pine D, et al. Rutter's child and adolescent psychiatry. 5 ed. Hoboken (NJ): Wiley-Blackwell; 2010.
13. Uçar H, Vural A, Kocael Ö, İH. K, Dağdelen F, Kırtıl İ. Bir çocuk ve ergen psikiyatrisi polikliniğine başvuran hastaların yakınma, tanı ve ilaç uygulamaları karakteristiklerinin değerlendirilmesi. Uludağ Üniversitesi Tıp Fakültesi Dergisi 2014;40:75–83.
14. Aras Ş, Ünlü G, Varol Taş F. Çocuk ve ergen psikiyatrisi polikliniğine başvuran hastalarda belirtiler, tanılar ve tanıya yönelik incelemeler. Klinik Psikiyatri 2007;10:28–37.
15. Renfrew CE, Geary L. Prediction of persisting speech defect. Br J Disord Commun 1973;8:37–41.
16. Bralley R, Stoudt R. A five-year longitudinal study of development of articulation proficiency in elementary school children. Language, Speech, and Hearing Services in Schools 1977;8:176– 80.
17. Catts HW, Fey ME, Tomblin JB, Zhang X. A longitudinal investigation of reading outcomes in children with language impairments. J Speech Lang Hear Res 2002;45:1142–57.
18. Tanrıdağ O. Speech and language disturbances in neurology practice. Turk Noroloji Dergisi 2009;15:155–60.
19. Rescorla L. Language and reading outcomes to age 9 in late-talking toddlers. J Speech Lang Hear Res 2002;45:360–71.
20. Rice ML, Taylor CL, Zubrick SR. Language outcomes of 7-year-old children with or without a history of late language emergence at 24 months. J Speech Lang Hear Res 2008;51:394–407.
21. McRae KM, Vickar E. Simple developmental speech delay: a follow-up study. Dev Med Child Neurol 1991;33:868–74.
22. Vandewater EA, Rideout VJ, Wartella EA, Huang X, Lee JH, Shim MS. Digital childhood: electronic media and technology use among infants, toddlers, and preschoolers. Pediatrics 2007;119:e1006–15.
23. American Academy of Pediatrics. Committee on Public E. American Academy of Pediatrics: Children, adolescents, and television. Pediatrics 2001;107:423–6.
24. Akkuş S, Yılmazer Y, Şahinöz A, Sucaklı İ. 3–60 ay arası çocukların televizyon izleme alışkanlıklarının incelenmesi. Hacettepe University Faculty of Health Sciences Journal 2015;1(Suppl 2): 351–60.
25. Öztürk C, Karayağız G. Okul öncesi dönemdeki çocukların televizyon izleme durumları ve bunu etkileyen incelemesi. Milli Eğitim Dergisi 2007;36(175):116–28.
26. Can E, Meral C, Süleymanoğlu S, et al. Bir eğitim hastanesine başvuran çocuklarda televizyon izleme sıklığının değerlendirilmesi. Çocuk Dergisi 2008;8:21–4.
27. Özakar S, Koçak C. Kitle iletişim araçlarından televizyonun 3–6 yaş grubundaki çocukların davranışları üzerine etkisi. Yeni Symposium Dergisi 2012;50:31–9.
28. Yalçın S, Tuğrul B, Naçar N, Tuncer M, Yurdakök K. Factors that affect television viewing time in preschool and primary school children. Pediatr Int 2002;44:622–7.
29. Dennison BA, Russo TJ, Burdick PA, Jenkins PL. An intervention to reduce television viewing by preschool children. Arch Pediatr Adolesc Med 2004;158:170–6.
30. Yavuzer H. Çocuk psikolojisi. 25th ed. İstanbul: Remzi Kitabevi; 2003.
31. Akçakın M, Altınoğlu Dikmeer İ. Bilişsel kuramlar: Piaget kuramına genel bakış. In: Çuhadaroğlu Çetin F, Coşkun A, İşeri E, Miral S, Motavallı N, Pehlivantürk B, et al., editors. Çocuk ve ergen psikiyatrisi temel kitabı. Ankara: HYB Basım Yayın; 2008. p. 199–215.
32. Samaniego C, Pascal A. The teaching and learning of values through television. International Review of Education 2007;53:5–21.
33. Büyükbaykal G. Televizyonun çocuklar üzerindeki etkileri. İstanbul Üniversitesi İletişim Fakültesi Dergisi 2007;28:31–44.
34. Arslan A. Bir sosyolojik olgu olarak televizyon. Uluslararası İnsan Bilimleri Dergisi 2004;1:1–17.
35. Milli Eğitim Bakanlığı. Milli eğitim istatistikleri: Örgün eğitim 2014/'15. Ankara: MEB Destek Hizmetleri Genel Müdürlüğü; 2015.
36. Tomblin B. Genetic and environmental contributions to the risk for spesific language impairment. In: Rice M, editor. Towards a genetics of language. Mahwah, NJ: Lawrence Erlbaum Associates; 1996.
37. Leung AK, Kao CP. Evaluation and management of the child with speech delay. Am Fam Physician 1999;59:3121–8, 35.
38. Redlinger WE, Park TZ. Language mixing in young bilinguals. J Child Lang 1980;7:337–52.
39. Akın Sarı B. Batman'da çocuk psikiyatrisi polikliniğine başvuran hastalarda belirti ve tanı dağılımları. Klinik Psikiyatri 2013;16:7–17.
40. Aydın Halk Sağlığı Müdürlüğü. Otizm Aile Destek ve Gebe Eğitim Destek Merkezi 2016 [Internet]. Aydın: Aydın Halk Sağlığı Müdürülüğü; [cited 2016 Jun 19]. Available from: http://aydin.hsm.saglik.gov.tr/hsm/kurumlarimiz/54/otizm-aile-destek-ve-gebe-egitim-destek-merkezi.html.

Please cite this article as: Yasin A, Aksu H, Özgür E, Gürbüz Özgür B. Speech and language delay in childhood: a retrospective chart review. ENT Updates 2017;7(1):22–27.

ENT updates
www.entupdates.org

Clinical Research

ENT Updates 2017;7(1):28–32
doi:10.2399/jmu.2017001003

Predictive role of neutrophil-lymphocyte and platelet-lymphocyte ratios in thyroid nodules with cytological diagnosis of "undetermined significance" and "suspicious for malignancy"

Ömer Bayır[1], Tuğba Karagöz[1], Bülent Öcal[1], Erman Çakal[2], Güleser Saylam[1], Mehmet Hakan Korkmaz[3]

[1]*Department of Otorhinolaryngology, Dışkapı Yıldırım Beyazıt Training and Research Hospital, Ankara, Turkey*
[2]*Department of Endocrinology & Metabolism, Dışkapı Yıldırım Beyazıt Training and Research Hospital, Ankara, Turkey*
[3]*Department of Otorhinolaryngology, Faculty of Medicine, Yıldırım Beyazıt University, Ankara, Turkey*

Abstract

Objective: To evaluate the predictive role of complete blood count (CBC) parameters in thyroid cytological diagnosis in patients with the diagnosis of undetermined significance (AUS) and suspicious for malignancy (SM) in hematological inflammatory parameters.

Methods: The preoperative CBC of 127 patients who underwent total thyroidectomy were retrospectively evaluated. While 52 patients were defined as AUS (Group 1), 75 patients were defined as SM (Group 2) in thyroid fine-needle aspiration cytology. Both groups were divided into benign and malignant sub-groups according to histopathological diagnosis of thyroidectomy specimens. In each group, the preoperative hematologic parameters (leukocyte, neutrophil, lymphocyte, platelet, neutrophil/lymphocyte ratio 'NLR', platelet/lymphocyte ratio, 'PLR') were compared with respect to malignancy, tumor size, stage and multicentericity of cancer.

Results: The statistical analysis showed that there was no significant difference in comparison of hematological parameters in benign and malignant groups.

Conclusion: Our study showed that there was no role of NLR and PLR in the cytological diagnosis of AUS and SM to predict malignancy. There was also no correlation of hematological parameters to tumor size, multicentricity, and central lymph node metastasis.

Keywords: Neutrophil-lymphocyte ratio, platelet-lymphocyte ratio, thyroid, fine-needle aspiration biopsy, undetermined significance, suspicious for malignancy.

Özet: Sitolojik tanısı "önemi belirlenememiş" ve "malignite kuşkusu" olan tiroid nodüllerinde nötrofil-lenfosit ve trombosit-lenfosit oranlarının prediktif rolü

Amaç: Önemi belirlenememiş tanısı alan ve hematolojik enflamatuar parametreleri malignite kuşkusu taşıyan tiroid hastalarının sitolojik tanısında tam kan sayımı (TKS) parametrelerinin prediktif rolünü değerlendirmek.

Yöntem: Total tiroidektomi geçirmiş 127 hastanın preoperatif TKS'leri retrospektif olarak değerlendirildi. İnce iğne aspirasyon sitolojisinde hastaların 52'si önemi belirlenememiş (ÖB, Grup 1) ve 75'i malignite kuşkusu (MK, Grup 2) olarak tanımlandı. Her iki grup, tiroidektomi numunesinin histopatolojik tanısına göre benign ve malign alt gruplara ayrıldı. Her bir grupta preoperatif hematolojik parametreler (lökosit, nötrofil, lenfosit, trombosit, nötrofil/lenfosit oranı 'NLO', trombosit /lenfosit oranı 'TLO') malignite, tümör büyüklüğü, evresi ve kanserin çok merkezli olması açısından karşılaştırıldı.

Bulgular: İstatistiksel analiz benign ve malign gruplarda hematolojik parametrelerin karşılaştırmasında önemli bir farklılık olmadığını gösterdi.

Sonuç: Çalışmamız maligniteyi öngörmede NLO ve TLO'nun sitolojik ÖB ve MK tanısında herhangi bir rolünün olmadığını göstermiştir. Hematolojik parametreler tümör büyüklüğü, çok merkezlilik ve santral lenf nodülü metastazı ile de korele değildir.

Anahtar sözcükler: Nötrofil-lenfosit oranı, trombosit-lenfosit oranı, tiroit, ince iğne aspirasyon biyopsisi, belirlenememiş önem, malignite kuşkusu.

Correspondence: Ömer Bayır. Dışkapı Yıldırım Beyazıt Eğitim ve Araştırma Hastanesi, KBB Kliniği, Şehit Ömer Halisdemir Cad., Dışkapı, Ankara, Turkey.
e-mail: bayiromer@hotmail.com

Received: July 27, 2016; **Accepted:** September 2, 2016

Online available at:
www.entupdates.org
doi:10.2399/jmu.2017001003
QR code:

deomed

Thyroid cancer is the most common malignancy of the endocrine system, and the incidence of thyroid cancer is increasing more rapidly than any other cancer.[1,2] Over the past few decades, there has been a dramatic increase worldwide in the number of people diagnosed with thyroid cancer and died of the disease.[2] This rise is attributable to the improved detection methods due to more sensitive diagnostic procedures. Most patients with thyroid cancer do not have any symptoms; typically, they present with a thyroid nodule discovered incidentally during a routine physical examination or on an imaging testing. The thyroid nodule refers to an abnormal growth of thyroid cells that forms a lump within the thyroid gland and majority of thyroid nodules are benign.[3] In the adult population, the incidence of thyroid nodules is 19–67% by high-resolution ultrasound examination. The incidence is relatively higher in women and the elderly, but just 5–15% of the nodules contain thyroid cancer.[4]

Fine-needle aspiration (FNA), as being the gold standard diagnostic method, can rule out cancer. Therefore, the use of FNA for cytopathologic evaluation helps to avoid unnecessary surgery. According to the result of FNA, 60–70% of thyroid nodules are benign, 4–10% are malignant. However, 20–30% of FNA are reported as "atypia of undetermined significance" (AUS), "suspicious for malignancy" (SM) or "nondiagnostic". For an accurate diagnosis, surgery is performed in 80% of these group of nodules and just 6–30% came out as malignant.[3] The group of FNA with the diagnosis of follicular neoplasm usually undergo a surgical procedure.

In the "suspicious" group of cytological diagnosis, further differentiating factors are needed. Various molecular markers have been examined to improve the sensitivity and specificity of FNA cytology, and some of them are being used as test panels in the clinical practice.[5,6] The neutrophil–lymphocyte ratio (NLR) and platelet-lymphocyte ratio (PLR) which are known markers of the systemic inflammatory response, have been associated with progression and survival in most cancers.[7,8] Therefore, we evaluated retrospectively the laboratory tests of our patients who underwent thyroid surgery. Preoperative complete blood counts values were used to predict malignancy rate of thyroid nodules defined as AUS or SM in FNA cytology.

Materials and Methods

The study protocol was approved by our Institutional Review Board. We performed a retrospective analysis, enrolling the preoperative documents of patients who underwent total thyroidectomy with the cytological diagnosis of AUS or SM between January 2010 and June 2014.

We evaluated preoperative hematological parameters; leukocyte, neutrophil, lymphocyte, platelet counts, and NLR and PLR values. The patients were divided into two groups; AUS patients as Group 1, SM patients as Group 2. Groups 1 and 2 were also divided into benign and malignant subgroups on postoperative pathological results. We also analyzed if the size of the tumor, multi-centricity, lymph node metastasis were correlated to NLR and PLR. Leukocytosis or thrombocytosis was not included in the analysis.

Other exclusion criteria were the presence of hematologic disorders, any kinds of infectious disease, patients with elevated thyroid antibodies or impaired thyroid function tests, recurrent disease, previous or accompanying other malignancies.

Statistical analysis

Data analysis was performed using SPSS 19.0 (SPSS Inc., Chicago, IL, USA) statistical package software. For the evaluation of study data, Pearson's chi-square, Fisher χ^2 or Yates χ^2 tests were used along with descriptive statistical methods (frequency, percentage, mean, standard deviation). The suitability of the normal distribution of the data was evaluated with Kolmogorov-Smirnov test. Independent samples t-test and one-way ANOVA were used for evaluation of quantitative data with a normal distribution. For the data that were not normally distributed Mann-Whitney U test and Kruskal-Wallis test were used. The p-value <0.05 was regarded as statistically significant.

Results

A total of 127 (F/M: 107/20) patients were enrolled in the study. The overall mean age was 47.17 years, and there was no statistical difference in mean ages of sexes. Fifty-two (F/M: 41/11) patients with the diagnosis of AUS and 75 (F/M: 66/9) patients with the diagnosis of SM were derived from the database. The postoperative histopathological examination of 60 patients was diagnosed as benign goiter, 37 patients with micropapillary carcinoma (PMTC) and 30 patients with papillary thyroid carcinoma (PTC). There was no correlation between the sex and the possibility of malignancy.

There were no statistical differences in the preoperative values of NLR and PLR in predicting malignancy (Table 1). When we analyzed the tumor size, there was no significant correlation found relevant to PMTC and PTC groups (Table 1). The data in Tables 2 and 3 show that no statistical differences were found when comparing NLR and PLR to stage, multicentricity of cancer and central lymph node metastases.

Table 1. The comparison of hematological parameters in benign and malignant groups including PMTC and PTC in all patients.

Parameters	Benign (n=60)	Malignant (n=67)	p^1	PMTC (n=19)	PTC (n=48)	p^2
Wbc	8±2.3	8±2.3	0.7	7.7±2.2	8.1±2.4	0.8
Neu	5±2.2	5±4.5	0.9	4.7±1.7	5.1±2.3	0.9
Lym	2.2±0.9	2.02±0.7	0.7	2.2±1.4	2.1±0.6	0.7
NLR	2.6±2.2	2.6±2.33	0.3	2.4±1.5	2.7±2.6	0.7
Plt	258.2±57.7	254.3±59.4	0.4	256.2±70	247.9±58.3	0.6
PLR	130.9±52.5	124.5±45.5	0.4	127.3±41.7	123.4±47.2	0.6

p^1: comparison of the hematologic parameters of benign group with malignant group' (Mann-Whitney U test), p^2: comparison of the hematologic parameters between benign, PMTC and PTC groups (Kruskal-Wallis test)

In Group 1, 52 (female/male: 41/11) patients with the diagnosis of AUS were identified from the database. The mean age was 50.5±14.4 years and there was no statistical difference in mean age between sexes. There was no significant correlation of the hematological parameters to malignancy and tumor size (Table 4). Due to the low numbers in sub-groups, it was not possible to compare NLR and PLR to stage and multicentricity of cancer.

In Group 2, we evaluated 75 (female/male: 66/9) patients with the diagnosis of SM-derived from the database. The mean age was 44.8±12.3 years, and there was no statistical difference in age between sexes. No correlation was found between sex and the possibility of malignancy. There was no statistical difference in the preoperative hematological parameters between the benign and malignant groups. According to tumor size, there was no significant difference of the hematologic parameters as well (Table 5). Stage of cancer, lymph node metastasis, and multicentricity analysis were not done due to low numbers in the sub-groups.

Table 2. Distributions of hematological parameters of malignant group by stage (Mann-Whitney test).

All groups	Stage 1 (n=53)	Stage 2–4 (n=9)	p
Wbc	7.9±2.3	8.3±2.7	0.7
Neu	5.0±2.2	5.1±2.1	0.9
Lym	2.1±0.7	2.3±0.7	0.5
NLR	2.7±2.6	2.2±1.1	0.6
Plt	250.6±60.9	248.1±67.2	0.8
PLR	127±46.3	112.5±36.5	0.3

Discussion

After an association between cancer and inflammation has been discovered, markers of the systemic inflammatory response have been used to predict relapse and survival in patients with various cancers.[9,10] Chronic irritation such as exposure to smoking and subsequent inflammation may predispose to cancer.[11] Chronic infection with hepatitis viruses causing carcinoma is a well-known fact. The inflammatory component is present in the microenvironment of tumors due to both cytokines being released from either tumor or the host immune system.[12] The resulting production of free radicals such as reactive oxygen intermediates and reactive nitrogen intermediates lead to oxidative damage and DNA mutations.[12] Cancer-related inflammation causes suppression of antitumor immunity

Table 3. Distributions of hematological parameters of malignant group by multicentricity and lymph node metastases (Mann-Whitney test).

	Unifocal disease (n=52)	Multifocal disease (n=9)	p	Lymph node metastases		
				Negative (n=12)	Positive (n=5)	p
Wbc	81±2.4	7.7±2.1	0.6	8.6±2.6	8.7±1.8	0.2
Neu	5.1±2.3	4.5±1,1	0.6	5.1±2.31	5.3±1.6	0.6
Lym	2.1±0.7	2.3 ±1.2	0.9	2.5±1	2.3±0.4	0.9
NLR	2.7±2.6	2.1±0.7	0.8	2.2±1	2.2±0.7	0.6
Plt	253.8±61.92	221.7±58.7	0.1	252±62.6	261.8±26.7	0.7
PLR	128.6±48.6	102.8±46.8	0.2	110.7±43	113.2±20.7	0.5

Table 4. The comparison of hematological parameters with respect to tumor size in Group 1.

Group 1	Benign (n=30)	Malignant (n=22)	p^1	PMTC (n=13)	PTC (n=9)	p^2
Wbc	8.3±2.8	7.5±2.3	0.3	7.6±2.6	7.4±1.9	0.9
Neu	5.4±2.8	4.8±2.5	0.4	4.9±3.0	4.6±1.5	0.6
Lym	2.1±0.9	2.0±0.6	0.7	2.1±0.7	2.0±0.4	0.8
NLR	3.1±2.8	2.9±3.6	0.8	3.4±4.6	2.2±0.6	0.5
Plt	253.7±64.5	237.3±64.4	0.3	244.5±74.9	226.8±47.6	0.9
PLR	139.3±51.1	125.4±51.2	0.3	133.6±63.1	113.6±25.4	0.7

p^1: comparison of the hematologic parameters of benign group and malignant groups' (Mann-Whitney U test), p^2: comparison of the hematologic parameters between benign, PMTC and PTC groups (Kruskal-Wallis test)

by recruiting T cells and activating chemokines, which results in tumor growth and metastasis.[13]

The mechanism of interaction between cancer and neutro¬philia and leukocytosis remains unclear; however, experimental data indicates that activated neutrophils may directly and indirectly stimulate tumor growth.[14] Also, low lymphocyte counts have been associated with generalized suppression of the immune systems of patients with cancer.[15] Impaired or ineffective innate cellular immunity against malignancy causes lymphopenia. Therefore, NLR elevation which facilitates tumor growth due to the imbalanced inflammatory state can be used as a possible indicator of underlying malignancy in benign neoplastic tumors.[15] NLR is an indicative of the balance between pro-tumoral inflammatory state and anti-tumoral immune state.

The combination of neutrophil lymphocyte ratio and platelet-lymphocyte ratio (CNP) was accounted for a predictor of postoperative survival in patients with esophageal squamous cell carcinoma, and CNP was associated with tumor length, depth of invasion and nodal metastasis.[13] In patients with nasopharyngeal carcinoma, NLR was significantly associated with overall survival and progression-free survival.[16] Hemoglobin, NLR and platelet count in patients with nasopharyngeal carcinoma are found useful to predict long-term mortality.[17] Another study suggests that high pretreatment NLR is significantly associated with poor disease-specific survival in oral cancer patients undergoing preoperative chemoradiotherapy.[18]

The results of studies suggested that high NLR was a negative indicator for breast cancer.[19] In the retrospective analysis of two hundred eighty-one colorectal cancer patients, high pre-treatment NLR was found to predict a shorter survival.[20] Higher PLR was also associated with higher mortality in breast cancer patients.[21] In another study, the preoperative value of PLR was a significant independent prognostic marker in patients with resected pancreatic adenocarcinoma.[22]

NLRs were found to be elevated in patients with PMTC and PTC in a pilot study.[13] In another study, although there was no difference in NLR between patients having benign and malignant thyroid nodules, larger tumor size had the higher NLR tertile.[23] However, in our study, the preoperative values of NLR or PLRs had no predictive role in malignancy status or size of tumors. Further studies with larger groups are needed to confirm these results.

Table 5. The comparison of hematological parameters with respect to tumor size in Group 2.

Group 2	Malign (n=45)	Benign (n=30)	p^1	PMTC (n=24)	PTC (n=21)	p^2
Wbc	8.3±2.4	7.6±2.3	0.2	8.0±2.2	8.7±2.7	0.6
Neu	5.2±2.1	4.6±1.7	0.2	4.9±1.8	5.5±2.5	0.6
Lym	2.3±0.9	2.5±0.9	0.3	2.3±1.0	2.3±0.7	0.9
NLR	2.5±1.5	2.1±1.5	0.2	2.5±1.7	2.5±1.4	0.9
Plt	256.6±59.4	262.9±50.8	0.6	261.7±67.6	253.3±50.2	0.7
PLR	124.1±43.1	122.6±53.5	0.8	130.4±48.2	118.1±37.9	0.5

p^1: comparison of the hematologic parameters of benign group to malignant group (Mann-Whitney U test), p^2: comparison of the hematologic parameters between benign, PMTC and PTC groups (Kruskal-Wallis Test)

One of our study's limitations was that we did not analyze the postoperative values of hematologic parameters and did not compare them with preoperative ones. Our aim was to explore a cost-effective preoperative test for a more accurate diagnosis of a thyroid nodule with a cytological diagnosis of AUS or SM. Thyroid cancer still has unsolved mysteries and secrets. Although FNA of a thyroid nodule is the gold standard test for the preoperative assessment, molecular markers or modern imaging techniques are needed to improve thyroid nodule diagnosis and distinguish benign from malignancy to avoid unnecessary surgery.

As a conclusion, we consider that preoperative NLRs and PLRs in AUS and SM groups can not be considered as a predictive diagnostic marker of malignancy. However, further studies with larger groups may reveal different results.

Conflict of Interest: No conflicts declared.

References

1. Hegedüs L. Thyroid size determined by ultrasound. Influence of physiological factors and non-thyroidal disease. Dan Med Bull 1990;37:249–63.
2. National Cancer Institute. A snapshot of thyroid cancer; 2015 [Internet]. Bethesda (MD): National Cancer Institute; [posted 2014 Nov 5] Available from: www.cancer.gov/researchandfunding/snapshots/thyroid.
3. Cibas ES, Ali SZ; NCI Thyroid FNA State of the Science Conference. The Bethesda System For Reporting Thyroid Cytopathology. Am J Clin Pathol 2009;132:658–65.
4. American Thyroid Association (ATA) Guidelines Taskforce on Thyroid Nodules and Differentiated Thyroid Cancer, Cooper DS, Doherty GM, Haugen BR, et al. Revised American Thyroid Association management guidelines for patients with thyroid nodules and differentiated thyroid cancer. Thyroid 2009;19:1167–214.
5. de Matos PS, Ferreira AP, de Oliveira Facuri F, Assumpcao LV, Metze K, Ward LS. Usefulness of HBME-1, cytokeratin 19 and galectin-3 immunostaining in the diagnosis of thyroid malignancy. Histopathology 2005;47:391–401.
6. Kim MI, Alexander EK. Diagnostic use of molecular markers in the evaluation of thyroid nodules. Endocr Pract 2012;18:796–802.
7. Hanahan D, Weinberg RA. The hallmarks of cancer. Cell 2000; 100:57–70.
8. Hanahan D, Weinberg RA. Hallmarks of cancer: the next generation. Cell 2011;14:646–74.
9. Mantovani A, Allavena P, Sica A, Balkwill F. Cancer-related inflammation. Nature 2008;454(7203):436–44.
10. Balkwill F, Mantovani A. Inflammation and cancer: back to Virchow? Lancet 2001;357(9255):539–45.
11. Rakoff-Nahoum S. Why cancer and inflammation? Yale J Biol Med 2006;79:123–30.
12. Chua W, Charles KA, Baracos VE, Clarke SJ. Neutrophil/lymphocyte ratio predicts chemotherapy outcomes in patients with advanced colorectal cancer. Br J Cancer 2011;104:1288–95.
13. Feng JF, Huang Y, Liu JS. Combination of neutrophil lymphocyte ratio and platelet lymphocyte ratio is a useful predictor of postoperative survival in patients with esophageal squamous cell carcinoma. Onco Targets Ther 2013;6:1605–12.
14. Mantovani A, Cassatella MA, Costantini C, Jaillon S. Neutrophils in the activation and regulation of innate and adaptive immunity. Nat Rev Immunol 2011;11:519–31.
15. Seretis C, Gourgiotis S, Gemenetzis G, Seretis F, Lagoudianakis E, Dimitrakopoulos G. The significance of neutrophil/lymphocyte ratio as a possible marker of underlying papillary microcarcinomas in thyroidal goiters: a pilot study. Am J Surg 2013;205:691–6.
16. He J-R, Shen G-P, Ren Z-F, et al. Pretreatment levels of peripheral neutrophils and lymphocytes as independent prognostic factors in patients with nasopharyngeal carcinoma. Head Neck 2012; 34:1769–76.
17. Chang H, Gao J, Xu BQ, et al. Haemoglobin, neutrophil to lymphocyte ratio and platelet count improve prognosis prediction of the TNM staging system in nasopharyngeal carcinoma: development and validation in 3,237 patients from a single institution. Clin Oncol (R Coll Radiol) 2013;25:639–46.
18. Perisanidis C, Kornek G, Pöschl PW, et al. High neutrophil-to-lymphocyte ratio is an independent marker of poor disease-specific survival in patients with oral cancer. Med Oncol 2013;30:334.
19. Chen J, Deng Q, Pan Y, et al. Prognostic value of neutrophil-to-lymphocyte ratio in breast cancer. FEBS Open Bio 2015;5:502–7.
20. Ozdemir Y, Akin ML, Sucullu I, Balta AZ, Yucel E. Pretreatment neutrophil/lymphocyte ratio as a prognostic aid in colorectal cancer. Asian Pac J Cancer Prev 2014;15:2647–50.
21. Azab B, Shah N, Radbel J, et al. Pretreatment neutrophil/lymphocyte ratio is superior to platelet/lymphocyte ratio as a predictor of long-term mortality in breast cancer patients. Med Oncol 2013;30: 432.
22. Smith RA, Bosonnet L, Raraty M, et al. Preoperative platelet-lymphocyte ratio is an independent significant prognostic marker in resected pancreatic ductal adenocarcinoma. Am J Surg 2009;197: 466–72.
23. Liu CL, Lee JJ, Liu TP, Chang YC, Hsu YC, Cheng SP. Blood neutrophil-to-lymphocyte ratio correlates with tumor size in patients with differentiated thyroid cancer. J Surg Oncol 2013;107:493–7.

Please cite this article as: Bayır Ö, Karagöz T, Öcal B, Çakal E, Saylam G, Korkmaz MH. Predictive role of neutrophil-lymphocyte and platelet-lymphocyte ratios in thyroid nodules with cytological diagnosis of "undetermined significance" and "suspicious for malignancy". ENT Updates 2017;7(1):28–32.

Clinical Research

ENT Updates 2017;7(1):33–37
doi:10.2399/jmu.2017001002

ENT updates
www.entupdates.org

Platelet distribution width (PDW) data of patients with nasal polyposis: is it important for clinical severity?

Ahmet Hamdi Kepekçi[1,2], Gökalp Dizdar[2], Ali Bestemi Kepekçi[3,4]

[1]*Department of Audiometry, Health Occupation High-School, Yeniyüzyıl University, Istanbul, Turkey*
[2]*Department of Otolaryngology, Meltem Hospital, Istanbul, Turkey*
[3]*Department of Anesthesiology, Meltem Hospital, Istanbul, Turkey*
[4]*Department of Anesthesia, Health Occupation High-School, Yeniyüzyıl University, Istanbul, Turkey*

Abstract

Objective: The purpose of the present study was to investigate whether high platelet distribution width (PDW) levels correlated with nasal polyps or not.

Methods: The study was performed retrospectively in 99 patients who underwent endoscopic sinus surgery for nasal polyposis. Data were collected from the routine preoperative hemograms of the patients. The study group was compared with an age- and sex-matched control group including 150 healthy subjects. The Mann-Whitney U test was used to compare the results of the two groups.

Results: The PDW level for the study group was 14.49±2.08, while for the control group it was 13.76±2.14. The PDW levels of the study group were higher than those of the control group, and this difference was statistically significant ($p<0.05$).

Conclusion: The rise of the PDW levels in patients with nasal polyposis should be investigated for the diagnostic value, and the rise of PDW levels in patients with nasal polyposis may be used for its diagnostic evaluation.

Keywords: Platelet distribution width, nasal polyposis, inflammation.

Özet: Nazal polipozisi olan hastaların trombosit dağılım aralığı (TDA) verileri: Klinik ciddiyet açısından önemli mi?

Amaç: Bu çalışmanın amacı yüksek trombosit dağılım aralığı (TDA) düzeylerinin nazal polipler ile korele olup olmadığını araştırmaktı.

Yöntem: Nazal polipozis için endoskopik sinüs cerrahisi geçirmiş 99 hastada retrospektif çalışma yapıldı. Hastaların rutin preoperatif hemogramlarının verileri toplandı. Çalışma grubu, yaş ve cinsiyet açısından eşleştirilmiş 150 sağlıklı kişiden oluşan kontrol grubu ile karşılaştırıldı. İki grubun sonuçlarını karşılaştırmak için Mann-Whitney U testi kullanıldı.

Bulgular: Çalışma ve kontrol gruplarının TDA düzeyleri sırasıyla 14.49±2.08 ve 13.76±2.14 idi. Çalışma grubunun TDA düzeyleri kontrol grubundan daha yüksek olup bu farklılık istatistiksel açıdan anlamlı idi ($p<0.05$).

Sonuç: Nazal polipozisi olan hastalarda TDA düzeylerinde yükselme tanısal değer açısından araştırılmalıdır ve nazal polipozisi olan hastalarda TDA'daki yükselme tanısal değerlendirme için kullanılabilir.

Anahtar sözcükler: Trombosit dağılım aralığı, nazal polipozis, enflamasyon.

Nasal polyposis is a result of inflammation, but its pathogenesis is not completely understood. Nasal polyposis is not a unique disease that appears by a single stimuli.[1] It is estimated that symptomatic nasal polyposis is seen in 1–2% of Europe's population.[2] Nasal polyps were seen in 3.6% of patients with chronic rhinitis and in 4.8% of patients with asthma.[3] Nasal polyps occurred much more frequently in patients with chronic rhinitis or pansinusitis. Asthma incidence is also high in patients with nasal polyposis. Almost 20–50% of patients with nasal polyposis suffers from bronchial asthma and 20–40% of patients with bronchial asthma develops nasal polyps.[4] Mucosal edema is the primary pathology in the formation of nasal polyps. Nasal polyps are found in 1–4% of the population. They

Correspondence: Ahmet Hamdi Kepekçi. Meltem Hospital, Haznedar Mah., Ergene Sokağı No: 52, Güngören, Istanbul, Turkey.
e-mail: ahmethamdi.kepekci@yeniyuzyil.edu.tr

Received: November 23, 2016; **Accepted:** December 28, 2016

Online available at:
www.entupdates.org
doi:10.2399/jmu.2017001002
QR code:

deomed

are more frequently seen in patients with asthma, aspirin hypersensitivity, and cystic fibrosis.[5] Nasal congestion, nasal flow, impaired sense of smell, and sneezing are the main complaints of patients. Endoscopic examination and computed tomography are used in the diagnosis of nasal polyps.[6]

Inflammation has an important role in the formation of nasal polyps. Studies performed in patients with nasal polyps found high levels of interleukin-2, -4, -5, -8, -10, -12, interferon-gamma, tumor necrosis factor-alpha, and -beta in the nasal secretions.[7] Activated eosinophils are involved in the formation of nasal polyps.[8] It was also determined that in nasal polyp tissue, eosinophils survive longer than normal tissue.[9,10] It is known that platelets play a key role in tissue repair and hemostasis.

In studies performed recently, platelets had determinant functions in the inflammation process. A study performed on lungs of allergen-sensitized mice showed that platelets play a part in the collection of eosinophils and have a role in inflammation development.[11] Furthermore, increased CD40L expression was shown in the activated platelets and CD40L had a role in platelet activation and directly stimulated endothelium inflammation.[12] After understanding the role of platelets in inflammatory processes, studies investigating the parameters that show platelet activation in certain diseases have increased. In most of these studies, the number of platelets in patients is significantly different from those in controls regarding mean platelet volume (MPV) and platelet distribution width (PDW) levels. PDW is a parameter that indicates the platelet activity and is included in routine hematological tests. The increase in the level of PDW means an increase in circulating platelets of different sizes, which indicates oscillation of young and more portly inflammatory and metabolically more active platelets from the marrow to the blood. On the other hand, a low PDW level means platelets in circulation have sizes closer to each other, indicating that they are metabolically and inflammatory less active and older platelets.[11] PDW gives information about the inflammatory processes of some diseases.[13,14]

In the present study, we examined the relation between nasal polyps and PDW retrospectively in 99 patients who underwent endoscopic sinus surgery for nasal polyposis. The measurement of PDW is very easy and practical for several minutes with the result of CBC parameters of the autoanalyzer. Thus, the rise of platelet PDW levels in patients with nasal polyposis may be used for its diagnostic evaluation.

Materials and Methods

Our study was conducted between December 2009 and March 2015 with 99 patients who applied to the ENT outpatient clinic because of nasal polyposis and who underwent endoscopic sinus surgery the results of the patient group were compared with those of a control group (150) that was similar in age, sex, and the number of patients. Hemogram (CBC) results from the autoanalyzer (ABX Micros; HORIBA Ltd., Kyoto, Japan) were investigated, retrospectively. Patient files were analyzed from the archives of the hospital computer automation program and data on white blood cell (WBC) count, red blood cell (RBC) count, hemoglobin (Hb), hematocrit (Hct), platelets (PLT), MPV and PDW were obtained and compared with those of the control group. Approval for the study was granted by the hospital ethics committee (no. 21.03.2016/20). Patients with chronic inflammatory diseases, acute infection, and diabetes mellitus patients with hypertension history were excluded from the study.

Data were analyzed using SPSS for Windows (Version 21.0; SPSS Inc., Chicago, IL, USA). In this study, nonparametric statistical tests were preferred because of abnormal distribution. Chi-square test was used for comparison of categorical variables. For quantitative variables, the Mann-Whitney U and Spearman correlation tests were used. $p<0.05$ was considered significant.

Results

There were 99 patients in the study group, and 64 of them (64.6%) were male and 35 (35.4%) were female. The youngest patient was 20 years old and the oldest wad 86 years old. The mean age of the study group was 44.41±13.74 years, where it was 45.87±14.49 years for male patients and 41.74±11.98 years for female patients.

The control group consisted of 150 subjects, and 81 of them (54%) were male and 69 (46%) of them were female. The mean age of male subjects in the control group was 41.81±14.01 years, and the mean age of female subjects in the control group was 42.34±17.34 years.

Age and sex ratios were not significantly different between the study group and the control group ($p>0.005$); and WBC, RBC, Hb, Hct, PLT, and MPV levels were not significantly different either ($p>0.005$). The PDW level for the study group was 14.35±2.04, while it was 13.73±2.01 for the control group. This difference was significant ($p<0.05$; Table 1)

According to the correlation test in the study group, we found a weak, positive, directional, and meaningful relationship (r=3) between PDW and MPV variables and this means that the high PDW level patients also have high MPV levels ($p<0.05$; Fig. 1).

The mean PDW level of the 99 patients in the study group was 14.49, and the mean PDW level of the 150 patients in the control group was 13.76.

Discussion

This study was the first of its kind in the literature conducted in patients with nasal polyposis. We compared the venous blood PDW levels of patients with nasal polyposis and those of normal individuals. We found that the mean PDW values of the study group were significantly higher than the control group.

The pathophysiology of nasal polyps is not fully understood, but it is believed that it is a multifactorial disease.[15] Moreover, on the nasal polyp tissue, several inflammatory molecules are shown. Many studies in the literature report that the inflammation occurring in the nasal polyp tissue depends on eosinophils and inflammatory products.[16] Among these, PDW and MPV are more reliable because they are not affected by some medications and pathological situations in the period between drawing the blood sample and investigating it. However, some new parameters, like PDW for example, have rarely been investigated, while MPV is frequently studied.[17,18] MPV and PDW are the parameters used for platelet size and the degree of differences in the size of platelets.[19] Our studies showed that there is a rise in biochemical mediators and free radicals in patients who have nasal polyps. In several studies, it was shown that the biochemical mediators and free radicals increased in patients with nasal polyposis.[20–22]

In recent studies, PDW has been found to be associated with several clinical conditions. In a study by Celikbilek et al., the platelet count, MPV, and PDW levels of 45 patients with benign paroxysmal positional vertigo (BPPV) were compared with a control group and all parameters were found statistically high in the BPPV group ($p<0.05$).[23]

In a study by Mirkavili et al., the PDW levels of 108 patients with sudden sensorineural hearing loss were investigated in a case-controlled prospective study and compared with a healthy control group; no statistically significant difference was found between the patient group and the control group, but a relationship between the rise in PDW levels and the severity of hearing loss was established.[24] In a study by Kurt et al., 98 OSAS patients were divided into 4 groups from mild to severe according to their apnea/hypopnea index; the PDW levels of the severe OSAS patients were found statistically higher than those of the other three groups, and it was thought that PDW could be an indicator of the severity of the disease.[25]

Jindal et al. designed a study of 75 diabetic patients, 50 of which had one or more than one microvascular complications; this study group was compared with a control group including 50 sex- and age-matched healthy individuals and the PDW levels were different from the control group. In the diabetic group, the PDW levels were higher in patients with microvascular complications.[26]

Table 1. Study parameters in patients with nasal polyposis.

	Study group (n=99) mean	Control group (n= 150) mean	p value*
Age (years)	44.41±13.74	42.06±15.58	0.077
Sex, F/M, n (%)	35 (35.4%) / 64 (64.6%)	69 (46.0%) / 81(54.0%)	0.096
WBC (/µL)	8.46±4.52	7.60±2.27	0.081
RBC (10^6/µL)	4.85±0.63	4.78±0.52	0.157
Hb (g/dL)	13.33±1.92	13.09±2.03	0.272
Hct (%)	41.25±5.62	40.95±4.91	0.383
PLT (K/mm^3)	242.95±54.86	238.14±64.99	0.295
MPV (fL)	8.03±0.68	8.10±1.05	0.903
PDW (fL)	14.49±2.08	13.76±2.14	0.022

COME: chronic otitis media with effusion; **F:** female; **Hb:** hemoglobin; **Hct:** hematocrit; **M:** male; **MPV:** mean platelet volume; **PLT:** platelets; **PDW:** platelet distribution width; **RBC:** red blood cell count; **WBC:** white blood cell count. ±: Standard deviation. *Statistical analysis was performed with the Mann-Whitney U test.

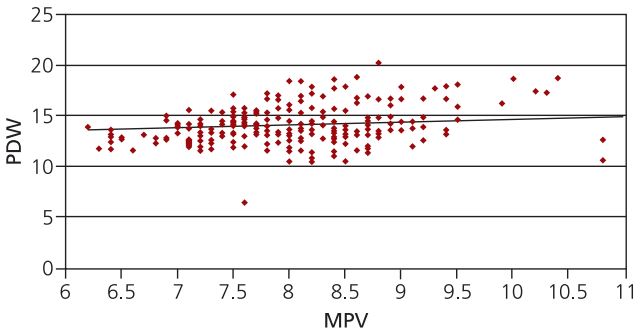


Fig. 1. The correlation between the MPV and PDW variables in the study group.

In a study by Topal et al.[27] conducted on 128 preschool patients with allergic eczema, their PDW levels were lower than those in the control group, but the MPV levels were higher. In a study by Chandrashekar et al.[28] carried out with 45 patients with chronic urticaria, both the MPV and PDW levels were significantly higher in the study group than they were in the control group and there was a correlation between the increase in disease severity and the increase in MPV and PDW levels. Patients with high PDW value in our study group also had high MPV values ($p<0.05$). The results of these studies are in agreement with our results.

Conclusions

The contribution of mediators released from the platelets to allergic inflammations is well known. In our study, the PDW as a parameter which indicates an increase in the number of metabolic and inflammatory active young platelets in circulation was significantly higher in patients with nasal polyps than in the control group. The measurement of PDW is very easy and practical for several minutes in CBC parameters of auto analyzer result. Thus, the rise of platelet PDW levels in patients with nasal polyposis may be used for its diagnostic value, and additional controlled studies are required to explain the role of PDW in the severity of nasal polyposis.

Conflict of Interest: No conflicts declared.

References

1. Mackay IS. Rhinitis: mechanisms and management. London: Royal Society of Medicine Services; 1989.
2. Hosemann W, Göde U, Wagner W. Epidemiology, pathophysiology of nasal polyposis, and spectrum of endonasal sinus surgery. Am J Otolaryngol 1994;15:85–98.
3. Grigoreas C, Vourdas D, Petalas K, Simeonidis G, Demeroutis I, Tsioulos T. Nasal polyps in patients with rhinitis and asthma. Allergy Asthma Proc 2002;23:169–74.
4. Arnold GDM, Lund VJ. Clinical rhinology. New York, NY: Thieme; 1990.
5. Settipane RA, Peters AT, Chiu AG. Chapter 6: Nasal polyps. Am J Rhinol Allergy 2013;27 Suppl 1:S20–5.
6. Newton JR, Ah-See KW. A review of nasal polyposis. Ther Clin Risk Manag 2008;4:507–12.
7. Peric A, Vojvodic D, Peric AV, Radulovic V, Miljanovic O. Correlation between cytokine levels in nasal fluid and scored clinical parameters in patients with nasal polyposis. Indian J Otolaryngol Head Neck Surg 2013;65(Suppl 2):295–300.
8. Bachert C, Geveart P. Effect of intranasal corticosteroids on release of cytokines and inflammatory mediators. Allergy 1999;54 Suppl 57:116–23.
9. Bachert C, Wagenmann M, Hauser U, Rudack C. IL-5 synthesis is upregulated in human nasal polyp tissue. J Allergy Clin Immunol 1997;99(6 Pt 1):837–42.
10. Simon HU, Yousefi S, Schranz C, Schapowal A, Bachert C, Blaser K. Direct demonstration of delayed eosinophil apoptosis as a mechanism causing tissue eosinophilia. J Immunol 1997;158: 3902–8.
11. Vagdatli E, Gounari E, Lazaridou E, Katsibourlia E, Tsikopoulou F, Labrianou I. Platelet distribution width: a simple, practical and specific marker of activation of coagulation. Hippokratia 2010;14:28–32.
12. Henn V, Slupsky JR, Grafe M, et al. CD40 ligand on activated platelets triggers an inflammatory reaction of endothelial cells. Nature 1998;391(6667):591–4.
13. Farias MG, Schunck EG, Dal Bó S, de Castro SM. Definition of reference ranges for the platelet distribution width (PDW): a local need. Clin Chem Lab Med 2010;48:255–7.
14. Yilmaz H, Yilmaz G, Menteşe A, Kostakoğlu U, Karahan SC, Köksal İ. Prognostic impact of platelet distribution width in patients with Crimean–Congo hemorrhagic fever. J Med Virol 2016;88:1862–6.
15. Rinia AB, Kostamo K, Ebbens FA, van Drunen CM, Fokkens WJ. Nasal polyposis: a cellular-based approach to answering questions. Allergy 2007;62:348–58.
16. Staikuniene J, Vaitkus S, Japertiene LM, Ryskiene S. Association of chronic rhinosinusitis with nasal polyps and asthma: clinical and radiological features, allergy and inflammation markers. Medicina (Kaunas) 2008;44:257–65.
17. Boos CJ, Beevers GD, Lip GY. Assessment of platelet activation indices using the ADVIATM 120 amongst 'high-risk'patients with hypertension. Ann Med 2007;39:72–8.
18. Van Cott EM, Fletcher SR, Kratz A. Effects of the blood-collection tube material and long-term storage on platelet activation parameters on the ADVIA 120/2120 hematology system. Lab Hematol 2004;11:71–5.
19. Ceylan B, Mete B, Fincanci M, et al. A new model using platelet indices to predict liver fibrosis in patients with chronic hepatitis B infection. Wien Klin Wochenschr 2013;125:453–60.
20. Taniguchi M, Higashi N, Ono E, Mita H, Akiyama K. Hyperleukotrieneuria in patients with allergic and inflammatory disease. Allergol Int 2008;57:313–20.
21. Di Capite J, Nelson C, Bates G, Parekh AB. Targeting Ca 2+ release–activated Ca 2+ channel channels and leukotriene receptors provides a novel combination strategy for treating nasal polyposis. J Allergy Clin Immunol 2009;124:1014–21.e1–3.
22. Tozkoparan E, Deniz O, Ucar E, Bilgic H, Ekiz K. Changes in platelet count and indices in pulmonary tuberculosis. Clin Chem Lab Med 2007;45:1009–13.
23. Celikbilek A, Tanik N, Zararsiz G, Celikbilek M. Do platelet indices have a role in benign paroxysmal positional vertigo? Neurol Res 2014;36:763–8.
24. Mirvakili A, Dadgarnia MH, Baradaranfar MH, Atighechi S, Zand V, Ansari A. Role of platelet parameters on sudden sensorineural hearing loss: a case-control study in Iran. PloS One 2016;11: e0148149.

25. Kurt OK, Yildiz N. The importance of laboratory parameters in patients with obstructive sleep apnea syndrome. Blood Coagul Fibrinol 2013;24:371–4.
26. Jindal S, Gupta S, Gupta R, et al. Platelet indices in diabetes mellitus: indicators of diabetic microvascular complications. Hematology 2011;16:86–9.
27. Topal E, Celiksoy MH, Catal F, Karakoc HT, Karadag A, Sancak R. The platelet parameters as inflammatory markers in preschool children with atopic eczema. Clin Lab 2015;61:493–6.
28. Chandrashekar L, Rajappa M, Sundar I, et al. Platelet activation in chronic urticaria and its correlation with disease severity. Platelets 2014;25:162–5.

Please cite this article as: Kepekçi AH, Dizdar G, Kepekçi AB. Platelet distribution width (PDW) data of patients with nasal polyposis: is it important for clinical severity? ENT Updates 2017;7(1):33–37.

ENT updates
www.entupdates.org

Clinical Research

ENT Updates 2017;7(1):38–41
doi:10.2399/jmu.2017001008

Orbital complications of sinusitis in children in Komfo Anokye Teaching Hospital

Joseph Opoku-Buabeng, Seth Yaw Lartey

Eye, Ear, Nose and Throat Department, Komfo Anokye Teaching Hospital, Kumasi, Ghana

Abstract

Objective: To evaluate the pattern and incidence of orbital complications due to sinusitis in children in Komfo Anokye Teaching Hospital.

Methods: Ninety-two children aged between 2 and 14 years who presented with various orbital complications as a result of sinusitis among 1627 children in a 5-year period were evaluated to analyze the pattern and the incidence of the various stages and forms.

Results: Of the 1627 children evaluated, 92 (5.7%) had orbital complications. Among those with complications, 52.2% presented with orbital cellulitis, 22.8% presented with subperiosteal abscess, 14.1% presented with periorbital cellulitis, 8.7% presented with orbital abscess, and 2.2% presented with cavernous sinus thrombosis.

Conclusion: Despite the low incidence of sinogenic orbital complications, this study showed that orbital cellulitis is the most common among all orbital complications as a result of sinusitis in children.

Keywords: Sinusitis, orbital complications, periorbital cellulitis, orbital cellulitis, subperiostal abscess, cavernous sinus thrombosis.

Özet: Komfo Anokye Eğitim Hastanesi'ndeki çocuklarda sinüzite bağlı orbital komplikasyonlar

Amaç: Çalışmanın amacı Gana, Kumasi'de bulunan Komfo Anokye Eğitim Hastanesi'ndeki çocuklarda sinüzite bağlı orbital komplikasyonların patern ve insidanslarını değerlendirmektir.

Yöntem: Hastalığın değişik evre ve formlarının patern ve insidanslarını değerlendirmek için beş yıllık dönemde 1627 çocuk arasında sinüzit sonucu değişik orbital komplikasyonlarla gelmiş 2 ila 14 yaşlarında 92 çocuk değerlendirilmiştir.

Bulgular: Değerlendirilen 1627 çocuktan 92'sinde (%5.7) orbital komplikasyonlar mevcuttu. Komplikasyon olanlar arasında %52.2'si orbital selülit, %22.8'i subperiostal apse, %14.1'i periorbital selülit, %8.7'si orbital apse, %2.2'si kavernöz sinüs trombozuyla gelmişti.

Sonuç: Sinojenik orbital komplikasyonların düşük insidansına rağmen bu çalışma çocuklarda sinüzit nedeniyle tüm orbital komplikasyonlar içinde en çok görülenin orbital selülit olduğunu göstermiştir.

Anahtar sözcükler: Sinüzit, orbital komplikasyonlar, periorbital selülit, orbital selülit, subperiostal apse, kavernöz sinüs trombozu.

Sinusitis is an inflammatory condition of the mucous membrane of the paranasal sinuses. This is normally a microbial infection commonly caused by viruses such as Rhinovirus, Myxovirus, Reovirus, etc. and bacteria such as Staphylococcus aureus, *Streptococcus*-β-*haemolyticus*, *Haemophilus influenzae*, *Neisseria catarrhalis* and *Proteus mirabilis*.[1] Sinusitis can result in nasal and postnasal space disorders, dental conditions, and traumatic conditions of the cranio- maxillofacial bones and also the blood stream septicemia. This condition often presents with frontal headache, fever, general malaise, offensive nasal discharge, blocked nose, and halitosis. It is best managed with the use of systemic antibiotics, analgesic/antipyretic and topical nasal decongestants.[1,2]

Sinusitis can complicate intracranial and extracranial conditions if the management is not properly administered. The intracranial complications include meningitis, epidural, subdural and cerebral abscesses, whereas some of the extracranial complications include orbital complications, otitis media, tonsillitis, the formation of nasal polyps and others. Orbital complications have been found to be one of the major challenges for ophthalmologists and the otorhinolaryngologists in the sense that it can result in loss of vision of the eye of the affected orbit or at times death when there is intracranial involvement.[2,3]

However, no studies have been performed in Ghana to determine the association between sinusitis and orbital com-

Correspondence: Joseph Opoku-Buabeng, MD. Eye, Ear, Nose and Throat Department, Komfo Anokye Teaching Hospital, Kumasi, Ghana.

e-mail: opokubuabeng75@yahoo.com

Received: February 5, 2017; **Accepted:** March 15, 2017

Online available at:
www.entupdates.org
doi:10.2399/jmu.2017001008
QR code:

plications in children. The aim of the present study was to evaluate the pattern and incidence of orbital complications due to sinusitis in children in Komfo Anokye Teaching Hospital.

Materials and Methods

A retrospective study by review of records was conducted in the Ear, Nose and Throat (ENT) and the Eye Departments of Komfo Anokye Teaching Hospital (KATH) between January 2010 and December 2014. Komfo Anokye Teaching Hospital is the second largest teaching hospital in Ghana with a bed capacity of 1500 and serves as a referral center for mid and northern parts of the country. Besides, it also receives referrals from neighboring countries like Burkina Faso, Ivory Coast and Togo.

Ninety-two patients out of 1627 cases diagnosed as sinusitis, who suffered sinusitis with eventual orbital complications and who had been attended to by the otorhinolaryngologist and the ophthalmologist, had their records evaluated.

Their diagnoses were established on the basis of their clinical presentations, clinical examinations, radiological and hematological findings as at the time of their visit.

The patients with a history of trauma to the orbit, those with thyroid orbitopathy and with dental extraction infection were excluded from the study.

The patients with a history of ocular pain and those with pain on moving the eye ball, proptosis, and chemosis were included in the study. In all of the patients, clinical ear, nose and throat examinations were performed together with the radiological investigation (a Conventional x-ray of the paranasal sinuses i.e. Water's view). The patient's visual acuity was checked using the Snellen's visual acuity chart and their intraocular pressure was measured with the Goldman's applanation tonometer to exclude any increase intra-ocular pressure disease. The presence of proptosis was confirmed by measuring with an exophthalmometer. Computerized tomography and ultrasonography were performed in some of the patients to establish their diagnosis.

Clinical presentation was assessed according to Chandler's classification:

- **Group I:** Pre-septal cellulitis eyelid edema without palpable pus and not associated to visual loss of extraocular mobility limitation.
- **Group II:** Orbital cellulitis without abscess, diffuse edema of orbital fat tissue without abscess forming.
- **Group III:** Orbital cellulitis with subperiosteal abscess, abscess forming between the orbit periosteum and bone, eyeball shift with or without movement limitation, with or without visual acuity reduction.
- **Group IV:** Orbital cellulitis with orbit fat tissue abscess, severe proptosis, may be frontal and not lateral or inferiorly shifting as in a subperiosteal abscess, a severe limitation in eye mobility, with or without ophthalmoplegia, with or without visual loss.
- **Group V:** Cavernous sinus thrombosis, orbital phlebitis expanding within the cavernous sinus and crossing the basilar plexus towards the other side, resulting in bilateral disease.

Ethical consent and approval were received from the Committee on Human Research, Publications and Ethics of the Kwame Nkrumah University of Science and Technology (KNUST), School of Medical Sciences and Komfo Anokye Teaching Hospital (KATH).

Results

Of the 1627 patients, whose data were analyzed, 92 were found to have developed orbital complications. The patients consisted of 61 males (66.3%) and 31 females (33.7%), and the male-to-female ratio was 2:1.

The patients were aged between 2 and 14 years and 6.5% were between 1 and 3 years, 16.3% were between 4 and 6 years, 30.4% were between 7 and 9 years, 38.1% were between 10 and 12 years and 8.7% were between 13 and 15 years.

The mean age of the patients in the study group was 8.8 (range: 2 to 14) years. The age distribution of the patients was shown in Table 1.

Using the Chandler's classification of orbital lesions, 14.1% presented with the stage of periorbital cellulitis, 52.2% with the stage of orbital cellulitis, 22.8% with the stage of subperiosteal abscess, 8.7% with the stage of orbital

Table 1. The age distribution of patients.

Age group (years)	n (%)
1–3	6 (6.5%)
4–6	15 (16.3%)
7–9	28 (30.4%)
10–12	35 (38.1%)
13–15	8 (8.7%)

abscess, and 2.2% presented with the stage of cavernous sinus thrombosis as shown in Table 2.

Discussion

Many studies in the literature reported orbital cellulitis as the most common complication of sinusitis, and it is most frequently associated with ethmoiditis in children.[4–9] Tobin et al., Hirsch et al. and Wells et al. also reported orbital cellulitis or abscess occurring most frequently from ethmoidal sinusitis and less frequently from maxillary sinusitis or frontal sinusitis and it is more common than intracranial extensions.[10–12]

Al-Madini et al. also reported 616 cases of acute sinusitis, of which 36 (5.8%) presented with orbital complications.[13] Of these patients, 26 (72.2%) were children and within them 21 (80.8%) had preseptal whereas 5 (19.2%) had orbital cellulitis. In a retrospective review study, Welkoborsky et al. analyzed the clinical records of 49 children (27 girls, 22 boys, with a mean age of 11.8 years).[14] They found out that 18 (36.7%) presented with orbital complications due to acute sinusitis. Using Chandler's classification, 10 (20.4%) were found to have preseptal whereas 8 (16.3%) had orbital cellulitis. Similarly, Stojanoviç et al. in the clinical center in Kragujevac, reported of orbital complications in 53 patients (1.35%) out of 3912.[15] This study has confirmed the relationship between sinusitis and orbital complications in children with an incidence rate of 5.7%. This seems in conformity with the literature published by Al-Madani et al. (5.8%) and Neto et al. (6.0%).[13,16] Stojanoviç et al. reported 1.4%, which is much lower whereas Welkoborsky et al. also reported 36.7%, which is much higher.[14,15]

There is a higher incidence in males than females with a male-to-female ratio of 2:1. This conforms to the study by Adedeji et al. and Neto et al.[4,16] The higher incidence in males as to the females will be difficult to explain. In the present study, the mean age of the patients was 8.8 years which conforms to other presentation which found it to between 6 and seven years. Neto et al. reported of a mean age of 6.5 years whereas Welkoborsky et al. also reported of 11.8 years.[14,16]

In the developed countries, most of the patients presented at the early stages. Sobol et al.[17] in Canada reported 72% of patients presenting with the stage of periorbital cellulitis, 19% with the stage of obital cellulitis, and 9% with the stage of orbital abscess, but they did not reported any incidence of the latter two stages of orbital complications which normally present with poor prognosis. However, it is worrying that severe complication like orbital abscess (8.7%), subperiostal abscess (22.8%) and cavernous sinus thrombosis (2.2%) in total accounted for 38.7% of all sinogenic orbital complications. Over one third of all orbital complications from sinusitis in children seen in Komfo Anokye Teaching Hospital were severe which may be life-threatening or at minimum a damage to the eye. Perhaps, these children are reporting late or the management of regime needs to be reviewed by all involved in the management.

Table 2. The pattern of orbital complications using Chandler's classification.

Group	Stage	Description	n (%)
I	Periorbital cellulitis	Edematous, non-tender eyelid	13 (14.1%)
II	Orbital cellulitis	Difference in edema and influential of orbital contents without abscess formation	48 (52.2%)
III	Subperiosteal abscess	Apparent collection of purulent exudates between the periostal and the bony orbital wall with exophthalmus and chemosis	21 (22.8%)
IV	Orbital abscess	Marked exophthalmus, chemosis and visual impairment	8 (8.7%)
V	Cavernous sinus thrombosis	Proptosis, globe fixation and severe loss of visual acuity	2 (2.2%)

Conclusion

Orbital complications are among the most common complications of sinusitis in children especially between seven and nine years of age. Orbital complications can present with various stages, of which orbital cellulitis is the frequent stage as it is the state where most patients start to manifest most of the clinical signs and symptoms.

Orbital complications can result in the loss of vision and even death and therefore, it is very important to refer to proper management for every child presenting with an offensive nasal discharge and periorbital swelling as it may be an indication of a sinogenic orbital complication.

We recommend the adoption of a more dynamic approach for the management of sinusitis. Early recognition and appropriate treatment may prevent these life-threatening complications.

Conflict of Interest: No conflicts declared.

References

1. Sinclair CF, Berkowitz RG. Prior antibiotic therapy for acute sinusitis in children and the development of subperiosteal orbital abscess. Int J Pediatr Otorhinolaryngol 2007;71:1003–6.
2. Sijuwola OO, Adeyemo AA, Adeosun AA. Orbital complications of rhinosinusitis. Ann Ib Postgrad Med 2007;5:6–8.
3. Ubah J, Nwaorgu OGB, Ogunleye O. Paranasal sinusitis in the aetiology of orbital cellulitis. Nigerian journal of Ophthalmology 2005;13:8–10.
4. Adedeji TO, Olaosun AO, Tobi JE, Adejumo OO. Sinugenic orbital infections in a Nigerian Teaching Hospital. Advance Tropical Medicine and Public Health International 2003;3:101–9.
5. Moloney JR, Bedham NJ, McRae A. The acute orbit. Preseptal (periobital) cellutitis, subperiostal abscess and orbital cellulitis due to sinusitis. J Laryngol Otol Suppl 1987;12:1–18.
6. Chandler JR, Lengenbrunner DJ, Stevens ER. The pathogenesis of orbital complications in acute sinusitis. Laryngoscope 1970;80:1414–28.
7. Schramm VL Jr., Myers EN, Kennerdell JS. Orbital complication of acute sinusitis: evaluation, management and outcome. ORL J Otolaryngol Relat Spec 1978;86:221–30.
8. Swift AC, Charlton G. Sinusitis and the acute orbit in children. J Laryngol Otol 1990;104:213–6.
9. Wald ER. Acute sinusitis and orbital complications in children. Am J Otolaryngol 1983;4:424–7.
10. Towbin R, Han BK, Kaufman RA, Burke M. Post-septal cellulitis; CT in diagnosis and management. Radiology 1986;158:735–7.
11. Hirsch M, Lifshitz T. Computerized tomography in the diagnosis and treatment of orbital cellulitis. Padiatr Radiol 1988;18:302–5.
12. Wells RG, Sty JR, Gonnening RS. Imaging of pediatric eye and orbit. Radiographics 1989;9:1023–44.
13. Al-Madani MV, Khatatbeh AE, Rawasdeh RZ, Al-Khatoum NF, Shawagfeh NR. The prevalence of orbital complications among children and adults with acute sinusitis. Braz J Otorhinolaryngol 2013;79:716–9.
14. Welkoborsky HJ, Graß S, Deichmüller C, Bertram O, Hinni ML. Orbital complications in children: differential diagnosis of a challenging disease. Eur Arch Otorhinolaryngol 2015;272:1157–63.
15. Stojanoviç J, Iliç N, Beliç B, Ziviç L,Stankoviç P, Erdevicki L, Jovanoviç S. Orbital complications of rhinosinusitis. [Article in Serbian] Acta Chir Iugosl 2009;56:121–5.
16. Neto LM, Pignatari S, Mitsuda S, Fava AS, Stamm A. Acute sinusitis in children – a retrospective study of orbital complications. Rev Bras Otorrhinolaringol 2007;73:81–5. PMID:
17. Sobol SE, Marchand J, Tewfik TL, Manoukian JJ, Schloss MD. Orbital complications of sinusitis in children. J Otolaryngol 2002;31:131–6.

Please cite this article as: Opoku-Buabeng J, Lartey SY. Orbital complications of sinusitis in children in Komfo Anokye Teaching Hospital. ENT Updates 2017;7(1):38–41.

ENT updates
www.entupdates.org

Clinical Research

ENT Updates 2017;7(1):42–46
doi:10.2399/jmu.2017001001

Head and neck fistulas of congenital or infectious etiology: retrospective analysis of 23 cases

Selçuk Arslan[1], Bengü Çobanoğlu[2], Ahmet Ural[1]

[1]*Department of Otorhinolaryngology - Head and Neck Surgery, Faculty of Medicine, Karadeniz Technical University, Trabzon, Turkey*
[2]*Department of Otorhinolaryngology - Head and Neck Surgery, Kanuni Training and Research Hospital, Trabzon, Turkey*

Abstract

Objective: In this study, we aimed to conduct a retrospective analysis of head and neck masses initially presenting with fistulas.

Methods: A total of 23 patients with head and neck fistulas who admitted to the otorhinolaryngology department of our tertiary care center between January 2011 and May 2012 were retrospectively reviewed. Age, sex, and duration of symptoms were noted from the case records. The side and site of the lesion and the opening of fistula were noted. Co-morbidities, post-operative complications and histopathological diagnosis were classified.

Results: Of the 23 patients with head and neck fistulas, (12 males, 11 females) the average age was 26.52±14.1 (range: 9 to 74) years. Of the 23 lesions, the most prevalent lesion was branchial fistulas (n=13, 56.52%) followed by thyroglossal fistulas (n=7, 30.43%), dermoid fistulas (n=2, 8.7%) and tuberculosis (n=1, 4.4%). Drainage (n=23, 100%) was consistently observed as the initial symptom in all patients while swelling (n=22, 95.6%) was the second most common presenting symptom.

Conclusion: Correct diagnosis is essential to avoid inadequate surgery and multiple procedures for head and neck fistulas of congenital or infectious etiology.

Keywords: Branchial, thyroglossal, congenital, fistula, head and neck.

Özet: Konjenital veya enfeksiyöz etiyolojili baş ve boyun fistülleri: 23 olgunun retrospektif analizi

Amaç: Bu çalışmada başlangıçta fistülle gelen baş ve boyun kitlelerinin retrospektif analizini gerçekleştirmeyi amaçladık.

Yöntem: Üçüncü basamak merkezimizin KBB Ana Bilim Dalına Ocak 2011 ila Mayıs 2012 arasında kabul edilmiş baş ve boyun fistüllü toplam 23 hasta retrospektif olarak gözden geçirildi. Olgu kayıtlarından yaş, cinsiyet ve semptomların süresi ile birlikte lezyon yeri ve tarafı, fistülün ağzı da not edildi. Komorbiditeler, postoperatif komplikasyonlar, histopatolojik tanı sınıflandırıldı.

Bulgular: Baş ve boyun fistülleri olan 23 hastanın (12 erkek, 11 kadın) yaş ortalaması 26.52±14.1 (aralık: 9–74) yıl idi. Yirmi üç lezyon arasında en yaygın olanları brankiyal fistüller (n=13, %56.52), ardından tiroglossal fistüller (n=7, %30.43), dermoid fistüller (n=2, %8.7) ve tüberküloz (n=1, %4.4) gelmekte idi. Hastaların hepsinde başlangıç semptomu sürekli olarak drenaj (n=23, %100) iken, şişlik (n=22, %95.6) ise ikinci sıklıkla en çok görülen semptom idi.

Sonuç: Konjenital veya enfeksiyöz etiyolojili baş ve boyun fistüllerinde yetersiz cerrahi ve çoklu girişimlerden kaçınmak için doğru tanı esastır.

Anahtar sözcükler: Brankiyal, tiroglossal, konjenital, fistül, baş ve boyun.

Congenital cysts and sinuses of the neck are common mostly in the pediatric population. These lesions can be safely excised usually not requiring a detailed preoperative workup.[1] However, rare lesions such as fistulas of the first cleft and cysts of the fourth pouch may be misdiagnosed. Congenital midline anomalies such as thyroglossal duct cysts and dermoid cysts are embryologically different from malformation of the lateral cervical region. Branchial anomalies are further classified as cysts, sinuses, and fistulas. Cysts are proposed to be entrapped remnants of branchial cleft or sinuses. Sinuses are remnants of cleft or pouches, and fistulas occur as a result of the persistence of both pouch and cleft.[2] Maldevelopment of branchial apparatus have been implicated in various anomalies of the head and neck region. The importance of understanding the anatomy and pathology of branchial apparatus is in

Correspondence: Bengü Çobanoğlu. Department of Otorhinolaryngology - Head and Neck Surgery, Kanuni Training and Research Hospital, Trabzon, Turkey.
e-mail: benguyc@gmail.com

Received: November 2, 2016; **Accepted:** December 17, 2016

Online available at:
www.entupdates.org
doi:10.2399/jmu.2017001001
QR code:

applying the knowledge during surgery, and handling complications.

Management of the congenital fistulas of the neck is possible by focusing on the specific lesion, and appropriate surgical treatment relies on a precise preoperative diagnosis. This discussion presents an overview of the embryology, pathophysiology, and diagnostic modalities for congenital neck fistulas. Additionally, we also described the current principles of surgical management. Although these anomalies are generally easily treated, accurate preoperative diagnosis and appropriate surgical therapy are essential to prevent recurrence and to ensure optimal cosmetic outcomes.[3]

Materials and Methods

Study design

A total of 23 patients, aged between 9–24 years, with neck fistulas who admitted to the department of otolaryngology of our tertiary care center between January 2011 and May 2012 were retrospectively reviewed. Age, sex, and duration of symptoms were noted from the case records. The side and site of the lesion and the opening of fistula were noted. All patients underwent routine pre-operative blood examination. Co-morbidities, post-operative complications and histopathological diagnosis were classified.

Statistical analysis

Data were analyzed using the Statistical Package for Social Sciences (SPSS Inc., Chicago, IL, USA) software (version 10.0 for Windows). Continuous variables were presented as mean±SD. Parametric tests were applied to data of normal distribution, and non-parametric tests were applied to data of questionably normal distribution.

Results

The patient data were shown in Table 1. The average age of the 23 patients with neck fistulas, (12 males, 11 females)

Table 1. An overview of data gathered from our series.

Patient no.	Age	Gender	Comorbidity diagnosis	Histopathological complications	Postoperative complaints	Chief
1	13	M	-	BF	-	S, D, P
2	28	M	-	Tbc		S, D, P, F
3	9	M	-	BF (PAF)	-	S, D
4	27	F	Hypothyroidism	DF	-	S, D
5	44	F	Diabetes mellitus	DF	-	S, D
6	20	M	-	BF (PAF)	-	S, D
7	29	F	-	BF	-	S, D, P
8	27	F	-	TGF	-	S, D, F
9	74	F	-	BF (PAF)	Infection	S, D, F
10	62	M	Hypothyroidism	TGF	Recurrence	S, D
11	42	F	Hypothyroidism	TGF	-	S, D, P
12	21	M	-	BF	-	S, D, F
13	16	M	-	BF (PAF)	-	S, D
14	17	M	-	TGF	-	S, D
15	32	M	Hypothyroidism	BF	Recurrence	S, D
16	35	F	Diabetes mellitus	BF	-	S, D
17	24	F	-	BF (PAF)	-	D
18	16	F	-	TGF	-	S, D, F
19	17	M	-	BF (bilateral)	-	S, D, P
20	16	F	-	TGF	Infection	S, D, F
21	15	M	-	BF (PAF)	-	S, D
22	17	M	-	TGF	-	S, D
23	19	F	-	BF (PAF)	-	S, D, P

BF: branchial fistula; **D:** drainage; **DF:** dermoid fistula; **DM:** diabetes mellitus; **F:** fever; **P:** pain; **PAF:** preauricular fistula; **S:** swelling; **Tbc:** tuberculosis; **TGF:** thyroglossal fistula

was 26.52±14.1 (range: 9 to 74) years. Male to female sex ratio was 1.09:1 with a slight male predominance. Of the 23 lesions, maximum incidence was of branchial fistulas (56.52%) followed by thyroglossal fistulas (30.43%).

Branchial fistulas (n=13, 56.52%) were frequently detected, and 7 of them were pre-auricular fistulas (n=7, 30.43%) located on the lateral cervical region (Fig. 1). Thyroglossal fistulas (n=7, 30.43%) (Fig. 2) and dermoid fistulas (n=2, 8.69%) located in the midline. One case was diagnosed as fistula of tuberculosis (n=1, 4.34%). Only one case with branchial fistula presented bilaterally. In this bilateral case, excision of the masses was performed in a two-stage operation three months after the first intervention.

Main symptoms at initial admission were swelling and drainage from a cervical mass. The other symptoms include pain and/or fever. Swelling and discharge were the presenting symptoms in all 23 cases. Six patients complained of pain regardless of etiology (26.08%).

Postoperative infection was the main postoperative complication encountered in 2 cases (8.69%). In addition to surgery, systemic antibiotics (amoxicillin-clavulanate) were administered to these cases for three days. In 1 patient (4.34%), diagnosis of cervical tuberculosis fistula was established. Anti-tuberculous treatment consisting of rifampicin and isoniazid were given for six months.

Co-morbidity is another parameter in our study. The most common co-morbidity was hypothyroidism (regardless of etiology) and diabetes mellitus. Four patients had hypothyroidism (17.3%) and 2 patients had diabetes mellitus (8.6%).

Operation type consisted of Sistrunk for thyroglossal duct fistulas (n=7, 30.43%) while complete surgical excision was the selected choice of treatment in the rest of cases.

In two cases with branchial fistula, additional pre-operative systemic antibiotics (amoxicillin/clavulanate 2 g/day orally) were administered due to acute infection. Such patients were taken to the operating room one week after antibiotic treatment. In one case with mycobacterial lymphadenitis, anti-tuberculous treatment was administered after histopathological diagnosis.

Recurrence was observed during postoperative recovery in 2 cases (8.69%) requiring re-operation within 12 months.

Discussion

Understanding the anatomical or clinical features of each lesion is a 'must' to make a right diagnosis and to avoid

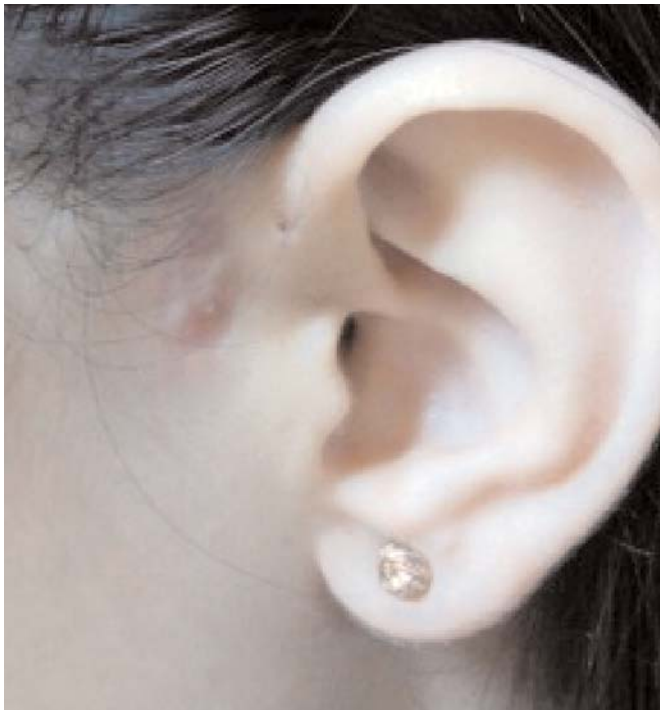


Fig. 1. Typical view of a left preauricular fistula.

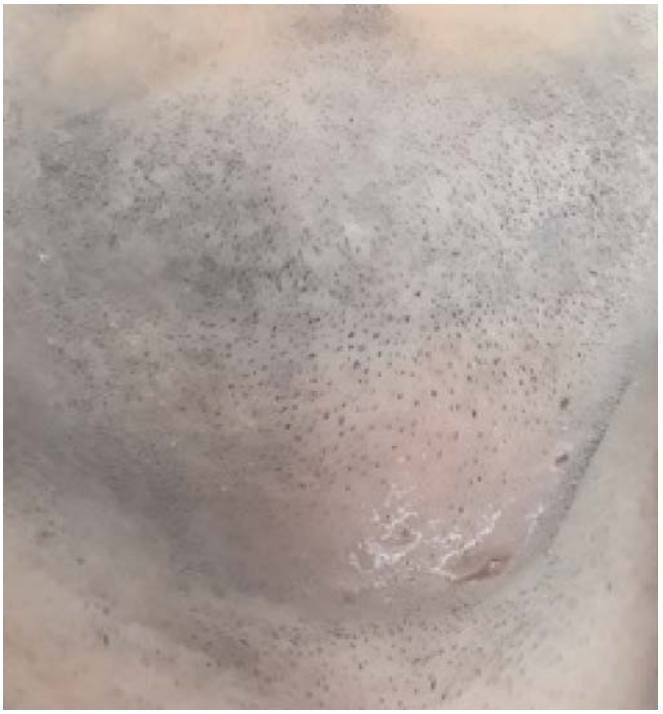


Fig. 2. A thyroglossal fistula with drainage.

recurrences of head and neck fistulas.[4] A high index of suspicion and clinical awareness as well as thorough physical examination can lead to a definitive diagnosis. Branchial anomalies should be involved in the differential diagnosis of any unexplained masses in the head and neck area or recurrent neck spaces infections. Radiological investigations should be used to evaluate neck lesions of congenital origin. The extent of the lesion can be defined by CT and/or MRI. The relation of the facial nerve to the first cleft anomaly can be assessed by imaging methods.[5]

Branchial cysts may present as circumscribed lesions or have tract-like extensions on one side.[6] According to anatomical location, second cleft cysts can be classified into four groups which are type I occurring under the superficial aponeurosis of the neck, type II located just to the front of the large vessels, type III usually between the branches of the carotid bifurcation, and type IV occurring beneath the large vessels and pharyngeal wall. After a complete surgical excision recurrence is uncommon.[7] Our cases of branchial fistulas are in type II, and no recurrence occurred after resection.

Branchial cleft anomalies such as branchial sinuses; cysts and fistulas are mostly found in pediatric population.[8] About 96–97% of these anomalies are unilateral, and only 2–3% have a bilateral presentation; the bilateral occurrence is higher in familial cases.[6] In our cases, one patient has bilateral branchial fistula but no familial history. The treatment protocol for such lesions is surgical excision. Antibiotics are only used to treat infections in the tract. Surgical excision is a definitive treatment; however, surgery should be avoided during the period of acute infection. If present, surgical drainage of the abscess is indicated along with concurrent antibiotherapy.[9]

Occasionally, a branchial anomaly may be a part of branchiootorenal (BOR) syndrome, which is defined with branchial arch anomalies, hearing loss and renal malformations. This genetic syndrome with autosomal dominant transmission has first been described by Melnick et al. and Fraser et al.[10,11] We had no BOR syndromic patients in this study, but BOR should be kept in mind for the patients with branchial fistulas that can be associated with external ear anomalies and/or a history of hearing loss and similar findings in other family members.

Lymphadenopathy due to tuberculosis is commonly encountered in endemic areas, and the cervical region is the most common site of tuberculous adenitis. The term "scrofula" refers to this condition. The tuberculous adenitis can be found at other sites such as axillary, intrathoracic, intramammary, intraabdominal (mesenteric lymph nodes or paraaortic), and occasionally inguinal sites.[12] In our study, the fistula was in the supraclavicular region and the patient has neither systemic symptoms nor tuberculosis history. Both tuberculosis and HIV prevalence has been reported to be higher in countries that have a higher incidence of tuberculous lymphadenitis. During recent years, it has been found that tuberculous lymphadenitis is common in the third-fifth decades of life and it consists of a predominantly female population. The lymph nodes can be infected by *Mycobacterium* through hematogenous route or by a local extension from tuberculous infection of adenotonsillar tissue.[13]

Thyroglossal duct cysts are the most common congenital neck masses with a typical presentation as a painless cystic mass or fistula in the region of hyoid bone at or near the midline. Due to the process of embryogenesis, thyroglossal duct cysts can be found at the base of the tongue to the lower midline of the neck. A midline location and close association with the hyoid bone is the only nearly universal components of these lesions.[14] Functional thyroid tissue can be contained in the thyroglossal duct remnants. Most thyroglossal duct cysts present during the first five years of life. Due to its close relation to the hyoid bone and foramen cecum, the cyst moves in craniocaudal direction with swallowing. These patients typically have fluctuations in the size of the neck mass. Although most thyroglossal duct remnants present as cystic masses, up to one-quarter of these lesions present as a draining sinus tract in the midline. The thyroglossal duct sinus occurs due to the spontaneous rupture of the cyst. Yet, fistulous communication between the skin and foramen caecum has been reported very rare.[15] In our cases, there might have been a rarely patent thyroglossal tract, which manifested as a cyst in childhood, which on rupture resulted in the formation of a fistula.

Dermoid cysts and fistulas account for up to 25% of midline cervical anomalies. Dermoid fistula typically present as painless, superficial subcutaneous masses in the anterior neck, but can occur in other locations, such as the occipital and frontal scalp. Most anterior neck lesions occur in relatively close proximity to the hyoid bone and are frequently misdiagnosed as thyroglossal duct pathologies.

Unlike thyroglossal duct cysts, dermoid cysts do not move with swallowing and tongue protrusion as they lack mesodermal attachments and have a superficial location. Because dermoid cysts have no connection to the oropharynx, infection is rare. Cyst rupture may, however, occur due to trauma or enlargement, and results in granulomatous

inflammation of the surrounding skin and soft tissues. It may be difficult to differentiate between an infected thyroglossal duct cyst and a ruptured dermoid. In these cases, fine needle aspiration with cytology and culture may be useful. Neck fistulas are common pathological disorders of neck surgery. Our study ınvolves fistulas of neck including thyroglossal fistulas, tuberculous fistula, branchial fistulas and dermoid fistulas. Limitations of our study are retrospective design, small sample size, and the absence of definitive criteria for the selection of patients for this method. However, we hope that this series highlights the clinical features of neck fistula and main diagnostic and therapeutic steps to be taken.

Conclusions

Head and neck fistulas are relatively common pathologies that can be treated successfully with the appropriate surgical method. Correct diagnosis is essential to avoid insufficient surgeries and or second procedures. The surgical approach needs to be tailored to the suspected arch of origin of the anomaly. Definitive excision is essential for good outcomes.

Conflict of Interest: No conflicts declared.

References

1. Nicollas R, Guelfucci B, Roman S, Triglia JM. Congenital cysts and fistulas of the neck. Int J Pediatr Otorhinolaryngol 2000;55: 117–24.
2. Prasad SC, Azeez A, Thada ND, Rao P, Bacciu A, Prasad KC. Branchial anomalies: diagnosis and management. Int J Otolaryngol 2014;2014:237015.
3. Singh AP, Kumar V, Narula V, Meher R, Raj A. Bilateral first and second arch anomalies: a rare presentation. Singapore Med J 2012; 53:e74–6.
4. Coppens F, Peene P, Lemahieu SF. Diagnosis and differential diagnosis of branchial cleft cysts by CT scan. J Belge Radiol 1990; 73:189–96.
5. Bajaj Y, Ifeacho S, Tweedie D, et al. Branchial anomalies in children. Int J Pediatr Otorhinolaryngol 2011;75:1020–3.
6. Lapeña JF Jr, Jimena GL. Coexisting first and bilateral second branchial fistulas in a child with nonfamilial branchio-otic syndrome. Ear Nose Throat J 2013;92:304, 306–9.
7. Gatti WM, Zimm J. Bilateral branchial cleft fistulas: diagnosis and management of two cases. Ear Nose Throat J 1998;67:256, 258, 261.
8. Miwa K, Fujioka S, Adachi Y, Haruki T, Taniguchi Y, Nakamura H. Mediastinal tuberculous lymphadenitis with intractable fistula to the neck. Thorac Cardiovasc Surg 2010;58:124–6.
9. Polesky A, Grove W, Bhatia G. Peripheral tuberculous lymphadenitis: epidemiology, diagnosis, treatment, and outcome. Medicine (Baltimore) 2005;84:350–62.
10. Senel E, Kocak H, Akbiyik F, Saylam G, Gulleroglu BN, Senel S. From a branchial fistula to a branchiootorenal syndrome: a case report and review of the literature. J Pediatr Surg 2009;44:623–5.
11. Madana J, Yolmo D, Saxena SK, Gopalakrishnan S. True thyroglossal fistula. Laryngoscope 2009;119:2345–7.
12. Dandapat MC, Mishra BM, Dash SP, Kar PK. Peripheral lymph node tuberculosis:a review of 80 cases. Br J Surg 1990;77:911–2.
13. Mert A, Tabak F, Ozaras R, Tahan V, Ozturk R, Aktuglu Y. Tuberculous lymphadenopathy in adults: a review of 35 cases. Acta Chir Belg 2002;102:118–21.
14. Al-Khateeb TH, Al Zoubi F. Congenital neck masses: a descriptive retrospective study of 252 cases. J Oral Maxillofac Surg 2007;65: 2242–7.
15. Solomon JR, Rangecroft L. Thyroglossal-duct lesions in childhood. J Pediatric Surg 1984;19:555–61.

Please cite this article as: Arslan S, Çobanoğlu B, Ural A. Head and neck fistulas of congenital or infectious etiology: retrospective analysis of 23 cases. ENT Updates 2017;7(1):42–46.

Review

ENT Updates 2017;7(1):47–52
doi:10.2399/jmu.2017001006

ENT updates
www.entupdates.org

Associations among high altitude, allergic rhinitis, and bronchial hyperreactivity

Fatih Oğhan[1], İbrahim Erdim[2]

[1]*Department of Otolaryngology, Faculty of Medicine, Dumlupınar University, Kütahya, Turkey*
[2]*ENT Clinic, Tokat Erbaa State Hospital, Tokat, Turkey*

Abstract

Allergic respiratory diseases are common public health problem. Although several treatment options, some of patients cannot manage to get satisfactory recovery. High altitude (HA) is shown as a natural additive and/or salvage therapy option for this patient group. We aimed to present the effect of HA on allergic rhinitis and bronchial hyperreactivity in company with literature.

Keywords: High altitude, allergic rhinitis, bronchial hyperreactivity.

Özet: **Yüksek rakımın alerjik rinit ve bronşiyal hiperreaktivite üzerindeki etkileri**

Alerjik solunum hastalıkları genel bir halk sağlığı sorunudur. Çeşitli tedavi seçeneklerine rağmen bazı hastalar tatmin edici bir iyileşme elde edemez. Yüksek rakım, bu hasta grubu için doğal bir ilave ve/veya kurtarma tedavisi seçeneği sunmaktadır. Bu çalışmamızda, yüksek rakımın alerjik rinit ve bronşiyal hiperreaktivite üzerindeki etkilerini literatür eşliğinde sunmayı amaçladık.

Anahtar sözcükler: Yüksek rakım, alerjik rinit, bronşiyal hiperreaktivite.

Allergic respiratory diseases, including allergic rhinitis and asthma, are common health challenges associated with social and economic problems worldwide.[1,2] Industrial development, exposure to pollutants, indoor mites and other allergens, and humidity problems are increasing the incidences of allergic airway disease, bronchial responsiveness, and airway inflammation.[3] Several treatment options have been developed. These include nasal steroids and antihistamines and inhaled steroids and β_2-agonists. Sometimes, however, these treatments are inadequate, and oral steroids are required to treat refractory disease. Side-effects may develop; thus, patients increasingly seek natural treatment options.

A therapeutic effect of high altitude (HA) has been shown in some studies.[4–7] HA reduces supposedly the incidence of allergic respiratory disease. The daily symptoms of asthma and the extent of bronchial obstruction are significantly less in children living in mountainous areas.[5] Reduced air pollution, humidity, pollen and house dust mite (HDM) concentrations facilitate airway recovery.[6,7] However, some studies found that HA did not benefit those with allergic respiratory disease.[8–10]

We sought associations among HA, allergic rhinitis, and bronchial hyperreactivity in which relevant literature was reviewed.

Discussion

HA differs physically from sea level. The air temperature, humidity, barometric pressure, and inspired oxygen pressure are significantly reduced at HA.[11–13] Several reports have explored the effects of HA on the human airway. The relationships between HA and allergic airway diseases, including allergic rhinitis, have received a great deal of attention. However, few definitive conclusions have emerged. Several parameters may change the effects of HA on the respiratory tract. We thus decided to investigate the topic by reference to three distinct features of HA

Correspondence: Fatih Oğhan. Çavuş Department of Otolaryngology, Faculty of Medicine, Dumlupınar University, Kütahya, Turkey.
e-mail: fatihoghan@hotmail.com

Received: January 10, 2017; **Accepted:** February 19, 2017

Online available at:
www.entupdates.org
doi:10.2399/jmu.2017001006
QR code:

(Table 1): (i) The altitude per se, (ii) the time spent at HA, and (iii) climatic features of HA regions.

Degree of altitude

The concentrations of HDMs and other allergens decrease when the altitude increases. One questionnaire study found a negative correlation between asthma symptoms and altitude. Each increment of 100 m in altitude was associated with a 0.88% reduction in wheezing symptoms among 13–14-year-old children.[14]

HDM concentrations at sea level and at HA did not differ significantly in one study performed at altitudes from 400 to 2600 meters in the Alps.[8] More than half of all dust samples (53.3%) were collected at altitudes below 1500 m.[8] Another study performed at over 1500 m in the Alps found that positive HDM skin test results were significantly fewer in mountain schoolchildren, and the levels of HDM antigens in mattresses were much lower than those at sea level.[7]

One study evaluated the prevalence of allergic diseases (rhinoconjunctivitis and asthma) in 3196 children living 3658 m above sea level in Lhasa, Tibet. The prevalence of "wheezing at any time", "diagnosed asthma", and "current wheezing" was 1.4, 1.1, and 0.8% respectively. The prevalence of current exercise-induced asthma and current nocturnal cough was 7.1 and 4.6%, respectively. The prevalence of allergic rhinoconjunctivitis was 5.2%. The International Study of Asthma and Allergies in Childhood (ISAAC) considered that these prevalence of asthma and allergic rhinoconjunctivitis was the lowest of all studies published worldwide in the previous 12-month period.[4]

Thus, when altitude increases, allergen concentrations and the incidence of allergic airway disease fall. Reductions in air pollution and pollen and HDM concentrations may reduce airway inflammation.[4]

Period Spent at HA

A short time at HA may create a sense of nasal obstruction. Inspiration of cold air causes congestion of the nasal erectile tissues and increases nasal secretions. Consequently, the number of breaths/min increases and the maximal possible work performance decreases. Nose and throat sores may develop at HA, compromising the ability of mountaineers to climb higher.[15,16] One study on climbers trekking at 5300 m on Mount Everest, Nepal, identified an increase in nasal blockage and reduced nasal mucociliary transport.[15]

Mildly asthmatic patients were studied while trekking at approximately 5000 m over 3 days. No subject had an asthma attack or acute mountain sickness either while trekking or during the stay at HA. The basal FEV_1 value did not differ significantly from the value at sea level; the reduction in the challenge-induced FEV_1 decrease at sea level was significantly greater than those at 5000 m ($p<0.001$).[11]

Table 1. Three describing parameters of high altitude.

Degree of altitude
Up to 1500 meters
Between 1500 and 2500 meters
Between 2500 and 5300 meters
Over 5300 meters
Staying period at HA
Climber trekking
Between 3 days to 2 weeks
Between 2 and 12 weeks
Residents at HA
Climate features of HA region
Alps
Andes
Mount Everest, Tibet, and Nepal region

A stay at HA for 2 weeks to 3 months is recommended before therapeutic effects are apparent. In a prospective cohort study, 137 adults with severe refractory asthma (92 with allergic asthma) lived at 1600 m in Davos, Switzerland for 12 weeks. The 6-min walk test, the sinonasal outcome test, and the asthma quality-of-life test were performed; the total IgE level, the postbronchodilator FEV1, medication requirements, the exhaled nitric oxide fraction (FeNO), and the serum eosinophil level were assessed at the beginning of the study and 12 weeks later.[17] After 12 weeks, the asthma symptoms were controlled and all of the quality-of-life, sinonasal symptoms, the FEV1, and the 6-min walk test score improved. The total IgE level and the requirement for oral corticosteroids also decreased. Fourteen (48%) of 29 patients sensitized to HDM and 15 (36%) of 41 not sensitized no longer required oral steroids. The oral steroid requirements of the remaining patients were reduced. Serum eosinophil and the exhaled nitric oxide levels decreased in HDM-sensitized patients but not in non-sensitized patients. No other parameter differed between HDM-sensitized and non-sensitized patients.[17]

In another study, patients in whom asthma persisted despite the use of inhaled steroids underwent 10 weeks of HA therapy. The quality-of-life, lung function, adenosine-

and histamine- aggravated bronchial hyperresponsiveness and the urinary eosinophil, leukotriene E4, and 9a11b prostaglandin F2 (U-9a11b PGF2) levels improved significantly after HA therapy (all p values <0.05).[6]

Natives become adapted to HA and inherit relevant, physiological phenotypic features. Additionally, those who live and/or work at HA for years become adapted. Life at HA is not without difficulties. The inspired oxygen and barometric pressures are reduced, as well as the temperature and humidity. But HA exerts a therapeutic effect in those with allergic airway diseases; the air is fresh, with low levels of pollen and HDMs.[4–7]

The prevalence of pediatric allergic rhinoconjunctivitis and asthma were evaluated (in conformity with the ISAAC Phase III guidelines) at an altitude of 3658 m in Lhasa, Tibet. The frequencies of allergic respiratory symptoms were evaluated in natives (3190 students) who were asked if they "experienced an asthma attack", "were wheezing", and "had asthma"; the prevalence of these conditions was 1.4%, 0.8%, and 1.1%, respectively. Current exercise-induced asthma and current nocturnal cough were evident in 7.1% and 4.6% of patients, respectively. Rhinoconjunctivitis was slightly more common than other diseases. The incidence of nose problems in the past, current nose problems, and itchy/runny eyes was 9.3%, 5.2%, and 1.5% respectively. Rhinoconjunctivitis was diagnosed in 1.3% of patients.[4] The prevalence of wheezing at rest, wheezing during exercise, nocturnal wheezing, nocturnal cough, and severe wheezing was 0.3%, 1.2%, 0.03% (only one student), 1.4%, and 0.3%, respectively.[4]

The lowest prevalence of "current wheezing" worldwide was evident in children living in urban Lhasa. In a questionnaire study, the prevalence was 0.8%. The prevalence of "current exercise-induced asthma" and dry cough at nights was 7.1% and 4.6%, respectively. The prevalence of current allergic rhinoconjunctivitis was 5.2%, and did not change throughout the year.[4]

Another study enrolled 2026 children aged 12–14 years living at 3900 m on the north face of Mount Everest, Tibet. Asthma and rhinitis symptoms were evaluated. Only a few children complained of asthma symptoms such as wheezing. Only 2.8% of children complained of ever-wheezing and 1.4% of severe wheezing. The frequencies of these symptoms over the previous 12 months were 1.1% and 0.5%, respectively. However, upper airway respiratory infections and rhinitis were common. Over 30% of the children had sneezing, runny noses, and nasal obstructions. Continual rhinitis symptoms were evident in 8.7% of children.[18] However, it was unclear whether the rhinitis symptoms were caused by cold air or allergens or not. The prevalence of "wheezing even at rest" and "severe wheezing" was 2.8% and 1.4% respectively. Adoption of a Western lifestyle increases the risk of asthma, in line with the observed low prevalence of the condition in rural regions.[18] The hygienic Western lifestyle also increases the risk of other allergic diseases. However, the harsh climate at HA causes sneezing, and runny and blocked nose symptoms.[18] Despite the low oxygen saturation, harsh climate, and their poor general health, asthma and related allergic diseases were reported only in a few children. This suggests that the immune system acts in a non-allergic manner under non-hygienic conditions.[18,19] Asthma is more prevalent in those living at higher temperatures,[14] and the prevalence decreases with altitude.[14,18,20]

Climatic Features of HA Regions

Studies at HA are usually performed in the Alps, the Andes, and the Mount Everest-Nepal-Tibet regions. The concentrations of HDMs, fungal spores, and pollen are low in the Alps.[20] Air pollution is less than those at many European sea-level locations.[20] Air density and respiratory resistance are lower at HA, rendering expiration easy. Lung resistance decreases and the lungs can enlarge completely. All of these effects render breathing easier.[17]

The Alps enjoy abundant sunshine, allowing photosynthesis of vitamin D and effective regulation of the immune system. Thus, the severity of chronic allergic respiratory disease is potentially decreased.[17] A study performed in Davos (1560 m) on 16 children with allergic asthma showed that airway inflammation decreased at altitude. The FEV_1 provoked by AMP improved significantly and the peak flow variability was reduced after 1 month at HA. The levels of total serum eosinophils and eosinophil cationic protein (ECP) decreased but the levels of serum IgE did not.[21]

Eighteen patients with severe asthma who were resistant to inhaled steroids were examined in another study. Ten patients stayed in the Swiss Alps (at an altitude of 1560 m) for 10 weeks and 8 patients remained home at sea level. The quality-of-life, lung function, adenosine- and histamine-challenged bronchial hyperreactivities, induced sputum levels, and urine chemistry were evaluated before and after the stay at HA; the control group was also evaluated. The required drug doses did not change over the course of the study. All of the quality-of-life, lung function, adenosine- and histamine- challenged bronchial hyper-reactivity, and induced sputum, urinary eosinophil protein-X, urinary

leukotriene E4, and urinary 9a11b prostaglandin F2 levels differed in the study group before and after the stay at HA (all p values <0.05). The quality-of-life and the adenosine- and histamine-challenged bronchial hyperreactivities were higher in patients who stayed at HA than controls (all p values <0.05). Thus, 10 weeks in the Swiss Alps (1560 m) improved bronchial hyperreactivity even in severely asthmatic patients resistant to inhaled steroids.[6]

On the contrary, in the HA environments of some South American countries, especially in the Andes of Colombia[22] Peru,[23] and Venezuela,[24] the prevalence of mites is high. Differences in the species and concentrations of mites among various places may be attributable to climatic features, especially humidity. These regions are in the equatorial tropics. Moderate temperature, high humidity, and heavy rainfall are the principal climatic characters. These characteristics, which induce the growth of mites, are not encountered in the Rockies of North America or the Alps of Europe.[10]

In Andean cities at 2500-2800 m, high concentrations of various HDM species were detected, unlike what was found in other HA studies. Dermatophagoides pteronyssinus and D. farina were much more prevalent than other species in patients with allergic respiratory disease, and sensitized such patients to disease.[9,25,26] One study was performed in Quito (at over 2800 m in the Andes). A total of 361 patients with allergic respiratory disease were screened in terms of mite sensitization; 182 were sensitized to *Dermatophagoides*. Asthma, rhinitis, and the combination were present in 45.6%, 97.8%, and 43.4% of sensitized patients, respectively.[25] The humidity and HDM levels are high all year in the Andes. The highest allergen concentration is seen in April, the lowest in August and September. Asthma and rhinitis symptoms were highest in the months of greatest allergen concentrations.[9]

Another study in HA areas of Ecuador investigated the prevalence of sensitization to HDMs, and the prevalence of allergic respiratory diseases. Mattress samples was collected from Quito (above 2800 m), Cuenca (above 2500 m), and Guayaquil (above 2500 m) in the Andes. Twenty-one mite species were detected. Of skin prick tests detecting antigens of *D. pteronyssinus*, *D. farinae*, *B. tropicalis*, *L. destructor*, *T. putrescentiae*, *A. ovatus*, *A. siro*, and *G. domesticus*, 60.9%, 56.8%, 17.0%, 19.3%, 10.6%, 15.8%, 8.8%, and 11.0% of them were positive, respectively. Thus, HDMs are present all year long in home products even above 2500 m in Ecuador. Patients from Quito who were sensitized to mites were evaluated, and it was found that 7.6% of them had asthma only, 67.1% of them had rhinoconjunctivitis only, and 25.3% of them had allergic asthma and rhinoconjunctivitis.[10]

The climate of the Mount Everest region (including Nepal and Tibet) is dry, windy, and frosty. Solar radiation is abundant. Ventilation is difficult.[18] The average temperature is approximately 8°C and the day-night temperature gap is 15.7°C. There are over 3000 hours of sunshine annually. The annual rainfall is 500 mm, of which 85% falls at night. Night falls reduce the temperature and remove dust formed during the day. All of these climatic features reduce mite and mold concentrations, decreasing exposure of the population to aeroallergens,[4] in turn explaining the low prevalence of asthma and allergic rhinoconjunctivitis.

Another study evaluated allergic respiratory diseases in 2026 children living at over 3900 m on the north face of Mount Everest, Tibet. Wheezing and other asthma symptoms were evident in a few of children. Wheezing and severe wheezing were detected in 2.8% and 1.4%, respectively. Upper airway and rhinitis symptoms were more common, independent of both gender and place of residence. Over 30% of children had sneezing, runny noses, and nasal obstructions, but it was uncertain whether the rhinitis was caused by allergy.[4]

Pathogenic hypotheses relevant to HA

HA mitigates allergic respiratory disease even when the allergen concentration is high; the mechanism remains poorly understood. The hypoxia-induced reduction in T-lymphocyte numbers may reduce local airway inflammation,[3] or the high levels of suprarenal hormones and/or atrial natriuretic peptide[4,11] may exert protective effects.

The activities of Th1 and Th2 cells are regulated principally by T-regulatory cells (Tregs). Th2 cells play roles in allergenic airway inflammation via secretion of IL-4, IL-5, and IL-13. Th1 cells stimulate the immune system by secreting interferon gamma (IFN-γ) when autoimmune and microbial challenges develop. Tregs create peripheral tolerance to allergens and autoantigens by secreting IL-10 and transforming growth factor-β1 (TGF-β1) (these are suppressive cytokines), and by stimulating synthesis of the key FOXP3 transcription factor.[3]

One study investigating the effects of HA on airway inflammation and the cell-mediated immune system showed that 3 weeks of HA therapy significantly reduced the exhaled nitric oxide (NO) level, a determinant of local airway inflammation, in patients with intrinsic moderate

and severe asthma. Peripheral blood mononuclear cells (PBMCs) secreting IL-10 increased in numbers in 6 of 11 patients, but the numbers of PBMCs secreting TGF-β1 remained unchanged over 3 weeks at HA. Moreover, expression of CD80, a determinant of monocyte activation, decreased significantly. The number of CRTH-2-secreting T cells decreased but the number of regulatory T cells (Tregs) did not. The expression levels of FOXP3 and GATA-3 mRNAs within CD4+ T cells did not change, but the expression of mRNA encoding IL-13 expression was reduced. Secretion of IFN-γ mRNA by CD8+ T cells was reduced. Thus, HA reduced local airway inflammation. Moreover, monocytes exhibit tolerogenic phenotypes at HA. The CD80 expression level decreased from 5.02% to 3.32% at the end of 3 weeks of HA therapy ($p<0.01$).[3] Also, and importantly, the Treg/Th2 ratio increased, showing that HA was useful for endogenous control of allergen-triggered disease.[3]

After a stay above 3000 m, the plasma levels of the suprarenal hormones norepinephrine, epinephrine, and cortisol elevated. Cortisol secretion increased over the first 2 weeks at an altitude of 5000 m but later returned to the concentration associated with life at sea level.[11] Catecholamine secretion increased over the first few days at intermediate altitudes. The bronchial responsiveness of sensitized patients decreased at HA due to the increases in the concentrations of cortisol and catecholamines.[11]

Even a mild elevation in ANP level may lead to bronchial responsiveness to recover under hypoxic conditions.[11]

Conclusion

According to the literature, allergen concentration is different by degree of altitude and region's climate features so allergic rhinitis incidence and severity may be changeable. But in common wisdom, HA prevents bronchial hyperreactivity.

Conflict of Interest: No conflicts declared.

References

1. Accordini S, Corsico AG, Braggion M, et al.; Therapy and Health Economics Working Group of the European Community Respiratory Health Survey II. The socio-economic burden of asthma is substantial in Europe. Allergy 2008;63:116–24.
2. Pesce G, Bugiani M, Marcon A, et al. Geo-climatic heterogeneity in self-reported asthma, allergic rhinitis and chronic bronchitis in Italy. Sci Total Environ 2016;544:645–52.
3. Karagiannidis C, Hensey G, Rueckert B, et al. High-altitude climate therapy reduces local airway inflammation and modulates lymphocyte activation. Scand J Immunol 2006;63:304–10.
4. DromaY, Kunii O, Yangzom Y, Shan M, Pingzo L, Song P. Prevalence and severity of asthma and allergies in schoolchildren in Lhasa, Tibet. Clin Exp Allergy 2007;37:1326–33.
5. Schultze-Werninghaus G. Should asthma management include sojourns at high altitude? Chem Immunol Allergy 2006;91:16–29.
6. Grootendorst DC, Dahlen SE, Van Den Bos JW, et al. Benefits of high altitude allergen avoidance in atopic adolescents with moderate to severe asthma, over and above treatment with high dose inhaled steroids. Clin Exp Allergy 2001;31:400–8.
7. Charpin D, Birnbaum J, Haddi E, et al. Altitude and allergy to house-dust mites. A paradigm of the influence of environmental exposure on allergic sensitization. Am Rev Respir Dis 1991;143:983–6.
8. Grafetstätter C, Prossegger J, Braunschmid H, et al. No concentration decrease of house dust mite allergens with rising altitude in Alpine regions. Allergy Asthma Immunol Res 2016;8:312–8.
9. Valdiviesoa R, Iraloab V. Monthly variation of Dermatophagoides allergens and its influence on respiratory allergy in a high altitude environment (Quito, 2800 m a.s.l. in Andean Ecuador). Allergol Immunopathol (Madr) 2011:39:10–6.
10. Valdivieso R, Iraola V, Estupinan M, Fernandez-Caldas E. Sensitization and exposure to house dust and storage mites in high-altitude areas of Ecuador. Ann Allergy Asthma Immunol 2006;97:532–8.
11. Allegra L, CogoA, Legnani D, Diano PL, Fasano V, Negretto GG. High altitude exposure reduces bronchial responsiveness to hypo-osmolar aerosol in lowland asthmatics. Eur Respir J 1995;8:1842–6.
12. West JB. High altitude. In: Crystal RG, West JB, (eds). The lung. New York, NY: Raven Press; 1991. p. 2093–107.
13. Heath D, Williams DR. Man at high altitude. Edinburgh: Churchill Livingstone; 1981.
14. Weiland SK, Hüsing A, Strachan DP, Rzehak P, Pearce N; the ISAAC Phase One Study Group. Climate and the prevalence of symptoms of asthma, allergic rhinitis, and atopic eczema in children. Occup Environ Med 2004;61:609-15.
15. Barry PW, Mason NP, O'Callaghan C. Nasal mucociliary transport is impaired at altitude. Eur Respir J 1997;10:35–7.
16. Rodway GW, Windsor JS. Airway mucociliary function at high altitude. Wilderness Environ Med 2006;17:271–5.
17. Rijssenbeek-Nouwens LH, Fieten KB, O. Bron A, Hashimoto S, Bel EH, Weersink EJ. High-altitude treatment in atopic and nonatopic patients with severe asthma. Eur Respir J 2012;40:1374–80.
18. Yanzong, Nafstad P, Madsen C, Bjertness E. Childhood asthma under the north face of Mount Everest. Journal of Asthma 2006;43:393–8.
19. Shimomura Y, Mizoguchi E, Sugimoto K, Kibe R, Benno Y, Mizoguchi A, Bhan AK. Regulatory role of B-1 B cells in chronic colitis. Int Immunol 2008;20:729–37.

20. Vargas MH, Sienra-Monge JJ, Diaz-Mejia G, DeLeon-Gonzalez M. Asthma and geographical altitude: an inverse relationship in Mexico. J Asthma 1999;36:511–7.
21. van Velzen E, van den Bos JW, Benckhuijsen JAW, van Essel T, de Bruijn R, Aalbers R. Effect of allergen avoidance at high altitude on direct and indirect bronchial hyperresponsiveness and markers of inflammation in children with allergic asthma. Thorax 1996;51:582–4.
22. Charlet LD, Mulla MS, Sanchez-Medina M. Domestic Acari of Colombia: abundance of the European house dust mite, Dermatophagoides pteronyssinus (Acari: Pyroglyphidae), in homes in Bogota. J Med Entomol 1997;13:709–12.
23. Caceres I, Fain A. Notes on the mite fauna of the house dust of homes in Peru. Bull Ann Soc Belge d' Entomol 1978;114:301–3.
24. Rangel A, Salmen S, Munoz J, Garcia F, Hernandez M. Dermatophagoides sp. and IgE anti-D. pteronyssinus and D. farinae detection in a Venezuelan community at more than 2000 m above the sea level. Clin Exp Allergy 198;28:1100 –3.
25. Valdivieso R, Estupinan M, Acosta ME. Asthma and its relation with Dermatophagoides pteronyssinus and Dermatophagoides farinae in Andean altitudes (Quito, Ecuador). J Invest Allergol Clin Immunol 1997;7:46–50.
26. Valdivieso R, Acosta ME, Estupinan M. Dust mites but not grass pollen are important sensitizers in asthmatic children in the Ecuadorian Andes. J Invest Allergol Clin Immunol 1999;9:288–92.

Please cite this article as: Oğhan F, Erdim İ. Associations among high altitude, allergic rhinitis, and bronchial hyperreactivity. ENT Updates 2017;7(1): 47–52.

Case Report

ENT Updates 2017;7(1):53–56
doi:10.2399/jmu.2017001007

ENT updates
www.entupdates.org

Giant angiomatous choanal polyp originating from the middle turbinate: a case report

Aleksandar Perić[1], Aleksandar Jovanovski[2], Biserka Vukomanović Đurđević[3]

[1]*Department of Otorhinolaryngology, Faculty of Medicine, Military Medical Academy, Belgrade, Serbia*
[2]*Institute for Radiology, Faculty of Medicine, Military Medical Academy, Belgrade, Serbia*
[3]*Institute for Pathology, Faculty of Medicine, Military Medical Academy, Belgrade, Serbia*

Abstract

Choanal polyps (CPs) can be defined as histologically benign, solitary, soft tissue lesions extending towards the junction between the nasal cavity and the nasopharynx through the choana. They usually originate from the maxillary sinus. In this report, we present an unusual case of a giant angiomatous CP arising from the inferior part of the middle turbinate that completely filled the nasopharynx. A 24-year-old man presented with five-year history of left-sided nasal obstruction, nasal discharge and mild-to-moderate epistaxis. The diagnosis was supported by contrast-enhanced computed tomography scan of the paranasal sinuses with angiography and confirmed by histopathological examination. The lesion was removed by combined endoscopic and transoral approach. In addition, we discuss the pathogenesis, clinical, radiological and pathological characteristics of angiomatous CPs, and their differential diagnosis.

Keywords: High altitude, allergic rhinitis, bronchial hyperreactivity.

Özet: Orta konkadan kaynaklanan dev anjiyomatöz koanal polip: Olgu sunumu

Koanal polip (KP) histolojik olarak benign, nazal kavite ile nazofarenks arası birleşme noktasına koana yoluyla uzanan, soliter yumuşak doku lezyonu olarak tanımlanır. Genellikle maksiller sinüsten köken alır. Bu olgu sunumunda orta konkanın alt bölümünden çıkan ve nazofarenksi tamamen dolduran olağandışı bir dev anjiyomatöz KP'yi sunmaktayız. Burnun sol tarafında tıkanma, burun akıntısı ve hafif-orta derecede burun kanaması üzerine 5 yıllık öyküsü olan 24 yaşındaki erkek hasta kliniğimize başvurdu. Tanı, paranazal sinüslerin kontrastlı bilgisayarlı tomografi taramasıyla kombine anjiyografiyle desteklendi ve histopatolojik incelemeyle doğrulandı. Lezyon kombine endoskopik ve transoral yaklaşımla çıkartıldı. Sunumumuzda ayrıca, anjiyomatöz KP'lerin patogenezini, klinik, radyolojik ve patolojik özelliklerini ve ayırıcı tanılarını tartışmaktayız.

Anahtar sözcükler: Epistaksis, nazal polipler, nazal cerrahi prosedür, konka.

Choanal polyps (CPs) are solitary, benign soft tissue lesions which originate from the nasal cavity or paranasal sinuses and extend into the nasopharynx through the choana. Although CPs most commonly originate from the maxillary antrum, named antrochoanal polyps (ACPs), other sites of origin may be sphenoid, ethmoid, nasal septum, cribriform plate, inferior and middle turbinate.[1] CP of middle turbinate is extremely rare and, according to the English literature, there are only six cases reported previously.[1–5] Angiomatous nasal polyps are rare subtypes of CPs, characterized by extensive vascular proliferation and ectasia.[6] As well as other CPs, angiomatous nasal polyps usually originate from maxillary sinus. We present an unusual case of a giant angiomatous polyp arising from the inferior part of the middle turbinate and, to our knowledge, this is the first such case reported.

Case Report

A 24-year-old male patient presented with a five-year history of bilateral nasal obstruction, snoring, left-sided nasal discharge and recurrent mild-to-moderate nasal bleeding. He had no significant past medical history. Anterior rhinoscopy and endoscopic examination identified a big,

Correspondence: Aleksandar Perić, MD, PhD. Department of Otorhinolaryngology, Faculty of Medicine, Military Medical Academy, Crnotravska 17, 11000 Belgrade, Serbia.
e-mail: alexneta@sezampro.rs

Received: November 19, 2016; **Accepted:** December 27, 2016

Online available at:
www.entupdates.org
doi:10.2399/jmu.2017001007
QR code:

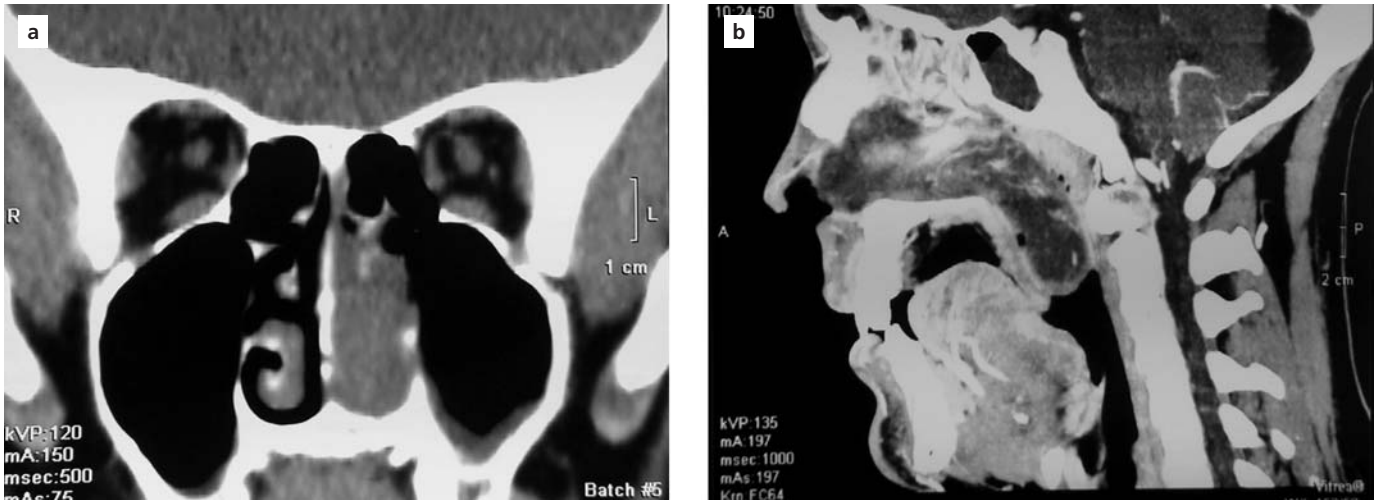


Fig. 1. (**a**) Coronal CT scan shows soft tissue lesion arising from the inferior part of the left middle turbinate extending to the choana. Note that the left maxillary and ethmoid sinus is clear. (**b**) Sagittal contrast-enhanced CT scan shows a giant soft tissue mass involving nasal cavity and extending to the nasopharynx which is completely filled by lesion. Note the presence of small feeding vessels and the absence of rich, irregular vascular supply characterized for angiofibroma.

reddish-grey polypoid mass originating from the inferior portion of the left middle concha, obliterating the left nasal cavity and extending posteriorly to the choana. Posterior rhinoscopy revealed a huge polypoid mass which completely filled the nasopharynx. Endoscopic finding of the right nasal cavity was normal. Computed tomography (CT) of the paranasal sinuses demonstrated a soft-tissue mass completely filling the left nasal cavity and nasopharynx. However, all paranasal sinuses were clear (Fig. 1a). As we supposed to diagnose an angiofibroma with extranasopharyngeal origin, we performed a contrast-enhanced CT scan with angiography. We found a vessel-like marked enhancement on contrast-enhanced CT scans of the mass in both early and delayed phase scans. These findings suggested that vessel-like marked enhancement is attributed to dilated neovascularization. On angiography, we found only a few demonstrable feeding vessels, without significant enlargement, and small areas of neovascularity are also seen within the mass in the late capillary-venous phase (Fig. 1b). So, CT angiography did not confirm a vascular lesion, and the diagnosis of angiofibroma was excluded.

At surgery, the nasal part of the lesion was debulked endoscopically. The nasopharyngeal part was removed transorally. This was followed by profuse bleeding, which was controlled by anterior nasal packing. The gross appearance of the excised mass demonstrated reddish-grey, soft, translucent areas, alternating with firm, black necrotic areas which were associated with a strong, offensive odor. The nasal part of the polyp with stalk arising from the anteroinferior part of the left middle turbinate was 5.5 cm in length, with maximum diameter of 1.4 cm. The dimension of nasopharyngeal part of the mass was 4.5×4.2×2.6 cm (Fig. 2). A nasal pack consisting of cotton gauze with ointment was removed on the fourth postoperative day. Histopathological analysis confirmed the diagnosis of an angiomatous CP. In the nasal part, the lesion was covered with ciliated pseudostratified respiratory epithelium. The stroma was strongly infiltrated by plasma cells, neutrophils and macrophages (Fig. 3a). In the nasopharyngeal part of the polyp, the metaplasia of the respiratory epithelium in stratified epithelium of the transitional type was found. A

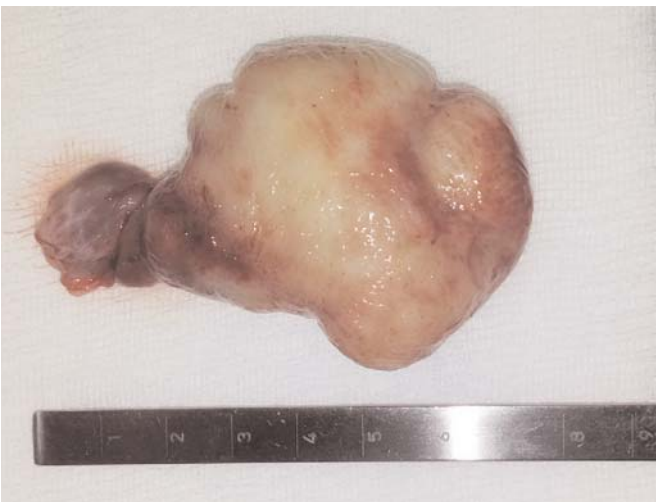


Fig. 2. The nasopharyngeal part of mass, excised transorally.

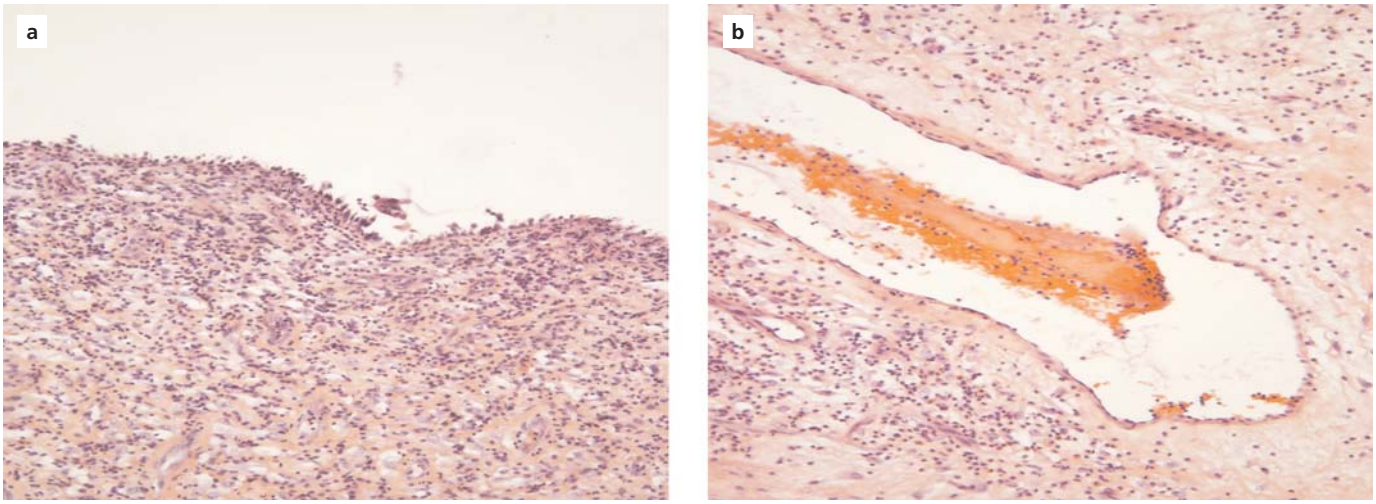


Fig. 3. (**a**) Photomicrograph of an angiomatous CP shows pseudostratified respiratory ciliated epithelium and strong plasma cell and macrophage infiltration of the polyp stroma. (**b**) Large, dilated, thin-walled capillary-like blood vessels in the polyp stroma. (Hematoxylin & Eosin, magnification ×100).

small number of goblet cells and a paucity of submucous glands were also seen in all sections of the excised mass. The examination revealed large, dilated, but thin-walled capillary-like blood vessels in the polyp stroma (Fig. 3b). The postoperative course of the patient was uneventful and 12 months of follow-up showed no recurrence.

Discussion

The etiology of CPs, first described by Killian in 1906, remains unclear. However, chronic inflammation is considered to play a role in the etiology of CPs.[7] CPs of the middle turbinate are extremely rare and there have been only six reported in the literature, of which one arose from the inferior, three arose from the medial and two arose from the posterior region.[1–5] One of the main characteristics of CPs is the tendency for rapid growth, resulting in their impressive dimensions. This could be due to the fact that expressions of basic fibroblast growth factor (bFGF) and transforming growth factor beta (TGF-β) are significantly higher in tissue of CPs than in bilateral nasal polyposis and, especially, in healthy nasal mucosa.[4] Angiomatous nasal polyps are an uncommon subtype of CPs, which are characterized by large numbers of dilated capillary spaces, with strong inflammatory infiltrates and abundant extracellular fibrin.[6] Batsakis and Sneige[8] suggests that angiomatous polyp most often develop secondary to change in a CP because of vascular compromise in four sites of the upper airway: the ostium of the paranasal sinus, the posterior end of the inferior turbinate, the choana and the nasopharynx. It is hypothesized that the initial vascular dilatation, stasis, edema, and infarction occur in these sites following compression of blood vessels. Reactive and repetitive changes lead to neovascularization and fibrosis.[8] In the case of our patient, instead of the paranasal sinus ostium, the first site of vascular compromise could be the inferior portion of the middle turbinate.

On the other hand, Sayed and Abu-Dief[9] suggest that angiomatous polyp is a distinct type of nasal polyp and not a derivate of the ordinary CP. They found that only angiomatous variant of nasal polyps presents with epistaxis. One of the main hystological characteristics of angiomatous nasal polyps is strong plasma cell infiltration of the polyp stroma. This finding could be linked with angiogenesis and vascular endothelial proliferation within the polyp stroma suggesting that significantly increased number of plasma cells may be the main cause of histological changes found in this variant of inflammatory nasal polyps. Blood flow in ordinary CPs is decreased with smaller number of blood vessels compared to with healthy nasal mucosa. The stroma of angiomatous polyps have large numbers of dilated capillary spaces and numerous large hemosiderin-laden macrophages suggesting the presence of two parallel processes: blood extravasation and stromal tissue reparation.[6,9]

Clinically and radiologically, angiomatous CPs may be confused with vascular neoplasms, including nasopharyngeal angiofibroma. The early identification of cases similar to angiofibroma is of crucial importance. This finding can have important implications for pre-surgical and surgical

management. A contrast-enhanced CT scan of the paranasal sinuses with angiography should be used to differentiate between nasopharyngeal angiofibroma and angiomatous CP. Regarding our case, it is particularly important in cases of angiofibroma with extranasopharyngeal primary localization. This is the rare form of angiofibroma originating from the paranasal sinuses, inferior and middle turbinate, and from the nasal septum.[10] On angiography, angiomatous CPs have only a few demonstrable feeding vessels compared to the rich irregular vascular supply of a nasopharyngeal angiofibroma. This is explained by the fact that angiomatous CPs do not have a normal arborizing vascularity pattern but rather irregular arrangements of dilated capillary-type vessels and newly endothelialized spaces with endoluminal thrombosis.[6] Thus, preoperative embolization is not necessary for management of angiomatous CPs. In contrast, the resection of a nasopharyngeal angiofibroma requires preoperative embolization due to the possible severe intraoperative bleeding. In patients with angiomatous CP, there was no finding on paranasal CT scan indicating bony destruction, which is a frequent radiological characteristic of angiofibroma. So, the excision of an angiomatous CPs, similarly to ordinary CPs, is a relatively simple surgical procedure and polyp recurrence is relatively rare.

Conclusion

We present an extremely rare case of an angiomatous CP originating from the middle nasal concha with its clinical, radiological and pathological characteristics. Angiomatous CPs should be considered as a subtype of CPs with unilateral nasal obstruction and epistaxis as main symptoms. Despite the benign nature of these lesions, they may be confused with neoplastic processes and vascular malformations. The main differential diagnostic problem is nasopharyngeal angiofibroma which can be excluded by contrast-enhanced CT scan with angiography.

Conflict of Interest: No conflicts declared.

References

1. İla K, Topdağ M, Öztürk M, İşeri M, Aydın Ö, Keskin G. Retrospective analysis of surgical treatment of choanal polyps. Kulak Burun Bogaz Ihtis Derg 2015;25:144–51.
2. Prasad U, Sagar PC, Shahul Mameed OAN. Choanal polyp. J Laryngol Otol 1970;85:951–4.
3. Özkan C, Duce MN, Görür K. Choanal polyp originating from the middle turbinate. Eur Arch Otorhinolaryngol 2004;261:184–6.
4. Özkırış M. Choanal polyp originating from the middle turbinate: a case report. Acıbadem Üniversitesi Sağlık Bilimleri Dergisi 2012;3:187–9.
5. Kim KS. Choanal polyp originating from the middle turbinate. Otolaryngol Head Neck Surg 2013;148:525–6.
6. Ceylan A, Asal K, Çelenk F, Uslu S. An angiomatous nasal polyp: a very rare variant of sinochoanal nasal polyps. B-ENT 2007;3:145–7.
7. Lopatin A, Bykova V, Piskunov G. Choanal polyps: one entity, one surgical approach? Rhinology 1997;35:79–83.
8. Batsakis JG, Sneige N. Choanal and angiomatous polyps of the sinonasal tract. Ann Otol Rhinol Laryngol 1992;101:623–5.
9. Sayed RH, Abu-Dief EE. Does antrochoanal polyp present with epistaxis? J Laryngol Otol 2010;124:505–9.
10. Perić A, Sotirović J, Cerović S, Živić L. Immunohistochemistry in diagnosis of extranasopharyngeal angiofibroma originating from nasal cavity: case presentation and review of the literature. Acta Medica (Hradec Kralove) 2013;56:133–41.

Please cite this article as: Perić A, Jovanovski A, Vukomanović Đurđević B. Associations among high altitude, allergic rhinitis, and bronchial hyperreactivity. ENT Updates 2017;7(1): 53–56.