Volume 15 / Number 3-4 / 2021

ISSN 1840-2291

HealthMED

Journal of Society for development in new net environment in B&H

ISSN 1840-1503

9 771840 150002

Volume 15 / Number 3-4 / 2021

HealthMED

Journal of Society for development in new net environment in B&H

Address
Bolnicka bb, 71 000 Sarajevo,
Bosnia and Herzegovina.

Editorial Board
e-mail: healthmedjournal@gmail.com
web page: http://www.healthmed.ba

Published by DRUNPP, Sarajevo

Volume 15 Number 3-4, 2021

ISSN 1840-2291 e-ISSN 1986-8103

HealthMED Journal is covered or selected for coverage in the following:

- EBSCO Academic Search Complete
- EBSCO Academic Search Premier,
- EMBASE,
- SJR Scopus,
- Index Copernicus,
- Universal Impact Factor: Impact Factor is 1.0312 (UIF 2012)
- Electronic Social and Science Citation Index (ESSCI),
- Direct Science,
- ISI - institute of science index,
- SCImago Journal and Country Rank,
- ISC Master Journal List,
- Genamics Journal Seek,
- World Cat,
- Research Gate,
- CIRRIE,
- getCITED and etc,
- Academic Resource Index /Research Bib.

Sadržaj / Table of Contents

Practical importance of knowing the morphological characteristics of the accessory mental foramina (AMF) of the human mandibles of Bosnia and Herzegovina population

Alma Voljevica[1], Amna Pleho – Kapic[2], Amra Catovic[3], Elvira Talovic[1]

[1] Department of Anatomy, Medical Faculty, University in Sarajevo, Sarajevo, Bosnia and Herzegovina,
[2] Department of Pathophysiology, Medical Faculty, University in Sarajevo, Sarajevo, Bosnia and Herzegovina,
[3] Department of Hygiene, Medical Faculty, University in Sarajevo, Sarajevo, Bosnia and Herzegovina.

Abstract

Objectives: Since numerous surgical procedures in oral and maxillofacial surgery as well as several aspects of dental practice involve the mental region, the knowledge of its anatomical variations is essential for the clinician. The aim of the study was to research the incidence and morphometric analysis of accessory mental foramina (AMF) in the dry human mandibles of Bosnia and Herzegovina population.

Methods: Our study was conducted on 250 adult dry human mandibles, known sex and age, from osteological collection of Department of Anatomy, Faculty of Medicine, University of Sarajevo. The location, shape and the presence of the accessory mental foramen were researced by visual examination.

The dimensions of AMF and its distance from symphysis menti, the posterior border of ramus of mandible, from lower border of the body of mandible and distance between MF and AMF were measured by using a digital vernier caliper.

Results: In our study, AMF were present in 2.8% mandibles (unilateral – 2.4% (1.6% - left, 0.8% - right) and bilateral 0.4%). The most common position was below the second premolar (42.85%). The AMF were round in shape in most of the mandibles (83.33%) and was often located either superomedial or inferolateral to MF. The mean vertical diameter of AMF was 1.50 ± 0.63 mm and horizontal diameter 1.27 ± 0.40 mm.

The AMF were situated at an average distance of 2.84 mm from the MF and at an average distance of 24.40 from symphysis menti. The mean distance of AMF from the lower border of the body of the mandible was 12.67 mm. The AMF were positioned at an average distance of 65.35 from the posterior border of ramus of mandible

Conclusion: The knowledge of the presence of AMF and its dimensions would enable the clinicians to do mandibular procedures carefully and avoid injury to the branches of mental nerve that may be passing through it.

Key words: accessory mental foramen (AMF), accessory mental nerve, dental implant, mandible

Introduction

The mental foramen (MF) is a bilateral small opening located on the anterolateral aspect of the mandible and transmits the mental nerve, a branch of the inferior alveolar nerve, the corresponding artery, and vein. It is round or oval and is usually located either between the roots of the first and second mandibular premolars or apical to the second premolar. The mental nerve represents one of the terminal branches of the mandibular nerve and divides into three branches supplying the lower lip, cheeks, chin, and the vestibular gingival of mandibular incisors (1). Anatomical variations in the position of MF are very rare but variations in the number of mental foramina have been reported with more than one MF present on one or both sides of mandible. These additional foramina located in the vicinity of MF are termed as accessory mental foramina (AMF) (2).

AMF are reported to be a rare anatomical variation and has been found to transmit myelinated nerves, one or more arterioles and venules. The accessory mental nerve traversing the AMF is considered to be a branch of the inferior alveo-

lar nerve and is distributed to the mucous membranes, the skin of the corner of the mouth, and the median labial region (3). The AMF is an important anatomical structure in local anesthesia and surgical procedures involving this area, such as genioplasty, mandibular rehabilitation after trauma, bone harvesting from the chin, root resection of mandibular premolars, and particularly placement of dental implants (4,5,6,7).

The incidence of permanent sensory disturbance to the lower lip after dental implant surgery in the MF area is reported to range from 7 to 10% (3). Sensation disturbance and severe pain may result if accessory mental nerve or mental nerve is entirely or partially damaged, and may lead to complications with significant impact on patients' quality of life (1).

Although AMF have been reported earlier, literature regarding its incidence and topography is sparse. The purpose of the present study is to analyze the incidence and topography of AMF in dry human mandibles of Bosnia and Herzegovina population.

Materials and methods

Study was carried out on 250 (165 male, 85 female) adult dry mandible of Bosnian and Herzegovina population in the Department of Anatomy, Faculty of Medicine, University of Sarajevo. The bones without pathological deformities were excluded from the study.

The number, shape and the positions of the AMF were determined by a visual examination. The positions of the mental foramens were measured with respect to the teeth, for which we followed this classification (Figure 1).

I. The accessory mental foramen is projected at the level of the first premolar
II. The accessory mental foramen is projected between the first and second premolars
III. The mental foramen is projected at the level of the second premolar
IV. The mental foramen is located in between the second premolar and first molar
V. The mental foramen is located at the level of the first molar

Morphometric analysis

We measured the distance of AMF (in mm) from various landmarks including symphysis menti, alveolar crest, posterior border of the ramus of mandible, lower border of mandible and distance between MF and AMF with digital vernier caliper and calculated the size of accessory mental foramen (Figure 2).

1. A: white arrow - Transverse and vertical diameters of AMF
2. B: distance between MF and AMF,
3. C: distance of AMF from symphysis menti,
4. D: distance of AMF from lower border of the body of mandible,
5. E: distance of AMF from the posterior border of ramus of mandible.

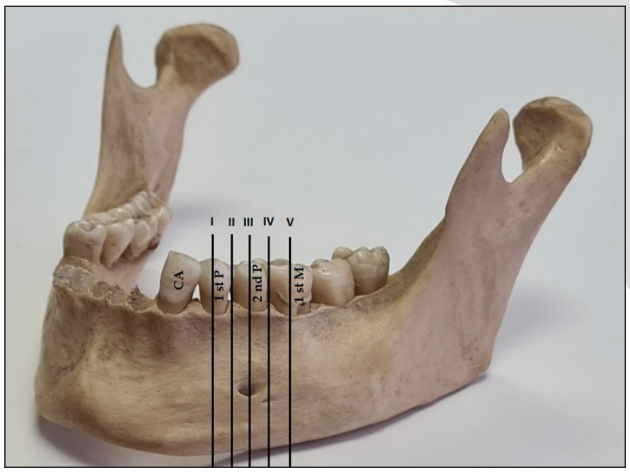


Figure 1. Location of the accessory mental foramen compared to the teeth (I – V): CA – canine, 1st P - first premolar, 2nd P – second premolar, 1st M – the first molar

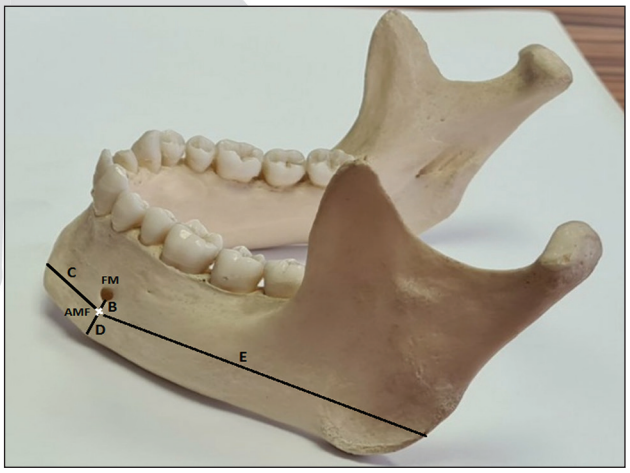


Figure 2. Position of accessory mental foramen and its size calculated by transverse and vertical measurements of mandible in relation to borders (B, C, D, E)

The measurement of all parameters was performed on the both sides.

Statistical analysis

Data were analyzed using SPSS version 17. Location and size of the accessory mental foramen was determined by the minimum and maximum value, mean and standard deviation. Testing the differences in the position and dimensions of accessory mental foramen between men and women was performed using the Mann – Whitney test. Chi-square method was used to examine the difference in the location of the accessory mental foramen compared to the teeth between left and right side. As well as we analyzed differences in those parameters between male and female. All statistical results with $p<0.005$ were considered statistically significant.

Results

Of the 250 (500 sides) dry human mandibles studied, AMF were present in 7 mandibles (2.8%). Unilateral AMF were noted in 6 cases (2.4%) (4 - left side (1.6%) and 2 - right side (0.8%) and bilateral in 1 case (0.4%).

In our study, AMF in each mandible showed a variable location, namely, below first premolar (14.29%), between premolars (14.29%), below second premolar (42.85%), between second premolar and first molar (28.57%), below first molar (0%) (Table 1) and (Figure 3).

Table 1. Position of accessory mental foramen (n=7)

Position of AMF	n (%)
Below first premolar	1 (14.29%)
Between first and second premolar	1 (14.29%)
Below second premolar	3 (42.85%)
Between second premolar and first molar	2 (28.57%)
Below first molar	0 (0%)

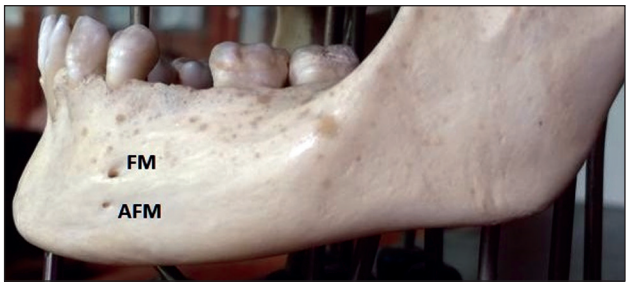


Figure 3. Typical location of the accessory mental foramen (AFM) in the area of the second premolar

The most common position of AMF was below the second premolar on the anterolateral surface of the mandible. The AMF were round in shape in most of the mandibles (83.33%) and elliptical in the rest. Most of the AMF were located either superomedial (28.57) or inferolateral (42.85%) in relation to MF (Table 2).

Table 2. Relation of accessory mental foramen to mental foramen (n=7)

Position of AMF	n (%)
Superior	1 (14.29%)
Superomedial	2 (28.57%)
Inferior	1 (14.29%)
Inferolateral	3 (42.85%)

The mean vertical diameter of AMF was 1.50 ± 0.63 mm and horizontal diameter 1.27 ± 0.40 mm. There was no statistically significant difference between the female and male patients regarding the diameters of AMF ($P > 0.05$, Table 3)

The AMF were studied at an average distance of 2.84 mm from the MF and at an average distance of 24.40 from symphysis menti. The mean distance of AMF from the lower border of the body of the mandible was 12.67 mm. The AMF were positioned at an average distance of 65.35 from the posterior border of ramus of mandible (Table 4).

Discussion

In dental practice, anatomical variations in the mandible can cause surgical complications if not properly identified (8). The mental foramen is incomplete until the 12th gestational week, when the mental nerve separates into several fasciculi at that site. It has been suggested that separation of the mental nerve earlier than the formation of the

Table 3. Diameters of AMF and MF – AMF distance

	Female	Male	Total	P value*
AMF diameter (mm)				
Vertical	1.50±0.59	1.50±0.51	1.50±0.63	0.524
Horizontal	1.27±0.37	1.27±0.45	1.27±0.40	0.285
MF – AMF distance (mm)	2.94±2.40	2.60±1.35	2.84±2.14	1.127

**t- test. Data are given as mean ± standard deviation, AMF - accessory mental foramen; MF – mental foramen*

Table 4. Distance of accessory mental foramen from various bony landmarks

Measurement	Mean ± SD	Minimum	Maximum
From symphysis menti	24.40±6.53	4.92	43.87
From lower border of body of mandible	12.67±2.62	7.07	18.27
From posterior border of ramus of mandible	65.35±5.98	51.4	79.30

SD – standard deviation

mental foramen could be a reason for the formation of the accessory mental foramen (9).

The incidence of accessory mental foramen varies between ethnic groups, and is reported as follows: 2.6% in French; 1.4% in American Whites; 5.7% in American Blacks; 3.3% in Greeks; 1.5% in Russians; 3.0% in Hungarians; 9.7% in Melanesians; and 3.6% in Egyptians (2). Studies performed in a Japanese population showed that accessory mental foramen is less rare, with a prevalence ranging from 6.7 to 12.5% in Japan (10). In a previous study of ours, we found a unilateral accessory mental foramen among 7 dry mandibles (2.8%). These reports reveal that non-Caucasians may have a higher incidence of accessory mental foramen than Caucasians.

In the present study, AMF were located more on the right side than on the left side. Singh and Srivastav found 8% AMF on the left side and 5% on the right side. Udhaya *et al*. found 3.33% AMFs on the left side and 2.22% on right side (11,12). Previous studies have shown that bilateral AMF is an extremely rare finding and has been reported only in 0.53% of total population (13). Contrary to that, bilateral occurrence of AMF has been reported in 2% of South Indian population (14). The present study revealed 0.4 % bilateral AMF.

Previous studies have reported that AMF are commonly located below the first molar tooth (12,15). In the present study, though it is present in various locations, in 48%, it was present below the second premolar. It has been reported earlier that most of the AMF were located in the distal region of MF and very few in the mesial region. Mostly, AMF were found to be located inferior to the MF (9,16). Sekerci and Sisman reported that, in two cases, AMF were located posterior to MF (17). The location of AMF in relation to MF might influence the planning of rehabilitating treatment since its presence would interfere with the dental implant procedures (18). In the present study, most of the AMF were either inferolateral (42.85%) or superomedial (28.57%) to MF.

Studies have reported MF diameters ranging from 2.38 mm to 2.64 mm (19) while AMF diameters varied between 0.74 mm and 0.89 mm (10). The AMF is generally smaller than the MF. Our results are consistent with this finding. We found no significant difference between the females and males regarding the size of the AMF. Our results show similarity with the results of Kalender etal (20).

In the literature, MF and AMF distance was reported between 2.5 mm and 6.3 mm (20,21,22). Similarly, the mean distance between MF and AMF was 2.85 mm without significant difference between the female and male patients in our study. The distance between AMF and MF is crucial while planning an implant placement in mandibular premolar region, to prevent injury to the neurovascular bundle exiting AMF, it has been recommended to consider a 2 mm distance between MF and the dental implant (23). We thus recommend careful exploration between 2 and 3 mm from MF

and determination of presence or absence of an AMF during dental implantation procedures.

Position of AMF from symphysis menti was 24.40 mm in present study as compared to 28.6 mm found by Suman P et al. (24). The distance of AMF from posterior border of ramus as well as from base of mandible was almost equivalent to that found by Suman P et al. (24). The distance from alveolar crest was less as compared to result of Suman P et al (24). These measurements provide an alternative way to locate AMF on the body of the mandible.

Presurgical imaging of AMF is recommended to enable accurate planning, prevent iatrogenic injury, and contribute to successful treatment. Three-dimensional evaluation with computed tomography (CT) and cone beam CT could demonstrate the presence and course of AMF. During various surgical procedures done on the mandible in the premolar and molar area such as genioplasty, bone harvesting from chin, root resection of mandibular premolars, mandibular rehabilitation after trauma, dental implant surgeries, and the presence of accessory mental nerve should be considered, to achieve a profound local anesthesia and to avoid neurovascular damage (17). Dental surgeons should bear in mind the possibility of an accessory mental nerve from AMF during apical curettage of mandibular premolars, filling procedures, fixation of bone fractures, surgical removal of roots, teeth, cysts, and tumors, and mandibular anterior segmental osteotomies (11,25).

Conclusion

Study of the incidence of accessory mental foramen is very important to localize the important neurovascular bundle passing through the mental foramen and accessory mental foramen. Knowledge of accessory mental foramen is important during anesthetics and surgical procedures involving mandibular region. Preoperative detection of AMF may reduce the rates of postoperative pain and paraesthesia in surgical procedures.

References

1. *Greenstein G, Tarnow D. The mental foramen and nerve: clinical and anatomical factors related to dental implant placement: a literature review. J Periodontol. 2006; 77: 1933-43.*
2. *Sawyer DR, Kiely ML, Pyle MA. The frequency of accessory mental foramina in four ethnic groups. Arch Oral Biol 1998; 43: 41720*
3. *Carter RB, Keen EN. The intramandibular course of the inferior alveolar nerve. J Anat 1971; 108: 43340.*
4. *Jacobs R, Mraiwa N, vanSteenberghe D, Gijbels F, Quirynen M. Appearance, location, course, and morphology of the mandibular incisive canal: An assessment on spiral CT scan. Dentomaxillofac Radiol 2002; 31: 322-7.*
5. *Jacobs R, Lambrichts I, Liang X, Martens W, Mraiwa N, Adriaensens P, et al. Neurovascularization of the anterior jaw bones revisited using high-resolution magnetic resonance imaging. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2007; 103: 683-93.*
6. *Pommer B, Tepper G, Gahleitner A, Zechner W, Watzek G. New safety margins for chin bone harvesting based on the course of the mandibular incisive canal in CT. Clin Oral Implants Res 2008; 19: 1312-6.*
7. *Mraiwa N, Jacobs R, Moerman P, Lambrichts I, van Steenberghe D, Quirynen M. Presence and course of the incisive canal in the human mandibular interforaminal region: Two-dimensional imaging versus anatomical observations. Surg Radiol Anat 2003; 25: 416-23.*
8. *Misch CE, Crawford EA. Predictable mandibular nerve location: A clinical zone of safety. Int J Oral Implantol 1990; 7: 37-40.*
9. *Naitoh M, Hiraiwa Y, Aimiya H, Gotoh K, Ariji E. Accessory mental foramen assessment using cone-beam computed tomography. Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 2009; 107: 289–294.*
10. *Toh H, Kodama J, Yanagisako M, Ohmori T. Anatomical study of the accessory mental foramen and the distribution of its nerve. Okajimas Folia Anat Jpn. 1992; 69: 85–87.*
11. *Udhaya K, Saraladevi KV, Sridhar J. The morphometric analysis of the mental foramen in adult dry human mandibles: A study on the South Indian population. J Clin Diagn Res 2013; 7: 1547-51.*
12. *Singh R, Srivastav AK. Study of position, shape, Size and incidence of mental foramen and accessory mental foramen in Indian adult human skulls. Int J Morphol 2010; 28: 1141-6.*

13. *Oliveira-Santos C, Souza PH, De Azambuja Berti-Couto S, Stinkens L, Moyaert K, Van Assche N, et al. Characterisation of additional mental foramina through cone beam computed tomography. J Oral Rehabil 2011; 38: 595-600.*

14. *Katikireddy RS, Setty SN. Incidence of accessory mental foramen in South Indian adult dried mandibles. Int J Anat Res 2016; 4: 1916-8.*

15. *Cağirankaya LB, Kansu H. An accessory mental foramen: A case report. J Contemp Dent Pract 2008; 9: 98-104.*

16. *Katakami K, Mishima A, Shiozaki K, Shimoda S, Hamada Y, Kobayashi K, et al. Characteristics of accessory mental foramina observed on limited cone-beam computed tomography images. J Endod 2008; 34: 1441-5.*

17. *Sekerci AE, Sisman Y. Bilateral accessory mental foramina and canals: Report of an extremely rare anatomical variation. J Dent Implant 2014; 4: 101-4.*

18. *Torres MG, Valverde Lde F, Vidal MT, Crusoé-Rebello IM. Accessory mental foramen: A rare anatomical variation detected by cone-beam computed tomography. Imaging Sci Dent 2015; 45: 61-5.*

19. *de Freitas V, Madeira MC, Toledo Filho JL, Chagas CF. Absence of the mental foramen in dry human mandibles. Acta Anat (Basel) 1979; 104: 3535.*

20. *Kalender A, Orhan K, Aksoy U. Evaluation of the mental foramen and accessory mental foramen in Turkish patients using conebeam computed tomography images reconstructed from a volumetric rendering program. Clin Anat 2012; 25: 58492.*

21. *Pancer B, GaraicoaPazmiño C, Bashutski JD. Accessory mandibular foramen during dental implant placement: Case report and review of literature. Implant Dent 2014; 23: 11624.*

22. *Goregen M, Miloglu O, Ersoy I, Bayrakdar IS, Akgul HM. The assessment of accessory mental foramina using conebeam computed tomography. Turk J Med Sci 2013; 43: 47983.*

23. *Khojastepour L, Mirbeigi S, Mirhadi S, Safaee A. Location of mental foramen in a selected Iranian population: A CBCT assessment. Iran Endod J 2015; 10: 117-21.*

24. *Suman P, Singh S, Mahato RK. Accessory Mental Foramen-An Anatomical Variation Mental Foramen in Human Mandibles. National Journal of Basic Medical Sciences 2017; 7(4): 209-214.*

25. *Voljevica A, Talović E, Hasanović A. Morphological and morphometric analysis of the shape, position, number and size of mental foramen on human mandibles. Acta Med Acad 2015; 44: 31-8.*

Corresponding Author:
Alma Voljevica,
Institute of Anatomy „Prof. dr Hajrudin Hadžiselimović”,
Faculty of Medicine,
University of Sarajevo,
Sarajevo,
Bosnia and Herzegovina,
E-mail: alma.voljevica@mf.unsa.ba

The incidence of positive eosinophils in nasal mucosa swab in kindergarden children in Tuzla Canton

Fejzo Dzafic[1], Maida Mulic[2], Samra Osmancevic[3], Selma Azabagic[2], Amer Custovic[4], Almira Cosickic[5], Adis Imsirovic[6]

[1] Polyclinic for Laboratory Diagnostics, University Clinical Center Tuzla, Tuzla, Bosnia and Herzegovina,
[2] Institute of Public Health in Tuzla Canton, Tuzla, Bosnia and Herzegovina,
[3] Quality Control Department, University Clinical Center Tuzla, Tuzla, Bosnia and Herzegovina,
[4] Department of Hygienic and Epidemiological Surveillance, University Clinical Center Tuzla, Tuzla, Bosnia and Herzegovina,
[5] Clinic for Children's Diseases, University Clinical Center Tuzla, Tuzla, Bosnia and Herzegovina,
[6] General Hospital Dr. Mustafa Beganovic, Gracanica. Bosnia and Hezegovina.

Abstract

The aim of this research was to present the frequency of the presence of positive eosinophil finding in the nasal mucosa and seasonal variations, in 258 children aged 1 to 11, in the kindergartens in eight municipalities of Tuzla Canton, with the nasal mucosa swab smear on eosinophil granulocytes. The results showed that 9.30% were eosinophil positive in autumn 2016, while there was a slight increase in the number of positive ones in spring 2017, i.e., 10.46%. Since the largest number of subjects was in Tuzla, the comparative analysis of the municipality of Tuzla with other municipalities was conducted in order to have the representation of seasonal variations. In autumn 2016, there were 9.30% of eosinophil findings, 5.81% in boys and 3.48 in girls, while in spring 2017, out of 10.46%, there were 5.81% boys and 4.65% girls with positive swabs. The results suggest that the boys have the increased eosinophil infliltration more often, while the girls have it during spring. The presence of eosinophils is a good indicator of posibility of allergic rhinitis and it is necessary to adopt the consensus that would define the adoption of the value of 'significant eosinophilia' in nasal cytology, which does not exist so far.

Key words: eosinophils, nasal cytology; nasal mucosa swab smear on eosinophils; allergic ailment.

Introduction

According to the figures by World Health Organisation hundreds of millions of people in the world suffer from allergic rhinitis. In the last 50 years, allergic diseases have grwon to the level of epidemics on global level (1). Allergic diseases are not limited to the season of outbreak or the particular region, people are allergic to numerous natural alergens that are manifested with symptoms combined with conditions like asthma, allergic rhinitis, allergies on food, medications and insect bites, eczema urticaria and angioedema (2).

In the recent few years there is a trend of allergic diseases in the western world countries, and especially in children. Allergic diseases are present to the level of 20% to 30% of child population. The reasons may be related to the changes in the environment and the way of living. To be more precise, it has been noticed that the children living in cleaner environment with high hyginic standards are more likely to get alergic diseases. It is about the immune system which not only reacts to pathogenic bacteria, but also to harmless allergens (3). Allergic rhinitis affects the sick person significantly depending on the severity of symptoms. It also affects the quality of life of the diseased person, interferes with his/her social activities, and causes the impact not only for the diseased but for his family as well, and the society in general (2). Allergic rhinits and asthma are a part of the same systemic disease (4-5). The disease usually starts in the childhood or adolescence and develps until the twentieth year of age. The development of the dicease is characterised with the occurence of deterioration of the disease during the 3-4 season, gradual stabilisation of the disease and its weakening that comes with age.

One of the diagnostic indicators of doubt to the allergic diseases is a positive finding in the nasal

mucosa, proved with the nasal swab on eosinophils. The method of taking the nasal swab on eosinophils is simple, does not traumatize the child, and can be conducted at any time of day regardless of food intake. The approach to the diagnostics is better than the determination of the number of eosinophils in peripheral blood, because the eosinophils are mostly tissue cells, and their number can be increased even without the accompanying increase in peripheral blood. The analysis is very suitable, because it is conducted in vitro, the taking and the technique are very simple, they do not require expensive apparatus, and the result is quickly obtained. Acording to the new research on the migration of eosinophils and their essential role in immune response, they can be defined as very active immune cells, with the effector function with the increased inflammatory and cytotoxic potential (6). Eosinophil granulocytes or eosinophil (Eo) are an importan component of innate immune system. They represent the main effector cells in the late phase of allergic reaction, that occurs a few hours after the exposure to the allergen. It is characterised with the occurence of inflammatory cells (eosinophils, neutrophils, basophils, mast cells, T lymphocitesEo accumulated at the place of inflammatory reaction have the dominant role and they release the inflammation mediators and lead to the sequence of secondary reactions harmful for the body and responsible for chronic symptomatology (7). Eosinophils are mostly present in two types of inflammation, i.e.: alergic reaction and parasite infections.

The presence of eosinophil granulocytes has not been recorded in nasal mucosa of healthy persons. In contrast, their presence has been proved on nasal mucosa of the diseased with allergic rhinitis, non-allergic rhinitis with eosinophilia and nasal polyposis, especially when it is combined with cystic fibrosis and Kartagener's syndrome (the syndrome of non-movable cilia). Eosinophils are also the dominant inflammatory cells in other chronic diseases of the respiratory system like asthma (8-9). During the nasal mucosal inflammation, the role of eosinophils is reflected in the release of themediators ofinflammation like ECP and MBP. It is considered that these mediators stimulate the late stage of the allergic reaction where the eosinophils are present in a large number and their influence in that phase of the inflammation is the key one. All proteins are released into the extracellular fluid under the influence of different secretory and anti-inflammetory cytokines like IL-5, GM-CSF (10). The diagnosis of the nasal cavity disorder is set with nasal citology, which is based on the proofs that in healthy subjects the nasal cavity is composed of four normal subgroups of cells, where except neutrophils, other cells are not found (11).

Nose has a function of immune barrier to external antigens. A large number of foreign particles enters the organism through nose, and that is why the nasal immune system is very developed. One of the basic protective mechanisms of upper and lower respiratory system is a mucociliary transport. Thanks to mucociliary transport, different particles and contaminations are removed from the surface of the mucosa in nasal cavity (12). There is a larger amount of secretory imunoglobulin (s-IgA) inside the nasal mucosa epithel, which reacts to specific antigenes, but also lysozyme, interferon Y aond other carriers of non-specific immunity. The organisation of imune system of nasal mucosa and paranasal sinuses include the interaction of cellular (T lymphocite) and humoral (B -lymphocite) mechanism. Those mecahnisms supplement each other. The special role in allergic rhinitis pathogenesis, and allergic diseases is described as the activation of so-called mast cells and the binding of the IgE immune complex and antigens with the consequent release of the chemical inflammation mediators. The inhalled air is moistened and it is presented to lungs in a conditioned and refined way. If the nostrills are blocked due to the inflammation or infection, the upper processes are not caried out, and the lungs are exposed to the intensified irritations, allergens and microorganisms. In predisposed people, such excessive exposure to allergens increases the allergic inflammatory processes, which results in asthma. Lots of patients with allergic rhinitis, but without asthma do not have proofs on changed lung function that appears either spontaneously or after bronchoprovocation with metacholine, histamine or cold air (4).

Sensibilisationos a first step of immune response in allergic reactions. In order to develop na allergy the reaction of two factors is necessary, which means that the person must have: the tendency to develop an allergy (genetic factor); to be

exposed to an allergen from the environment. In support of the activity of genetic factors is the information on more common appearance of allergic diseases in children of parents with an allergic disease. If one of the parrents has an allergic disease, the risk of the occurence of an allergic disease in their children is 20%, and if both parents have an allergic disease, the risk reaches 70% (13).

The basis of preserving the human health and quality of life is a healthy environment. Air pollution is considered to be one of the most provocative factors for the development of allergic diseases and it is defined as the atmospheric accumulation of irritants in the concentration harmful for the people, animals and plants, and it is often referred to industrial (sulfur dioxide) and photochemical (ozone, nitrogen oxides) air pollution (14). The exposure to external allergens is an important factor for the development of allergic diseases.

Methods

The study included 258 children from the kindergartens in 8 municipalities of Tuzla Canton at the age 1 to 11. The taking of the nasal swab in children was conducted after the written approval from their parents. The children whose parents did not sign a written consent and those with higher body temperature, systemic disease or those using antihistamines, bronchodilatators, expectorants or systemic corticosteroids were excluded from the research. The taking of nasal swabs was conducted by healthcare workers. The taken nasal swabs (from both nostrils) were cytologically processed in the microbiology laboratory of the Public Health Bureau of Tuzla Canton in a way that the smear was made on the test slide, and then they were positioned over the light and dyed by May-Greenwald and Giemsa Dyes method. The smears were fixed so they could not be mechanically removed from the test slide. Besides that, the fixation prevents the cell and tissue denaturation by autolytic enzymes present in cells and helps to preserve the cell. The test slide was labeled with subject's name, surname and number. After drying, the samples were analysed under the light microscope with immersion magnification (with the drop of cedar oil).

Statistical analysis

All data were analysed with the SPSS 20.0 statistical package (SPSS Inc, Chicago, IL, USA). t-test, correlation and non-parametric tests, chi-square test and Wilcoxon Signed Rank Test were used for testing. The statistical tests were conducted with the predefined materiality threshold of 5% (0.05). The structure of data, mostly, implies to the use of so called per-post tests, where the differences in results are detected on the same sample in cases where the measurements of any kind are conducted before and after the treatment or in two time intervals. In that sense, the analysis of the level of statistical significance in this case can be conductd in a way that the data from two years, i.e. two seasons are compared.

Results

Out of 258 children aged 1-11 in total where the frequency of eosinophils in nasal swab was analysed, there were 54.26% boys and 45.74% girls (Table 1). The analyses were conducted in two seasons, autumn and spring, i.e: October 2016 and April 2017 in 8 municipalities in Tuzla Canton.

The Frequencies column (columns 2, 3, and 4) show the data on the number of children from whom the swabs had been taken. The group of columns Percentages 1 (columns 5 and 6) shows the percentages per sex in each municipality (the sum in each row is 100%). The last row shows the precentagescompared to the whole sample. The group of columns Percentages 2 shows the percentages for one sex (columns 7 and 8) and the cummulative for both sexes (column 9). The largest number of children is from Tuzla (113) and Lukavac (36), and the smallest numberiz from Doboj Istok and Srebrenik (7 each). Chi-square test shows that there is no statistically significant difference in frequencies per sex per municipalities ($p = 0.1572$) compared to theoretical values

The age structure in of children at the moment of first swab taken is shown in Table 2. Columns *Frequencies* (columns 2, 3, and 4) show the data on the number of children from whom the swabs had been taken. Groups of columns *Percentage 1* (columnas 5 and 6) show the percentages per sex per each municipality (the sum in each row is 100%). The row Total shows the precentages compared to

Table 1. Children's sex structure

	Frequencies			Percentages 1		Percentages 2		
Municipality	**Male**	**Female**	**Total**	**Male**	**Female**	**Male**	**Female**	**Total**
1	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**
Banovići	8	7	15	53,33	46,67	5,71	5,93	5,81
Doboj Istok	7	10	17	41,18	58,82	5,00	8,47	6,59
Gračanica	16	9	25	64,00	36,00	11,43	7,63	9,69
Gradačac	8	14	22	36,36	63,64	5,71	11,86	8,53
Lukavac	26	10	36	72,22	27,78	18,57	8,47	13,95
Srebrenik	7	4	11	63,64	36,36	5,00	3,39	4,26
Tuzla	59	54	113	52,21	47,79	42,14	45,76	43,80
Živinice	9	10	19	47,37	52,63	6,43	8,47	7,36
Total	**140**	**118**	**258**	**54,26**	**45,74**	**100,00**	**100,00**	**100,00**

Table 2. Children's age structure

	Frequencies			Percentages 1		Percentages 2		
Age	**Male**	**Female**	**Total**	**Male**	**Female**	**Male**	**Female**	**Total**
1	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**
0	1	1	2	50,00	50,00	0,71	0,85	0,78
1	3	3	6	50,00	50,00	2,14	2,54	2,33
2	11	6	17	64,71	35,29	7,86	5,08	6,59
3	19	19	38	50,00	50,00	13,57	16,10	14,73
4	28	27	55	50,91	49,09	20,00	22,88	21,32
5	48	42	90	53,33	46,67	34,29	35,59	34,88
6	12	18	30	40,00	60,00	8,57	15,25	11,63
7	10	1	11	90,91	9,09	7,14	0,85	4,26
8	5	1	6	83,33	16,67	3,57	0,85	2,33
9	0	0	0	0,00	0,00	0,00	0,00	0,00
10	1	0	1	100,00	0,00	0,71	0,00	0,39
11	2	0	2	100,00	0,00	1,43	0,00	0,78
Total	**140**	**118**	**258**	**54,26**	**45,74**	**100,00**	**100,00**	**100,00**
Average	4,63	4,35	4,50					
St. D.	1,794	1,336	1,607					

the whole sample. Groups of columns *Percentages 2* shows the percentages per on sex (columns 7 and 8) and per cummulative for both sexes (column 9). The last two rows show the data on average value and standard deviation of data on children's age.

Towards the analysis of the number of positive and negative cases, there was a calculation of the correlation coefficient conducted, which should show if, and to what extent, the dynamics of positive cases in municipalities is dependent from the total number of swabs taken in 206 (table 3) and 2017 (table 4). The last row in both tables contains the coefficients of correlation between the number of positive and negative swab results. In all cases the coefficient of correlation points to the high degree of relation of positive cases to the place of living.

In the data for the year 2016, the value for the male children was close to the value for the whole sample, but significantly higher compared to the value for the female children. This may indicate the increased seasonal impact on male children in autumn.

In the data for April 2017 the values of the correlation coefficient for male and female children are very close, and both significantly different from the correlation at the whole sample level.

Table 3. Correlation coefficients for the year 2016

2016	Total			Male			Female		
Municipality	**Taken**	**Positive**	**Negative**	**Taken**	**Positive**	**Negative**	**Taken**	**Positive**	**Negative**
Banovići	15	0	15	8	0	8	7	0	7
Doboj Istok	17	1	16	7	0	7	10	1	9
Gračanica	25	3	22	16	1	15	9	2	7
Gradačac	22	2	20	8	1	7	14	1	13
Lukavac	36	2	34	26	2	24	10	0	10
Srebrenik	11	0	11	7	0	7	4	0	4
Tuzla	113	16	97	59	11	48	54	5	49
Živinice	19	0	19	9	0	9	10	0	10
Total	**258**	**24**	**234**	**140**	**15**	**125**	**118**	**9**	**109**
Correlation		0.98068			0.96238			0.90107	

Table 4. Correlation coefficients for the year 2017

2017	Total			Male			Female		
Municipality	**Taken**	**Positive**	**Negative**	**Taken**	**Positive**	**Negative**	**Taken**	**Positive**	**Negative**
Banovići	15	2	13	8	0	8	7	2	5
Doboj Istok	17	0	17	7	0	7	10	0	10
Gračanica	25	1	24	16	1	15	9	0	9
Gradačac	22	0	22	8	0	8	14	0	14
Lukavac	36	1	35	26	1	25	10	0	10
Srebrenik	11	1	10	7	1	6	4	0	4
Tuzla	113	22	91	59	12	47	54	10	44
Živinice	19	1	18	9	1	8	10	0	10
Total	**258**	**28**	**230**	**140**	**16**	**124**	**118**	**12**	**106**
Correlation		0.94908			0.91358			0.90918	

Table 5. Summative display of the number of positive findings per children's age and sex

	October 2016			April 2017			Percentages	
Municipality	**Male**	**Female**	**Total**	**Male**	**Female**	**Total**	**Oct 2016**	**Apr 2017**
1	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**
Banovići	0	0	0	0	2	2	0,00	7,14
Doboj Istok	0	1	1	0	0	0	4,17	0,00
Gračanica	1	2	3	1	0	1	12,50	3,57
Gradačac	1	1	2	0	0	0	8,33	0,00
Lukavac	2	0	2	1	0	1	8,33	3,57
Srebrenik	0	0	0	1	0	1	0,00	3,57
Tuzla	11	5	16	12	10	22	66,67	78,57
Živinice	0	0	0	1	0	1	0,00	3,57
Total	**15**	**9**	**24**	**16**	**12**	**28**	**100,00**	**100,00**

This indicates the possible and significant shift regarding seasonal impact on the incidence, i.e. on more even distribution by sexes.

In both cases, the correlation coefficient for female children does not have any important variations, which indicates the possible lower seasonal impact on female children compared to the male ones. The variability for the male children between two years of age may indicate the fact that male children have the higher sensibility risk of this type, and that the seasonal factor is more significant than the place of living.

The percentage of positive nasal mucosa swab findings is presented in table 5. The Percentage columns shows the percentage of positive findings at a particular year level, for each municipality, compared to the figure on the number of samples (258), so their sum is 100%. Since the data are shown in two periods on the same data, the percentages per each municipality do not count (per rows) but only per years (columns).

Seasonal variations are presented providing that the largest part of samples is from Tuzla, it was of interest to make comparison with other municipalities (Table 6. and Table 7.)

The first part, named All means the whole sample, and other two parts are male and female patients. The analysis per sexes was conducted in a way that a part of population was taken for a particular sex, so the basis for the male children was 140 (54.26%), and for the female ones 118 (45.73%) patients. The last row shows the p-value of Chi-square test, for each group of data. The value lower than 0.05 (5%) means that there is a statistically significant difference in the tested sample.

The statistical tests show that in five of six groups there is a statistically significant difference concerning the distribution of the number of

Table 6. Parallel display of the number of positive and negative findings for Tuzla and other municipalities for October 2016

October 2016	All			Male			Female		
	Positive	Negative	Sum	Positive	Negative	Sum	Positive	Negative	Sum
Tuzla	16	97	113	11	48	59	5	49	54
Others	8	137	145	4	77	81	4	60	64
	24	234	258	15	125	140	9	109	118
	p=0,0177			p=0,0096			p=0,5395		

Table 7. Parallel display of the number of positive and negative findings for Tuzla and other municipalities for April 2017

April 2017	All			Male			Female		
	Positive	Negative	Sum	Positive	Negative	Sum	Positive	Negative	Sum
Tuzla	22	91	113	12	47	59	10	44	54
Others	6	139	145	3	2	5	2	62	64
	28	230	258	15	125	140	12	106	118
	p=0,0001			p=0,000			p=0,0058		

Table 8. Summative display of the number of positive swabs per age groups and the sex of the children

	Year 2016			Year 2017		
Age	**Male**	**Female**	**Total**	**Male**	**Female**	**Total**
0	0	0	0	0	0	0
1	0	0	0	1	0	1
2	1	0	1	1	1	2
3	1	2	3	0	2	2
4	5	2	7	4	3	7
5	4	4	8	5	5	10
6	1	0	1	1	0	1
7	1	0	1	0	0	0
8	0	0	0	1	0	1
10	0	0	0	0	0	0
11	0	0	0	1	0	1
Total	**13**	**8**	**21**	**14**	**11**	**25**
Average	4,46	4,25	4,38	4,93	4,09	4,56
St. D.	1,216	0,829	1,090	2,313	0,996	1,899

patients with positive and negative findings. The only group where such difference does ont exist is the female children group in 2016. The increase in the female children group in Tuzla in 2017 is noticeable, which is a possible source of variance with theoretical frequencies in 2017.

Table 8 shows the summative display of the number of positive swabs per age groups and the sex of the children in the last two rows there are the elements of descriptive statistics as average age and standard deviation, per sex and integrated for each group. There are differences in grouping among sexes noticeable. The positive findings for female children in both years are in the range of 2 to 5 years. Positive findings for the male children are in much larger range, which is noticeable in the standard deviation values. The difference between the standard deviations for male children in two seasons is particularly noticeable.

In order to verify these facts, a statistical test was conducted where the comparison of seasonal data for the integrated data was conducted, and then individually for male and female children. Wilcoxon signed rank test was used for such purposes, which neasures the size and the sign of the change between the two samples.

The test results show that there is no statisticaly significant difference in seasonal changes if the data are observed as integrated (for both sexes) and especially in the case male children data. On the other side, there is a statistically significant difference in seasonal changes in the case of female children data.

Discussion

The upper respiratory system allergic diseases are the diseases that are most frequently present in child population. The early diagnosing of respiratory allergies in children, especially the preschool children could help in timely and more efficient treatment of respiratory diseases, and to stop the development of complications. However, to make adiagnose of respiratory allergic diseases, especially of the aforementioned age presents a great challenge due to the presence of different disaese symptoms. Although the cytological analysis is a fast, non-invasive method, its use for diagnostic purposes is relatively rare. Most reasearch conducted on the nasal cytology topic are related to the presence of eosinophils in the nasal mucosa swab and their relation to the allergic rhinitis, asthma and atopic dermatitis (15). Most research in previous years also resulted with the identification of different antigens that are responsible for seasonal allergic rhinitis (16). The risk factors that lead to the allergic rhinitis are the exposure to the allergens in closed and open space, socioeconomic factor, and the air pollution by chemical pollutants. The products of fossil fuels combustion (CO, CO2, metals, NOx, SO2, PM10, PM2,5, nanoparticles) and light volatile organic compounds (VOC) that create ground-level ozone in reaction with NO2 and other compounds in the air and increase the allergic inflammation (17) have the greatest impact on the allergic rhinitis and asthma increased prevalence. The research conducted by Braun-Fahrlender C. et. al in Switzerland in 1992 included the preschool children and showed the increased irritation of upper respiratory pathways in children who lived near roads with large traffic frequency and in that way exposed to high concentration of nitrogen dioxide (18). Decreased secretion of nasal mucosa and its resistance occurs as the consequence of exposure to the increased concentration of sulfur dioxide (19). Floating particles that are formed by incomplete combustion of fuels are divided by size on PM10 (aerodynamic diameter < 10μm), PM 2,5 (<2,5 μm) and nanoparticles (<1 μm). The siye of the particles is particularlz important for the depth of penentration into the respiratory pathways. The smaller the particle is, the deeper the penentration is, and in that case it goes through the alveolar-capillary membrane (20). The results of the studies show that the people who were exposed to higher concentrations of PM10 have the greater symptoms related to upper respiratory pathways than the people who were exposed to lower concentrations of such (21). The floating particles of smaller diameter (PM2.5) induce the nasal eosinophillia (22). Except the chemical pollutants from the air and climate changes that are manifested thourgh global warming of the atmosphere affect the allergens, expecially the fungal and mold spores and pollen (23). As far as our results are concerned, in relation to the greater presence fo EO positive

nasal mucosa swab findings, we can clearly confirm that the results match the aforementioned. A larger number of EO positive findings in nasal mucosa swab was noticed in the municipalities of Tuzla, Banovići, Živinice, and Srebrenik which can be connected to the thesis that those municipalities are the most developed in Tuzla Canton according to the population, increased urbanisation, and industrial development.

In addition, according to our research, the incidence data confirm the thesis on a significant presence of eosinophils and thier increase. 24 (9.30%) in October 2016 and 28 in April 2017 (10.85%) were detected eosinophil positive. A particular increase was shown during the season of spring vegetation. However, we cannot say if such increase was or was not related to children who had already had nasal symptoms present, as it was the case in the study conducted by Okano et. al.

In the study conducted by Okano et.al, in the results of their research that lasted for three years, they clearly suggested that nasal eosinophillia in children was related to the subsequents nasal symptoms, and that nasal smear check can be potentially valuable test for the prediction of long term or repeated rhinitis. It is interesting that those who showed the positive eosinophillia in 1992, especially those who had eosinophillia with nasal symptoms, had more frequent nasal symptoms three years later, in 1995, than those who showed the negative eosinophillia in 1922.

The prevalence of asthma symptoms in younger age was higher in boys around the world, while with ageing, there is a more frequent prevalence of symptoms in girls (24). in the study conducted in Korea in 2011, on the sample of 67,300 children, the obtained results also show the aforementioned diference in prevalence of atopic diseases between girls and boys. The boys had more frequent asthma and allergic rhinitis symptoms, while the atopic dermatitis was more frequent in girls (24). The reasons for this sex difference are not well known (25), although there is a hypothesis that the possible cause is in sex hormones (24). in our researc, we have concluded that the increased infliltration of nasal mucosa eosinophils was increased in female children, during the spring vegetation, but when taking into account the overall number of positive findings, it is clear that the number of positive findings is more common in male children, which corresponds with otherresearch.

The study conducted by Nowacki et. al included the analysis of the usefulness of nasal mucosa cytology in predicting the occurence of atopic diseases (atopic dermatitis, asthma, and allergic rhinitis) in 146 children in total (60 girls and 86 boys) aged up to 4. On the basis of that research it was proved that the eosinophillia in nasal cytology, at leat in 8%, related to the high risk of the development of allergic rhinitis and that as the indicator of the occurence of risk for the allergic march the increased nasal eosinophillia in children can be taken. The average percentage of eosinophils in the initial phase was significantl higher in children who were finally diagnosed allergic rhinitis compared to the children who were diagnosed atopic dermatitis. After 4 years, the allergic rhinitis was diagnosed in 85 children (58.2%), atopic eczema / dermatitis in 51 (34.9%), and asthma in 48 (32.9%). Non-allergic etiology was determined in 36 patients (22.5%).

The aforementioned brings to the conclusion that allergic rhinitis in early childhood is a risk factor for asthma in late childhood and adulthood. There are lots of co-morbidities that can affect the occurence of allergic rhinitis in chlidren including conjunctivitis, impaired hearing, rhinosinusitis, problems with sleep and pollen-food syndrom, and that is why it is important to ask the parents about these rpblems (26).

In the 90s of the prevoius century there was a prospective study conducted which showed the increase of eosinophils and basophils in four-year-olds with positive family anamnesis (the presence of allergic diseases in parents) unlike children in which allergic diseases were not recorded (27).

By studying the relations between the nasal eosinophillia in patients with allergic rhinitis and their bronchial reactivity, it was concluded that half of the diseased with bronchial reactivity had positive nasal swab on eosinophillia compared to only 17% of the patients from the group of patients who did not have broncial reactivity. These results suggest the relations between the nasal eosinophillia and bronchial reactivity, which supports the concept of close relation between the upper and lower airways that were included in respiratory allergy (28).

Conclusion

On the basis of the results of the research, the presence of eosinophils in nasal cytology is a good indicator of possibility of allergic rhinitis, and in combination with other diagnostic tests it contributes the making the right diagnosis. in the case of asthma nad atopic dermatitis its sensibility is significantly lower and insufficient to recommend this test as an independent test for making a diagnosis of the aforementioned diseases. It is necessary to point out that unitl now there have not been any standards for the examination and the analysis of samples and that there is no consensus that would define the value of 'significant eosinophillia' in nasal cytology.

References

1. *Ninan T, Russell G. Respiratory symptoms and atopy in Aberdeen schoolchildren: evidence from two surveys 25 years apart. BMJ 1992; 304: 873-875.*
2. *Pawanker R, Canonica G, Holgate S, Lockey R. World Allergy Organisation (WAO) White Book on Allergy. 2013.*
3. *Von Mutius E. Environmental factors influencing the development and progression of pediatric asthma. J Allergy Clin Immunol. 2002; 109: 525-32.*
4. *Braman SS, Barrows AA, DeCotiss BA, Settipane GA, Corraso WM. Airway hyperresponsiveness in rhinitis, a risk factor for asthma. Chest. 1987; 91: 671–674.*
5. *Chandler D, McFadden E. Jr, Ingram ER. Jr, Breslin RH. Jr., Jaeger JJ. Airway responsiveness to cold air and hyperapnea in normal subjects and in those with hayfever and asthma. Am Rev Respir Dis. 1980; 121: 621–8.*
6. *Alvadaro A. The eosinophile: Physiology and Pathology. Clinical Research and Trials. 2020; Vol 6: 1-11.*
7. *Karamehić J, Dizdarević Z, Dizdarević S, Cupač-Vujčić Lj. Allergic Rhinitis- Clinical Immunology. (Alergijskirinitis- Kliničkaimunologija.) Svjetlost, Sarajevo. 2007.*
8. *Tos M, Mogensen C. Mucous glands in nasal polyps. Arch Otolaryngol. 1997; 103: 407-413.*
9. *Stoop AE, Van der Heijden HA, Biewenga J, Van der Baan S. Eosinophils in nasal polyps and nasal mucosa: An immunohistochemical study. J Allergy Clin Immunol. 1993; 91: 616- 622.*
10. *Chanda R, Aggarwal AK, Kohli GS, Jaswal TS, Gupta KB. Comparative study of nasal smear and biopsy in patients of allergic rhinitis. Indian J Allergy Asthma Immunol. 2002; 16: 27-31.*
11. *Gollash H. Fortschr Med. 1889; 7: 361–365.*
12. *Cole P. Pathophysiology and treatment of airway mucociliary clearance. A moving tale. Minerva Anestesiol. 2001; 67: 206-9.*
13. *Škvorc M, Plavec D, Nogalo B, Turkalj M. The prevalence of symptoms of allergic diseases among younger school children in Međumirje country. 2014; 136: 3-4.*
14. *Gauderman WJ. Avol E, Lurmann F. Childhood asthma and exposure to traffic and nitrogen dioxide. Epidemiology. 2005; 16: 737–43.*
15. *Chad Z. Allergies in children. Paediatr Child Health. 2001; 6(8): 555–566.*
16. *Barnes K, Marsh D. The genetics and complexity of allergy and asthma. Immunol Today. 1998; 19: 325-32.*
17. *Saxon A, Diaz-Sanchez D. Air pollution and allergy: you are what you breathe. Nat Immunol. 2005; 6: 223-6.*
18. *Braun-Fahrlender C, Ackermann-Liebrich U, Schwartz J, Gnehm HP. Air pollution and respiratory symptoms in preschool children. Am Rev Respir Dis. 1992; 145: 42-7.*
19. *McManus MS, Altman LC, Koenig JQ, Luchtel DL, Covert DS, Virant FS, Baker C. Human nasal epithelium: characterization and effects of in vitro exposure to sulfur dioxide. Exp Lung Res. 1989; 15: 849-65.*
20. *Seaton A, Macnec WK, Donaldson D. Particulate air pollution and acute health effects. Lancent. 1995; 345: 176-178.*
21. *Pope CA, Burnett TR, Thun JM, Calle EE, Krewski D, Ito K, Thurston DG. Lung cancer, cardiopulmonary mortality and long term exposure to fine particulate air pollution. J. Am. Med. Assoc. 2002; 287(9): 1132–1141.*
22. *Nikasinovic L, Just J, Sahraoui F, Seta N, Grimfeld A, Momas I. Nasal inflammation and personal exposure to fine particles PM2,5 in astmatic children. J Allergy Clin Immunol. 2006; 117: 1382-88.*
23. *Beggs PJ, Bambrick HJ. Is the global rise of asthma an early impact of anthropogenic climate change? Environ Health Perspect. 2005; 113: 915-9.*

24. *SuhM, Kim HH, Sohn MH, Kim KE, Kim C, Shin DC. Prevalence of allergic diseases among Korean school-age children: a nationwide cross-sectional questionnaire study. J Korean Med Sci. 2011; 26: 332-8.*

25. *Bacharier LB, Bonner A, Carlsen K-H. The European Pediatric Asthma Group. Diagnostis and treatment of asthma in childhood: a PRACTALL consensus report. Allergy. 2008; 63: 5-34.*

26. *Scadding G, Kariyawasam H, Scadding G. BSACI guidelines for the diagnosis and treatment of allergic and non-allergic rhinitis. Clin Exp Allergy. 2017; 47(7): 856–889.*

27. *Zeiger RS, Heller S. Development of nasal basophilic cells and nasal eosinophils aged 4 months to 4 years in children of atopic parents, Journal of Allergy and Clinical Immunology. 1993; 91(3): 723–734.*

28. *Abdel-Hamid HM, Abdel-Rehim AS, Mahmoud NA, Abdel Fattah MF, Husein AY. Relationship between nasal eosinophilia and airway resistance in patients with persistent rhinitis. Department of Clinical Pathology, School of Medicine, Ain Shams University, Cairo, Egypt. 2018; 67(2): 191-194.*

Corresponding Author:
Fejzo Dzafic,
Polyclinic for Laboratory Diagnostics,
University Clinical Center Tuzla,
Tuzla,
Bosnia and Herzegovina,
E-mail: fejzo9@hotmail.com

The Effects of Antipsychotics and Mood Stabilizers on The Quality of Life in Schizophrenic Patients

Zaliha Akkadin Candan[1], Demet Unalan[2], Saliha Demirel Ozsoy[3]

[1] Department of Psychiatry, Ministry of Health, Kayseri City Education and Research Hospital, Kayseri, Turkey,
[2] Erciyes University Health Services Vocational College, Kayseri, Turkey,
[3] Department of Psychiatry, Erciyes University, Medical faculty, Kayseri, Turkey.

Abstract

Aim: In this study, we aimed to determine quality of life and factors affecting it, and effects of antipsychotics and mood stabilizers on the quality of life in patients with schizophrenia.

Method: Obtaining the informed consent, 103 (53 women, 50 men) patients with schizophrenia and 20 (9 women, 11 men) healthy controls were enrolled to the study. The Brief Psychiatric Rating Scale, the Calgary Depression Scale for Schizophrenia, the Scale for the Assessment of Negative Symptoms and the Scale for the Assessment of Positive Symptoms were applied to the patient group and the Short Form-36 (SF-36) scale was applied to the both the patient and the control groups.

Results: Scores on the subscales of the SF-36 scale were significantly lower in patient group than in control group. There were no significant differences according to the scores on the SF-36 scale between female and male patients, except for higher scores on the "emotional role" subscale of the SF-36 scale in male patients. No significant difference was found among the sub-domain scores of the Short Form-36 scale belonging to the patient groups using typical antipsychotics, atypical antipsychotics alone and antipsychotics together with mood stabilizers.

Conclusion: This study has shown that the quality of life in patients with schizophrenia is lower than the healthy controls. We conclude that the goal of the treatment in patients with schizophrenia is not only to treat symptoms and to prevent relapses, but also to improve the quality of life.

Key words: Antipsychotic drug, mood stabilizer, schizophrenia, quality of life

Introduction

The measurements of the quality of life have been the center of interest of health researchers for over 40 years, and they have been started to be considered in clinical psychopharmacology studies.[1] An increasing interest in the issue of evaluating the qualities of life of schizophrenic patients has been arisen and the related studies have been increased considerably. Schizophrenic patients have problems in the fields such as daily activities, motivation, communication skills, productivity and adaptation depending on the nature of the disease and the treatments.[2]

The quality of life is defined by The World Health Organization (WHO) as "individuals' perception of their position in life in the context of the culture and value systems in which they live and in relation to their goals, expectations, standards and concerns".[3] The concept of the quality of life has both subjective and objective dimensions. While the subjective dimension includes states as feeling well, satisfaction with life and happiness, the objective dimension includes situations such as living independently, interpersonal relationships and being productive [4] It is reported that the relation between objective and subjective evaluations do not always correspond to each other.[5]

It is highly controversial whether patients with schizophrenia can evaluate their quality of life.[6] While some authors argue that the evaluation of the quality of life of a person with mental illness will be meaningful when it is only considered by him / her[7], some other authors approach the information obtained from patients suspiciously due to the reasons such as judgment disruption, lack of insight and various neurocognitive deficiencies in schizophrenic patients, and they claim that it will be more accurate to focus on the measurable data.[8]

In many studies comparing schizophrenic patients with healthy controls and individuals having physical chronic diseases it is reported that the qualities of life of schizophrenic patients have been decreased.[2, 6, 7, 9] Although the clinic variables related to the disruption in the qualities of life of schizophrenic patients can be summarized as the age, negative symptoms, overall psychopathology, the span of the disease and the period of hospitalization, tardive dyskinesia and the presence of the medication adverse effect, the results of those studies reveal contradictory data.[5,6] There are some studies reporting there is a strong relation between the quality of life and overall psychopathology levels in schizophrenia.[10] In many studies, it is reported that there is a strong negative relation between negative symptoms and the quality of life.[6,7,9,11,12] In some cross-sectional studies, it is stated that there is a weak relation between positive and negative symptoms and the quality of life.[5]

In some studies, it is reported that the qualities of life of female patients, married patients and the patients having low educational level are better, but the qualities of life of the patients having extrapyramidal symptoms and stigmatization are lower. [6,7,11] In many studies, negative effects of the depression have been reported on the quality of life. [2, 9, 10, 13, 14] The effects of antipsychotics on the quality of life are controversial. [14] In many studies it is reported that negative symptoms recover more in patients treated with atypical antipsychotics (AA), [6] and, accordingly, the quality of life scores of these patients are higher than those treated with typical antipsychotics (TA). [14,15]

In this study, it is aimed to investigate the quality of life levels and the factors affecting the quality of life in schizophrenic patients, and to determine the effects of the antipsychotics and mood stabilizers on the quality of life.

Subjects and Method

I. Subjects

103 patients (53 females and 50 males) who had schizophrenia diagnosis according to DSM-IV-TR (Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revised) diagnosis criteria between the age range of 17-65 and who received inpatient treatment in Psychiatric Clinic, Faculty of Medicine, Erciyes University were included in the study. The average age of the patient group was 35.22 ± 11.87. The 50 of the patients were using AA (olanzapine, quetiapine, risperidone, clozapine, ziprasidone and aripiprazole) with mood stabilizer (MS) (lithium, sodium valproate and carbamazepine), 41 of them were using only AA (olanzapine, quetiapine, risperidone, clozapine, ziprasidone and aripiprazole), and 12 of them were using only TA (haloperidol, zuchopenthixol and flupenthixol).

The diagnosis was established with clinical interview by a senior psychiatric resident and a psychiatrist independently from each other, and the patients were staying in the hospital during the study.

The exclusion criteria for the patient group are as following:

- Having a medical history of comorbid or previous additional psychiatric disease
- Receiving ECT in the last 6 months,
- Substance use or addiction except for smoking,
- Having neurological diseases that cause organic brain disorder such as epilepsy and head trauma,
- Having a psychotic disorder due to a medical reason.

The control group was constituted with voluntary 20 healthy people (9 females and 11 males) who did not have any psychiatric, neurological and metabolic diseases. The average age of the control group was 40.25 ± 10.69.

II. Method

Psychometric Measurements:

- "Brief Psychiatric Rating Scale" (BPRS)[16] was applied to the patients. The scale was developed by Overall et al, and it was adapted into Turkish. [17]
- The Scale for the Assessment of Positive Symptoms (SAPS)[18] was applied to the patients. The reliability and validity study of the Turkish form was carried out by Erkoç et al. [19]
- The Scale for the Assessment of Negative Symptoms (SANS) (18) was

applied to the patients. The reliability and validity study of the Turkish form was carried out by Erkoç et al. [20]

- Calgary Depression Scale for Schizophrenia (CDSS) [21] was applied to the patients. The reliability and validity study of the Turkish form was carried out by Aydemir et al. [22]
- Medical Outcomes Study Short Form-36 Health Survey Questionnaire (SF-36) [23] was applied to the patients. It is the most common generic scale used to measure the quality of life. The reliability and validity study of the Turkish form was carried out. [24] The Quality of Life Scale Short Form includes 36 items. These items measure 8 dimensions as physical function, role physical, pain, general health perception, vitality, social function, role emotional and mental health.
- SF-36 scale was applied to the control group.

Statistical Analysis

Whether the distribution of all data obtained was normal or not was evaluated by "Kolmogorov-Simirnov test." The demographic characteristics of the patients and controls were compared by "independent samples t-test." Since SF-36 scores of the patients and controls did not reveal normal distribution, they were compared by "Mann Whitney-U test." In the comparison of the SF-36 scores of the patient groups in terms of the medication they use, "one-way ANOVA test" was used. Variance analysis was performed for "Post hoc test" selection, and "Tukey test" was performed in the comparison of the data where the variances were homogeneous and "Tamhane test" for the comparisons of the data where the variances were not homogeneous.

Spearman correlation test was performed to investigate the relation between the demographic and clinic features of the patients and SF-36 scores. In statistical analysis, $p<0.05$ was accepted significant.

Ethics: The study was approved by the Ethics Committee of Erciyes University, Faculty of Medicine. Participants were provided with an obligatory informed consent form before they accessed the questionnaire forms.

Results

The average age of the patient group was 35.22 ± 11.87 and the average age of the control group was 40.25 ± 10.69. Patient group included 53 women (51.50%) and 50 men (48.50%). The average age of the male patient group was 34.42 ± 10.48 and the female patient group's was 35.98 ± 13.10. Control group included 9 women (45%) and 11 men (55%), and the average age of the female control group was 44.55 ± 12.76. A statistically significant difference was not found between the patient and control groups in terms of gender (χ^2=0.279, p= 0.633).

Table 1. Clinical features and psychometric evaluations of the patient group

Clinical Data	Patient n=103 (mean ± SS)
Age of onset	26.57 ± 10.14
Disease period (year)	8.63 ± 6.44
Medication use period (month)	67.89 ± 49.01
BPRS score	37.14 ± 9.93
SAPS score	56.82 ± 15.87
SANS score	54.98 ± 14.00
CDSS score	11.23 ± 6.24

BPRS: *Brief Psychiatric Rating Scale,*
SAPS: *The Scale for the Assessment of Positive Symptoms*
SANS: *The Scale for the Assessment of Negative Symptoms,*
CDSS: *Calgary Depression Scale for Schizophrenia*

The average age of onset of the patient group was 26.57 ± 10.14, average disease period was 8.63 ± 6.44 years and average medication use period was 67.89 ± 49.01 months (Table 1).

When SF-36 subscale scores of the patient and control groups were compared, it was found that patient group's scores were found statistically significantly lower than the control group's (Table 2).

When SF-36 subscale scores of the female and male patient groups were compared, it was determined that only "role emotional" score of the male patient group (29.33 ±39.63) was statistically significantly higher than that of female patient group (14.46 ± 30.31) (Z= 2.028, p=0.043).

No statistically significant difference was found between SF-36 subscale scores and the BPRS

Table 2. The comparison of the SF-36 scale scores of the patient and control groups

SF-36 subscales	Patient n= 103 (ort ± SS)	Control n= 20 (ort ± SS)	Comparison
Physical Function	55.63 ± 26.41*	87.50 ± 12.61	Z=4.864 p≤0.001
Role Physical	38.34 ± 42.41*	83.75 ± 16.77	Z=4.128 p≤0.001
Pain	53.72 ± 17.40 *	83.00 ± 14.95	Z=5.877 p≤0.001
General Health Perception	43.54 ± 21.61*	81.10 ± 10.05	Z=6.500 p≤0.001
Vitality	40.09 ± 21.60*	83.50 ± 11.13	Z=6.693 p≤0.001
Social Function	35.65 ± 21.92*	89.37 ± 14.13	Z=6.797 p≤0.001
Role Emotional	21.68 ± 35.76*	85.00 ± 20.15	Z=6.382 p≤0.001
Mental Health	48.87 ± 18.02*	88.90 ± 11.01	Z=6.729 p≤0.001

**Lower than those of controls.*

scores, positive symptoms and negative symptoms, depression levels which were measured by CDSS, age of onset and disease period.

When the patients were compared in terms of the medication they use, no statistically significant difference was found between the patients using AA together with MS, using only AA and using only TA.

Discussion

In this study, SF-36 subscale scores of the schizophrenic patient group were found statistically significantly lower than those of control group. In many studies, the qualities of life of schizophrenic patients were lower than healthy controls and those having physical chronic diseases[2,6,7,9,12,25], and in a few study it was reported that there was no significant difference.[9]

In this study, a statistically significant difference was not found between female and male schizophrenic patient groups in any of the subscales except for "role emotional" (higher in the male patient group). In some studies carried out on schizophrenic patients, it was reported that the qualities of life of the female patients were better than the male patients[7,9,11,26,27], and in some other studies it was stated that there was no significant relation between the quality of life and gender.[2,5,6,14,28,29,30] Also, there are studies stating the quality of life in female patients is lower than male patients.[10,25,31] From all these findings, it is understood that gender alone is not sufficient in determining the quality of life in patients with schizophrenia, and other clinical features and socio-cultural factors also come into play.

In this study, no statistically significant relation was found between SF-36 subscale scores and BPRS scores, positive symptoms and negative symptoms of the schizophrenic patient group. In many studies conducted on patients with schizophrenia it was reported that there was a strong relation between the quality of life and general psychopathology levels but the relation between the quality of life and positive and negative symptoms is weaker.[2,10,30,32,33,34] In some studies, it was reported that there was no significant relation between the quality of life and psychopathology scores.[14,25] In many studies conducted with patients with schizophrenia, it was reported that there was a stronger relationship between negative symptoms and quality of life than positive symptoms, and negative symptoms reduced the quality of life more.[6,7,9, 11,12,26]

In this study, no statistically significant relation was determined between the depression levels measured by CDSS and the subscales of SF-36 scale. In many studies, it was reported that depression affected the quality of life in patients with schizophrenia in a negative way, and as depression scores got higher, the quality of life got lower.[2,5,12,13] The relationship between depression and the quality of life is in mutual interaction. In other words, the presence of depression decreases the quality of life and a low quality of life increases depression.

In this study, no statistically significant relationship was found between the subscales of SF-36 scale and the age of onset and disease period in schizophrenic patient group. In some studies, it was reported that there was no statistically significant relation between the quality of life and age of onset and disease period. [5,6,25,30] In some other studies, a significant relation was reported be-

tween the quality of life and age of onset.[10] Also, there are studies reporting that as the disease period extended, the quality of life decreased. [6, 9, 30]

In this study, no statistically significant relation was determined between the subscale scores of SF-36 scale and the patient groups using AA together with MS, using only AA and using only TA. It was reported that the quality of life was lower in patients with chronic schizophrenia in relation to the undertreatment of symptoms and the side effects of the medications (30). Atypical antipsychotics affect the quality of life more positively than TAs by improving negative symptoms and depression known to have negative effects on quality of life.[14,15,35,36,37] In some studies investigating the effects of atypical and TA drugs, it was reported that there was very little difference between the quality of life of patient groups.[38]

This study has some limitations. Firstly, it would be more appropriate for the patient group and especially the control group to consist of more subjects in order to determine the quality of life levels better and to perform healthier statistical applications. Secondly, using more specific scales in different periods would give more accurate results since the socio-cultural levels and the current clinical situations of the patients cause differences in the application of the quality of life scale.

Consequently, schizophrenia is a disease that reduces the quality of life. The purpose of the maintaining pharmacological treatment in patients with schizophrenia should not only be to prevent recurrences and reduce chronic side effects, but also to improve the quality of life.

References

1. *Voruganti LNP, Heslegrave RJ, Awad AG. Quality of life measurement during antipsychotic drug therapy of schizophrenia. J Psychiatry Neurosci 1997; 22(4): 267-274.*

2. *Eren İ, Şimşek D, Çalişkan AM. Şizofreni hastalarinda yetiyitimi ve belirti şiddetinin yaşam kalitesine etkisi. Düşünen Adam 2007; 20(2): 68-78.*

3. *Fidaner H, Elbi H, Fidaner C, et al. Yaşam kalitesinin ölçülmesi, WHOQOL-100 ve WHOQOL-BREF. 3 P dergisi 1999; 7(2): 3-66.*

4. *Bobes J, Gonzales MP. Quality of Life in schizophrenia. In: Katsching H, Freeman H, Sartorius N (eds). Quality of life in mental disorders. John Wiley & Sons, New York 1997, pp. 165-178.*

5. *Carpiniello B, Lai GL, Pariante CM, et al. Symptoms, standards of livingand subjective quality of life: A comparative study of schizophrenic and depressed out-patients. Acta Psychiatr Scand 1997; 96: 235-241.*

6. *Browne S, Roe M, Lane A, et al. Quality of life in schizophrenia: relationship to sociodemographic factors, symptomatology and tardive dyskinesia. Acta Psychiatry Scand 1996; 94: 118-124.*

7. *Katschnig H. Schizophrenia and quality of life. Acta Psychiatry Scand 2000; 102(407): 33-37.*

8. *Laliberte RD, Yu B, Scott E, et al. Exploration of the perspectives of persons with schizophrenia regarding quality of life. The American Journal of Occupational Therapy 2000; 54(2): 137-147.*

9. *Soygür H. Şzofreni ve yaşam niteliği. Klinik Psikiyatri 2003; 1: 9-14.*

10. *Huppert JD, Weiss KA, Lim R, et al. Quality of life in schizophrenia: Contributions of anxiety and depression. Schizophrenia Research 2001; 51: 171-180.*

11. *Bobes J, Gonzales MP. Quality of life in schizophrenia. Quality of life in mental disorders. In: Katschnig H, Freeman H, Sartorius N (Eds). John Wiley & Sons, England 1999: 165-178.*

12. *Ritsner M, Modai I, Endicott J, et al. Differences in Quality of Life Domains and Psychopathologic and Psychosocial Factors in Psychiatric Patients. J Clin Psychiatry 2000; 61(ll): 880-888.*

13. *Lehman AF. Convergent validation of quality of life assessment for persons with severe mental illnesses. Quality of Life Research 1993; 2: 327-333.*

14. *Franz M, Lis S, Plüddemann K, Gallhofer B. Conventional versus atypical neuroleptics: Subjective quality of life in schizophrenic patients. British Journal of Psychiatry 1997; 170: 422-425.*

15. *Lieberman JA. Metabolic changes associated with antipsychotic use. Prim Care Companion J Clin Psychiatry 2004; 6(2): 8-13.*

16. *Overall JE, Gorham DR: The brief psychiatric rating scale. Psychological Reports 1962; 10: 799-812.*

17. *Soykan C. Institutional differences and case typicality as related to diagnosis system severity, prognosis and treatment. Master tezi, Ortadoğu Teknik Üniversitesi, Ankara,1989.*

18. *Andreasen NC. Methods for assessing positive and negative symptoms. Mod probl Pharmacopsychiatry 1990; 24: 73-88.*

19. *Erkoç Ş, Arkonaç O, Atakli C, Özmen E. Pozitif semptomlari değerlendirme ölçeğinin güvenilirliği ve geçerliliği. Düşünen Adam 1991; 4: 20-24.*

20. *Erkoç Ş, Arkonaç O, Atakli C, Özmen E. Negatif semptomlari değerlendirme ölçeğinin güvenilirliği ve geçerliliği. Düşünen Adam 1991; 4: 16-19.*

21. *Addington D, Addington J, Maticka-Tyndale E, Joyce J. Reliability and validity of a depression rating scale for schizophrenics. Schizophr Res 1992; 6: 201-208.*

22. *Aydemir Ö, Esen Danaci A, Deveci A, İçelli İ. Calgary şizofrenide depresyon ölçeği'nin Türkçe versiyonunun güvenilirliği ve geçerliliği. Nöropsikiyatri arşivi 2000; 37: 82-86.*

23. *Ware JE, Sherbourne CD. The MOS 36-item short-form health survey (SF-36). I. Conceptual framewok and item selection. Med Care 1992; 30: 473-483.*

24. *Koçyiğit H, Aydemir Ö, Ölmez N, Memiş A. Kisa form-36 (KF-36)'nin Türkçe versiyonunun güvenilirliği ve geçerliliği. İlaç ve Tedavi Dergisi 1999; 12: 102-106.*

25. *Kugo A, Terada S, Ishizu H, et al. Quality of life patients with schizophrenia an a japanese psychiatric hospital. Psychiatry Research 2006; 144: 49-56.*

26. *Norman RMG, Mall AK, McLean T, et al. The relationship of symptoms and level of functioning in schizophrenia to general wellbeing and the Quality of Life Scale. Acta Psychiatr Scand 2000; 102: 303-309.*

27. *Shtasel Pl, Gur RE, Gallacher F, Heimberg C, Gur R. Gender differences in the clinical expression of schizophrenia. Schizophr Res 1992; 7: 225-231.*

28. *Meltzer HY, Burnett S, Bastani B, Ramirez LF. Effects of six months of clozapine treatment on the quality of life chronic schizophrenic patients. Hosp Commun Psychiatry 1990; 41: 892-897.*

29. *Fitzgerald PB, Williams CL, Corteling N, et al. Subject and observer-rated quality of life in schizophrenia. Acta Psychiatr Scand 2001; 103: 387-392.*

30. *Browne S, Clarke M, Gervin M, Waddington JL, Larkin C, O'Callaghan E. Determinants of quality of life at first presentation with schizophrenia. British Journal of Psychiatry 2000; 176: 173-176.*

31. *Kolotkin RL, Crosby RD, Corey-Lisle PK, et al. Performance of a weight-related measure of quality of life in a psychiatric sample. Quality of life research 2006; 15: 587-596.*

32. *Packer S, Husted J, Cohen S, Tomlinson G. Psychopathology and quality of life in schizophrenia. J Psychiatry Neurosci 1997; 22(4): 231-234.*

33. *Kaiser W, Priebe S, Hoffmann K, et al. Subjective quality of life in patients with chronic schizophrenia. Nervenarzt 1996; 67: 572-582.*

34. *Kaiser W, Priebe S, Barr W, et al. Profiles of subjective quality of life in schizophrenic in-and out-patient samples. Psychiatry Research 1997; 66: 153-166.*

35. *Meltzer HY. Dimensions of outcome with clozapine. Br J Psychiatry 1992; 160(17): 46-53.*

36. *Tollefson GD, Beasley CM, Tran PV, et al. Olanzapine versus haloperidol in the treatment of schizophrenia, schizoaffective and schizophreniform disorders: Results of an international collaborative trial. Am J Psychiatry 1997; 4: 457-465.*

37. *Coşar B, Candansayar S. Olanzapin ve şizofrenide kullanimi. Klinik Psikiyatri Dergisi 2003; 1: 15-23.*

38. *Tempier R, Pawliuk N. Influence of novel and conventional antipsychotic medication on subjective quality of life. J Psychiatry Neurosci 2001; 26(2): 131-136.*

Corresponding Author:
Zaliha Akkadin Candan,
Department of Psychiatry,
Ministry of Health,
Kayseri City Education and Research Hospital,
Kayseri,
Turkey,
E-mail: zkokbudak@gmail.com

Financial representation of consumption of the most qualified medicines by ATC classification in the canton of Sarajevo

Vedina Cordalija[1], Nermina Ziga Smajic[2], Edisa Trumic[3], Amir Ljubovic[4], Fahir Becic[2], Kemal Kozaric[5], Emir Kurtovic[5]

[1] Public Institution Psychiatric Hospital of Canton Sarajevo, Sarajevo, Bosnia and Herzegovina,
[2] Faculty of Pharmacy, University of Sarajevo, Sarajevo, Bosnia and Herzegovina,
[3] Faculty of Pharmacy, University of Tuzla, Tuzla, Bosnia and Herzegovina,
[4] Health Insurance for The Canton of Sarajevo, Sarajevo, Bosnia and Herzegovina,
[5] Faculty of Economics, University of Sarajevo, Sarajevo, Bosnia and Herzegovina.

Abstract

Introduction: Health is a basic human right, and the right to health care, which includes the availability of essential medicines, is a basic precondition for exercising this right.

Material and methods: The paper presents an overview of drug consumption by ATC classification for the period 2011-2016, with a review of 2017. The consumption of medicines for the specified period from the essential list was analyzed, as well as the number of prescribed-realized prescriptions of the Health Insurance Institute of the Canton of Sarajevo.

Results: The number of realized recipes grew from year to year. We observed growth from the first quarter to the second quarter, and a decrease in the number of prescriptions made in the third quarter and an increase in the number of prescriptions in the fourth quarter, for the research period. These curves are almost the same for the specified period, except for 2016 when there was a change in the list of essential medicines, where we had an increase in the number of realized prescriptions in the first and second quarters, and then a sharp decrease in the number of prescriptions in the third quarter, and a slight increase in the fourth for 23,786 prescriptions. As for 2017, there are fewer prescriptions than in the previous two years of 2015 and 2016, in the second and third quarters there was a decrease in the number of realized recipes, and in the last quarter an increase in the same.

Discussion: It is clearly noticeable the trend of increasing both the cost of medicines from the essential list and the number of realized prescriptions. Drug consumption grew year on year and in 2016 it was 14,781,418 KM higher than in 2011, the number of prescriptions increased by 26% in 2016 compared to 2011. But rationalization measures in 2017 reduced the consumption of essential list medicines and amounted to 56,995,853, which is 10,811,321 KM less than in 2016. The number of prescriptions is also lower in 2017 and amounts to 4,573,552, or 337,297 recipes in comparisons to 2016. Conclusion: From the above data it can be seen that the inhabitants of the Canton of Sarajevo most often suffer from cardiovascular and metabolic diseases, and often from nervous diseases, and that they are not exempt from diseases that accompany the inhabitants of Europe and other countries.

Key words: *Anatomical-therapeutic-chemical classification of drugs, prescription, rationalization of drug consumption.*

Introduction

Anatomical-therapeutic-chemical classification of WHO drugs (ATC). It is a classification that classifies drugs into 14 groups according to the anatomical groups affected by the group of medicinal products, with the division going up to level 5 i.e., medicinal products with internationally unprotected names generic name of the drug (INN).(1)

ATC system levels: main anatomical group, main therapeutic group, therapeutic subgroup, chemical-therapeutic subgroup, INN (international unprotected name). (1)

The ATC system is information about who's classification of drugs: (1)

A–Medicines with action on the digestive tract and metabolism
B–Medicines with effects on the blood and blood organs
C–Medicines with effects on the cardiovascular system
D–Medicines with effect on the skin
G–Drugs with action on the urogenital tract
H–Drugs with effect on the system of glands with internal secretion (except sex hormones)
J–Medicines for the treatment of systemic infec-tions (except infections caused by parasites)
L–Medicines for the treatment of malignancies and immunomodulators
M–Medicines with effect on the bone-muscular system
N–Medicines with action on the nervous system
P–Medicines for the treatment of infections caused by parasites
R–Drugs with effect on the respiratory organ system
S–Drugs with action on the senses
V–Various

Material and methods

The paper presents an overview of drug consumption by ATC classification for the period 2011-2016, with a review of 2017. The consumption of medicines for the specified period from the essential list was analyzed, as well as the number of prescribed-realized prescriptions of the Health Insurance Institute of the Canton of Sarajevo. In addition, it analyzed the number of prescriptions realized per quarter for the same period, how much consumption per insurer was year-on-year, what the number of prescriptions per insurer was, and whether all insurers of the Canton of Sarajevo were also users of pharmaceutical services. The total consumption of medicines for the specified period and the number of prescriptions realized for the same period was analyzed, as well as the average price of medicine per prescription.

Results

According to the cost of drugs, the highest cost belongs to drugs used in diseases of the cardiovascular system (group C) and ranged from almost 19 to 24 million, that is, an average participation of 31.71%. After them, the most prevalent are drugs that act on the digestive tract and metabolism (group A) and ranged from 17 to almost 21 million, with an average participation of 27.90%. Third place belongs to a group of drugs that act on the nervous system (Group N) with cost participation of 6 to 8 million, or 9.94%. This is followed by a group of drugs that operate on the respiratory system (Group R) at a cost of 4.6 million to 6.7 million, or 7.54%. In fifth place is the group of drugs for the treatment of systemic infections (group J), with a cost reduction movement of 5.3 to 3.9 million, with an average participation of 6.90%. This group has had a cost reduction since 2012 compared to 2011 by about 400,000 KM. Also, the same decrease in 2016. compared to 2015, and the total decrease in consumption amounts to about 800,000 KM.

The following tables will show the medicines represented on the essential list of Sarajevo Cantons with protected drug names, as well as the display of the ten most qualified medicines, as well as the index compared to consumption in the previous year.

Plavix generic clopidogrel increased consumption by 58% in 2011 compared to 2010. *Noviix* (insulin) increased consumption by 28%, *Lantus* (insulin) increased consumption by 22%, and *Seretide* by 24%.

In the first place in this table is *Lantus* with a cost of 2,920,705KM (insulin), then *Enap H* (hypertensive) at a cost of 2,009,705KM, then again, we have insulin Noviix at a cost of 2,007,974KM, and again the antihypertensive *Lopril H* at a cost of 1,890,031 KM. Insulins are on the rise with consumption, as is Controloc generic pantoprazole, which increased consumption by 27% year-on-year.

The table shows that in the first place at the cost of funds is again insulin *Lantus*, as in the previous year, with consumption increased to KM 3,103,490 by KM 182,785, or by 6%, followed again by insulin *Noviix*, whose consumption amounted to KM 2,090,615, which also increased

Table 1. Consumption of medicinal products by ATC classification for the period 2011-2016 (KM)

ATC klasification	2011.	2012.	2013.	2014.	2015.	2016.
A (Medicines with action on the digestive tract and metabolism)	16.858.064	17.893.723	17.930.974,44	20.257.288	21.685.643	20.757.511
B (Medicines with effects on the blood and blood organs)	2.018.317	2.047.834	1.275.024,07	1.322.385	1.449.810	1.147.462
C (Medicines with effects on the cardiovascular system)	18.956.184	21.456.762	22.690.779,36	21.042.473	23.237.651	24.382.596
D (Medicines with the effect on the skin)	1.412.203	391.301	399.248,04	496.842	493.431	382.583
G (Drugs with action on urogenital tract)	910.538	1.098.810	1.365.660,35	1.828.060	2.054.284	1.917.460
H (Drugs with effect on the system of glands with internal secretion (except sex hormones)	1.412.203	1.563.287	1.972.299,30	2.163.491	2.301.372	2.372.509
J (Medicines for the treatment of systemic infections (except infections caused by parasites)	5.358.895	4.929.627	4.744.614,36	4.874.346	4.394.081	3.967.749
L (Medicines for the treatment of malignancies and immunomodulators)	172.957	205.191	312.602,79	378.319	361.109	340.908
M (Medicines with effect on the bone-muscular system)	1.555.754	2.082.021	2.360.245,24	2.069.502	2.172.186	1.925.407
N (Medicines with action on the nervous system)	6.049.179	5.896.407	6.416.874,80	7.364.829	7.738.925	8.207.268
P (Medicines for the treatment of infections caused by parasites)	204	12.064	15.978,52	14.328	10.727	1.446
R (Drugs with effect on the respiratory organ system)	4.610.567	4.500.151	4.594.039,99	5.179.523	5.739.137	6.699.479
S (Drugs with action on the senses)	639.562	1.031.268	1.376.699,30	1.354.868	1.481.663	1.566.710
V (various)	1.847.711	2.104.598	2.491.571,27	2.860.233	3.018.742	2.642.359
TOTAL	60.807.926	65.213.044	67.946.612	71.206.487	76.138.761	76.311.447

Table 2. A review of the 10 most-written drugs in 2011 By Cost Amount

Ordinal number	Name of medicine	Amount 2010	Amount 2011	Index 11/10
1	LANTUS maxi pad 100i.j./ml 5x3ml	2.151.792	2.631.080	122
2	LOPRIL H pills (10+12,5) mg 20 pills	2.754.503	2.217.370	80
3	ENAP H pills 10+25mg 20 pills	1.938.559	2.059.426	106
4	NOVOMIX 30 flex pen 100 i.j./ml 5 x 3ml	1.346.924	1.730.647	128
5	NITROGLICEROL RETARD ret. caps. 2,5mg 20 capsules	1.439.692	1.425.159	99
6	SERETIDE nebulizer 25/250 mcg 120 dose	881.868	1.091.335	124
7	PLAVIX film pills 75 mg 28 pills	633.794	1.002.649	158
8	DILATREND pills 6,25mg 28 pills	934.568	993.351	106
9	CONTROLOC pills 20mg 28 pills	933.330	949.292	102
10	HUMULIN M3 injections 100i.j./ml 5x3ml	1.133.517	919.911	81

Table 3. Review of the ten most prescribed medicines in 2012 by cost amount

Ordinal. number	Name of medicine	Amount 2011	Amount 2012	Index
1	LANTUS maxi pad 100i.j./ml 5x3ml	2.631.080	2.920.705	111
2	ENAP H pills (10+25) mg 20 tbl.	2.059.426	2.009.449	98
3	NOVOMIX 30 flex pen 100 i.j./ml 5 x 3ml	1.730.647	2.007.974	116
4	LOPRIL H pills (10+12,5) mg 20 pills	2.217.370	1.890.031	85
5	NITROGLICEROL ret. capsules 2,5 mg 20 caps.	1.425.159	1.394.863	98
6	SERETIDE CFC FREE NEBULIZER 25/250 mcg 120 dose	1.091.335	1.240.878	114
7	CONTROLOC pills 20mg 28 pills	949.292	1.210.024	127
8	BERLITHION capsules 300 mg 30 caps.	864.409	923.369	107
9	PLAVIX film pills 75 mg 28 pills	1.002.649	917.966	92
10	HUMALOG mix 25 kwik pen injections 100i.j./1ml 5x3 ml	759.027	886.557	117

Table 4. A review of the ten most-written drugs in 2013 by cost amount

Ordinal number	Name of medicine	2012	2013	Index 13/12
1	Lantus u 100i.j./ml 5x3ml	2.920.705	3.103.490	106
2	Novomix 30 flex pen 100 i.j./ml 5 x 3ml	2.007.974	2.090.615	104
3	Enap H pills (10+25) mg 20 pills	2.009.449	1.801.809	90
4	Lopril H pills (10+12,5) mg 20 pills	1.890.031	1.651.272	87
5	Seretide cfc free inebulizer 25/250 mcg 120 dz	1.240.878	1.321.992	107
6	Controloc pills 20mg 28tbl.	1.210.024	1.300.824	108
7	Nitroglicerol ret. capsules2,5 mg 20 caps.	1.394.863	1.096.674	79
8	Norditropin nordilet 10mg/1,5ml	720.035	953.725	132
9	Humalog mix 25 kwik pen injections 100i.j./1ml 5x3 ml	886.557	949.238	107
10	Levemir flexpen injections 100i.j./ml 5x3ml	830.684	901.134	108

Table 5. A review of the 10 most--written drugs in 2014 by cost amount

Ordinal number	Name of medicine	2013	2014	Index 14/13
1	LANTUS maxi pad 100i.j./ml 5x3ml	3.103.489,50	3.233.152,98	104
2	NOVOMIX 30 flex pen 100 i.j./ml 5 x 3ml	2.090.614,77	1.983.485,39	95
3	LOPRIL H pills (10+12,5) mg 20 pills	1.651.271,65	1.499.459,98	91
4	JANUVIA film.obl.tbl. 28x100 mg	101.581,98	1.442.537,04	1.420
5	ENAP H tablete (10+25) mg 20 tbl.	1.801.809,32	1.405.979,68	78
6	SERETIDE CFC FREE INHALER 25/250 mcg 120 dose	1.321.991,54	1.400.574,58	106
7	CONTROLOC pills 20mg 28tbl.	1.300.823,96	1.385.151,14	106
8	NORDITROPIN NORDILET 10mg/1,5ml	953.724,66	1.057.263,62	111
9	HUMALOG mix 25 kwik pen inj. 100i.j./1ml 5x3 ml	949.238,08	1.024.216,49	108
10	LEVEMIR FlexPen injections 100i.j./ml 5x3ml	901.133,75	972.811,00	108

by 4% compared to the previous year. *Norditropin Nordilet* (growth hormone) increased consumption by 32% compared to 2012

From the table it is apparent that most of the cost of the drugs went back to insulin – *Lantus*, with a cost share of 3,233,152, the cost increased by 4% from the previous year, followed by Insulin *Noviix*, whose cost has been reduced by 5% compared to 2013, and the antihypertensive Lopril H with a cost share of 1,499,459 KM. Compared to the previous two years, we have the drug *Januvia,* which is one of the new medicines for metabolic

diseases (in diabetes), costing 1,442,537 KM and up 420% from the previous year. In fifth place we have the antihypertensive *Enap H* with a cost share of 1,405,979 KM.

In 2015, the drug *Lantus* came first as in previous years, followed by *Januvia* medicine, which again increased the cost from the previous year by 179% to 2,582,990KM. Then insulin *Noviix* with a cost participation of 1,904,865KM, in fourth place is the drug *Lopril H* with a cost of 1,469.717KM, in fifth place is the *Seretide* inhaler with a cost of 1,379,493KM.

In the first place for financial spending for 2016, the number of people who have been affected by the financial crisis has been 1.5%. In 2014, the drug *Lantus*, as well as the previous analyzed years, with a cost of 3,298,871 KM and increased consumption by 2%, is the second medicine of *Januvia* as in 2015. 2015 with a cost share of 2,649,896 and increased consumption by 3% compared to 2015. Insulin *Noviix* with a 4% reduction in costs, in fourth place is also insulin Humalog, which in previous years was not in the top five at the expense, and whose spending for 2016 was $1.25 per person. Year is 1,391,929 KM and increased from 2015 to 2016. 13%, followed by antihypertensive *Lopril H* with a cost of 1,258,609 KM and a 14% reduction in consumption compared to 2015.

Analysis and report of prescribed prescriptions from 2011 to 2014 until 2016

It analyzed the number of prescribed prescriptions by age, while separating the number of recipes per quarter, where in some quarters the number of prescriptions decreased and, in some quarters, grew, as can be seen in one of the following charts.

Table 6. A review of the 10 most-written drugs in 2015 by cost amount

O.n.	Name of medicament	2014	2015	Index 15/14
1	LANTUS maxi pad 100i.j./ml 5x3ml	3.233.152,98	3.242.390,05	100
2	JANUVIA film.obl.pills 28x100 mg	1.442.537,04	2.582.990,94	179
3	NOVOMIX 30 flex pen 100 i.j./ml 5 x 3ml	1.983.485,39	1.904.865,45	96
4	LOPRIL H pills (10+12,5) mg 20 pills	1.499.459,98	1.469.717,81	98
5	SERETIDE CFC FREE INHALER 25/250 mcg 120 dose	1.400.574,58	1.379.493,65	98
6	CONTROLOC pills 20mg 28 pills	1.385.151,14	1.336.308,50	96
7	HUMALOG mix 25 kwik pen inje 100i.j./1ml 5x3 ml	1.024.216,49	1.234.124,03	120
8	ENAP H tablete (10+25) mg 20 pills	1.405.979,68	1.186.730,27	84
9	NORDITROPIN NORDILET 10mg/1,5ml	1.057.263,62	1.132.573,98	107
10	LEVEMIR FlexPen injections 100i.j./ml 5x3ml	972.811,00	1.037.897,85	107

Table 7. Overview of the ten most prescribed medicines from the positive list in 2016 by cost amount

O.n.	Name of medicament	2015	2016	Index 16/15
1	*LANTUS maxi pad 100i.j./ml 5x3ml*	3.242.390,05	3.298.871,85	102
2	JANUVIA film.obl.pills 28x100 mg	2.582.990,94	2.649.896,52	103
3	NOVOMIX 30 flex pen 100 i.j./ml 5 x 3ml	1.904.865,45	1.825.111,98	96
4	HUMALOG mix 25 kwik pen injections 100i.j./1ml 5x3 ml	1.234.124,03	1.391.929,99	113
5	LOPRIL H pills (10+12,5) mg 20 tbl.	1.469.717,81	1.258.609,78	86
6	SERETIDE CFC FREE INHALER 25/250 mcg 120 dose	1.379.493,65	1.166.378,84	85
7	Victoza ras.za inj. 6mg/ml (18mg/3ml)x2	901.136,90	1.045.973,26	116
8	Foster suspension p od prit.180d(6+100)mcg/d.	585.516,65	1.042.331,57	178
9	LEVEMIR FlexPen injections 100i.j./ml 5x3ml	1.037.897,85	988.379,00	95
10	Onbrez Breezhaler powder for inh.caps. 30x150 mcg	663.866,72	909.760,11	137

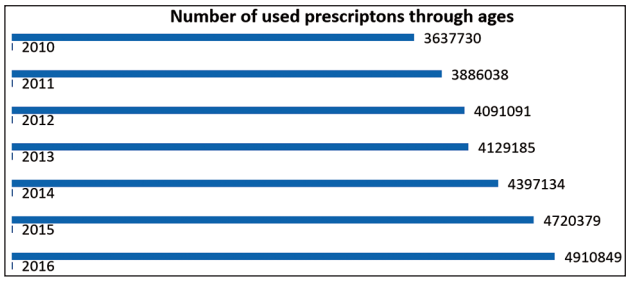
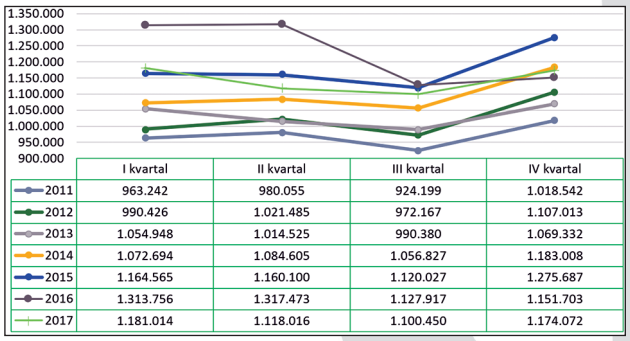


Chart 1. View the number of prescribed prescriptions for 2010 to 2014–2016.

The chart shows the number of recipes realized by age, where the number of recipes has clearly increased year after year, the number of prescriptions realized in 2010. In 2014, it was 3,637,730, bringing the number of prescriptions realized in 2016 to 3,637,730. In 2014 it was 4,910,849. The number of prescriptions realized in 2016 was 12,000. In 2010, it was up 35 per cent from 2010.

The following graphic shows a trend in the number of recipes per quarter for the period in question.



	I kvartal	II kvartal	III kvartal	IV kvartal
2011	963.242	980.055	924.199	1.018.542
2012	990.426	1.021.485	972.167	1.107.013
2013	1.054.948	1.014.525	990.380	1.069.332
2014	1.072.694	1.084.605	1.056.827	1.183.008
2015	1.164.565	1.160.100	1.120.027	1.275.687
2016	1.313.756	1.317.473	1.127.917	1.151.703
2017	1.181.014	1.118.016	1.100.450	1.174.072

Chart 2. Number of used recepies according to quarters for period 2011 – 2017.

The table shows that the average price of a drug of 13.65 KM per prescription in 2011 was 13.65 KM per prescription. In 2013 it grew to 17.10 KM in 2013. In 2014, and then declined regardless of the increased total number of prescriptions, but given the revision of the list of essential medicines each year and the price drop that was evident, there was also a drop in the average price of prescription medicines.

The number of prescriptions per insurer has increased year after year, despite the growing number of insured persons in the Canton of Sarajevo from 414,566 (2011) to 430,900 (2016), and the number of prescriptions increased from 3,886,038 (2012), to 4,910,849, or 35% increased the number of prescriptions for the period specified.

The table shows data with the number of service users moving through the system relative to the number of insurers per month, and the percentage of service users at the year level. The percentage of users ranged from 60 per cent in 2011 to 60 per cent in 2014. 2017 to the number of insured persons from 414,566 to 57.2% in 2017. In 2014, when there were 428,470 insured persons.

It can be concluded from this table that about 60% of service users take medicines, while the remaining 40% do not use them, i.e. 60% of users make the specified medical expenses and other health care costs.

Table 8. Overview of the consumption of medicines from the essential list and the number of prescriptions for the period 2011-2017

Description	2011	2012	2013	2014	2015	2016	2017
Cost of medicines from the essential list of C.S	53.025.756	57.161.642	59.798.476	62.320.766	66.674.441	67.807.174	56.995.853
Number of prescription	**3.886.038**	**4.091.091**	**4.129.185**	**4.397.134**	**4.720.379**	**4.910.849**	**4.573.552**

Table 9. Presentation of the average price of medicaments and the number of prescriptions per insurer for the period 2011-2016

Description	2011	2012	2013	2014	2015	2016
Average prize of drug according to prescription	13,65	16,5	17,1	16,8	16,7	16,2
Number of prescriptions per insurer	9,37	9,69	9,81	10,41	11,04	11.39

Table 10. View the number of service users (insured persons) per month for the period 2011 to 2014 until 2017

Period	2011	2012	2013	2014	2015	2016	2017
January	97.827	96.412	106.918	106.487	109.284	110.534	113.153
February	97.359	92.424	106.839	105.225	109.071	119.393	111.177
March	105.539	107.534	105.916	111.803	116.768	123.871	116.635
April	102.373	106.991	107.982	111.144	114.856	116.900	111.444
May	97.917	102.192	102.284	104.458	103.923	113.092	112.543
June	97.581	98.042	95.737	102.135	104.039	112.692	107.557
July	87.511	93.426	98.775	98.123	98.491	104.088	104.082
Avgust	88.457	91.733	90.496	95.600	96.683	105.774	106.020
September	98.968	95.924	99.404	107.681	104.128	106.791	107.583
October	100.572	104.652	105.899	113.025	115.158	111.597	110.597
November	100.772	108.755	104.856	107.047	109.744	114.264	114.991
December	107.783	108.576	111.730	121.791	116.399	120.826	115.748
Annual number of users	**248.537**	**250.056**	**253.159**	**259.270**	**255.059**	**252.598**	**245.248**
Number of insurers	**414.566**	**421.962**	**420.880**	**422.235**	**427.359**	**430.900**	**428.470**
% users	**60,0%**	**59,3%**	**60,1%**	**61,4%**	**59,7%**	**58,6%**	**57,2%**

Discussion

By analyzing the drugs in ATC groups through these periods, it is evident that the percentage and financially most represented drugs of Group C and A. So the insurers of the Canton of Sarajevo suffer the most from cardiovascular disease, which normally accounts for 53% of the causes of mortality.

In recent years, the Federation of Bosnia and Herzegovina has seen a continuous increase in mortality rates from cardiovascular diseases expressed as a rate per 100,000 inhabitants, up from 335.2 in 2010. 507.5 in 2016. (Data from the Institute of Public Health of the Federation of Bosnia and Herzegovina) The leading diseases in the cardiovascular disease group are: stroke, cardiomyopathy, cardiac arrest, acute myocardial infarction and hypertension.

The increase in mortality is recorded especially in hypertension, at a rate of 24.5 per 100,000 inhabitants in 2010. 2016 to 41.2 per 100,000 inhabitants in 2016. In 2014, as well as an increase in mortality from acute myocardial infarction, rates of 69.2 per 100,000 to 90.6 per 100,000 inhabitants in 2016 were 100,000.(2)

According to WHO data, non-infectious diseases kill about 40 million people each year, 15 million of whom are between the ages of 30 and 70. More than 80% of those deaths fall into the "premature" category. The majority of lives are taken by cardiovascular disease, 17.7 million a year, followed by cancer with 8.8 million, respiratory diseases with 3.9 million and diabetes that kills 1.6 million people.(3) The above mentioned data shows that the insurers of the Canton of Sarajevo are not exempt from diseases that accompany the inhabitants of Europe and other countries.

It is clearly a noticeable trend of rising costs for essential list medicines as well as the number of realized prescriptions. Drug consumption grew year after year and in 2016. In 2014, it was 14,781,418 KM higher than in 2011. In 2016, the number of prescriptions increased by 26% in 2016. 2011 compared to 2011. But the rationalization measures of 2017 are not going to change. In 2014, the consumption of medicines from the essential list decreased to 56,995,853, down 10,811,321 KM from 2016. Year. The number of prescriptions is also lower in 2017. In 2014, it stood at 4,573,552, or 337,297 recipes in 2016.

Costs for medicines have also risen even as drug prices have fallen each year and the list has been revised, but new medicines have also been put on the list.

Conclusion

By analyzing drug consumption by ATC classification, it was observed that the first consumption was group C drugs that worked on the cardiovascular system, whose consumption was up to 24 million KM, followed by Group A, with nearly 21 million KM, and group N drugs that worked on the nervous system, which was represented with cost participation of up to 8 million KM. This analysis can indeed show that the inhabitants of Sarajevo Canton most often suffer from cardiovascular and metabolic diseases, and often from nervous diseases. According to WHO data, cardiovascular diseases are the leading non-communicable diseases that cause high mortality in residents.

There was a 3% increase in sanitary materials compared to the previous year, but at the same time registered a slight increase in insulin users compared to the previous year.

Consumption of sanitary material is directly correlated with the growing number of insulin patients and the way of dosing insulin, as well as the total number of insulins patients in the canton of Sarajevo.

References

1. *Anatomical Therapeutic Chemical (ATC) classification index, WHO Collaborating Centre for Drug Statistics Methodology, Oslo, Norway, 2012. www.whocc.no*
2. *Zdravstveno stanje stanovništva i zdravstvena zaštita u Federaciji Bosne i Hercegovine 2017. Godina - Zavod za Javno zdravtsvo FBiH.*
3. *World Heart Federation 2017. – ZZJZFBiH.*
4. *Podaci preuzeti od Zavoda zdravstvenog osiguranja Kantona Sarajevo.*
5. *Odluka o pozitivnoj, bolničkoj i magistralnoj listi Kantona Sarajevo, „Službene novine Kantona Sarajevo" br. 27/16.*
6. *Odluka o izmjeni i dopuni odluke o listi lijekova obaveznog zdravstvenog osiguranja Federacije Bosne i Hercegovine, Službene novine FBiH broj 27/16.*
7. *The WHO Action Programme on Essential Drugs (DAP) 1997., Pharmaceutical markets:structure and performance page 14.*
8. *WHO Medicines Strategy 2008 – 2013.*
9. *World Health Organization. WHO Medicines Strategy. Countries at the core 2004.-2007.*
10. *Obračun sredstava u zdravstvu za 2014.godinu, Zavod zdravstvenog osiguranja i reosiguranja Federacije Bosne i Hercegovine, Sarajevo, juni 2015.*

Corresponding Author
Vedina Cordalija,
Public Institution Psychiatric Hospital of Canton Sarajevo,
Sarajevo
Bosnia and Herzegovina,
E-mail: cordalija.vedina@gmail.com

One-year results of Covid 19 pandemia in our intensive care units

Harun Tolga Duran, Ulku Ince

Unye state hospital, Anesthesiology and reanimation department, Ordu, Turkey.

Abstract

Introduction: COVID-19 infection is a disease characterized by acute respiratory distress syndrome (ARDS) and hypoxia. It is known that features such as advanced age, male gender, and the presence of additional disease play a role in the clinical course of the disease in COVID-19 patients. The aim of our study is to reveal the clinical course and mortality of patients infected with COVID 19 in the anesthesia intensive care units of our hospital over a one-year period.

Method: The data of all patients who were treated for covid 19 in anesthesia intensive care units between March 31, 2020 and March 31, 2021 were scanned. 134 patients were enrolled in the study. The patients who lost their lives were grouped as Group 1, and the patients discharged from the intensive care unit as Group 2. Groups were compared in terms of age, gender, comorbidity, length of stay, application of invasive mechanical ventilation support, and death.

Results: The mean age of Group 1 was 74 ± 12 and the mean age of Group 2 was 67 ± 11. 54 of the patients in group 1 and 80 of those in group 2 were female. The condition of having 2 or more diseases in group 1 was found to be significantly higher than group 2. MV support was used in the follow-up of all patients in Group 1. It was observed that 7 of those in group 2 were applied mv support.

Conclusion: During the Covid 19 pandemic, many studies were added to the literature, and many studies emphasized that advanced age, comorbidity and male gender have an effect on the severity and mortality of the disease, and patients who receive IMV support have a more mortal course. The results of our study were found similar to those studies. It was observed that the results did not change in the patients who were followed for a year. Still co-morbid disease poses a risk for male gender and advanced age covid 19.

Key words: Covid 19, Intensive care unit, Mechanical ventilation

Introduction

COVID-19 infection is a disease characterized by acute respiratory distress syndrome (ARDS) and hypoxia (1). With the COVID-19 pandemic, the health systems of countries all over the world are struggling due to the increasing number of cases and deaths. One of the heaviest burdens falls on intensive care units. It is known that features such as advanced age, male gender, and the presence of comorbidity play a role in the clinical course of the disease in COVID-19 patients [2]. Numerous studies have shown that advanced age is an independent risk factor for death in COVID-19 patients. Patients over the age of 75 account for almost half (47%) of all deaths, and the mortality rate of infected patients over 80 years old is 14.8% [3-4-5.] The most common cause of death is acute hypoxemic respiratory failure from acute respiratory distress syndrome (ARDS). [6] For all these reasons, many patients need to be followed up in the intensive care unit. More than a year has passed since the Covid 19 pandemic began. In this process, many treatment methods have been applied and the virus has mutated many times. The aim of our study is to reveal the clinical course and mortality of Covid 19 disease in a one-year period by reviewing the medical records of patients hospitalized for one year after the first follow-up of patients infected with COVID 19 in the anesthesia intensive care units of our hospital.

Method

After the approval of the ethics committee; The data of all patients who were treated for covid 19 in anesthesia intensive care units between March 31, 2020 and March 31, 2021 were scanned. 7 pa-

tients who were hospitalized after March 31, 2021 were excluded from the study. A total of 204 patients who were contacted with vertebral column were included in the study. It was observed that 134 patients died and 70 patients were discharged from the intensive care unit. The patients who lost their lives were grouped as Group 1 and the patients discharged from the intensive care unit as Group 2. Groups were compared in terms of age, gender, comorbidity, length of stay, application of invasive mechanical ventilation support, and death.

Inclusion criteria

Patients aged 18 and over who admitted to our hospital with complaints such as fever, cough and shortness of breath, and whose diagnosis of COVID-19 was supported by the detection of nucleic acid by polymerase chain reaction in the respiratory tract after the diagnostic imaging findings of COVID-19 infection were confirmed by a radiologist and met the criteria for admission to intensive care.

Exclusion criteria from the study

Patients who were incomplete in the data and whose hospitalization continued after 31 March 2021 were not included in the study.

Criteria for admission to intensive care

Respiratory rate above 20 and oxygen saturation of 90 and below despite the 100% oxygen support of 5 lt / min with a reservoir oxygen mask, or invasive mechanical ventilation support was applied to emergency departments with respiratory distress.

Invasive mechanical ventilation application criteria

In spite of HFNO or CPAP support, he was taken to invasive mechanical ventilation support in cases with oxygen saturation below 90%, respiratory rate above 20 20 and deterioration of the patient's hemodynamic findings.

Statistical analysis

SPSS v20 program was used to analyze the data. Categorical variables were presented as number and percentage, numerical variables as mean and standard deviation. The distribution of categorical variables between groups was analyzed with the KI-Square test. The compatibility of the numerical variables to the normal distribution was investigated by the kolmogrof-simirnov test and graphing method. Mann Whitney-U test was used for comparisons of numerical variables that were not distributed normally. $P < 0.05$ was considered statistically significant. Pearson correlation analysis was conducted to examine the correlation of the data.

Results

The mean age of Group 1 was 74 ± 12 and the mean age of Group 2 was 67 ± 11. The mean age of Group 1 was significantly higher than the average age of Group 2 (p: 0.00). The average length of stay in Group 1 was 11 ± 8 and 15 ± 19 in Group 2. There was no difference between the groups (p: 0.26).

54 of the patients in group 1 and 80 of those in group 2 were female. The groups were not different in terms of gender (p: 0.72).

The condition of having 2 or more diseases in group 1 was found to be significantly higher than group 2.

It was observed that 14 of the patients in group 1 and 1 of the patients in group 2 came to the intensive care unit due to intubation and MV (p: 0.01).

MV support was used in the follow-up of all patients in group 1. In group 2, it was observed that 7 members of the group received mv support (p: 0.00). One of these 7 patients was tracheostomized and sent to another intensive care unit because the isolation period from MV support ended and the pcr test became negative twice in a row. Other patients were discharged to the service. Another patient was transferred to the intensive care unit again due to status epilepticus after leaving the mechanical ventilator and discharged to the service. Intensive care admission for the second time was not included in the study. The rate of discharging from the mechanical ventilator from

Table 1. Comparison of the groups in terms of demographic data and comorbid diseases

	Grup1 (N:134)	Grup2 (N:70)	p
AGE	74±12	67±11	0,00
Duration hospital	11±8	15±19	0,26
F/M	54/80	30/40	0,72
DM	49	27	0,77
HT	104	49	0,23
Cardiovascular disease	38	14	0,19
Pulmonary disease	34	14	0,39
Cerebrovascular disease	21	13	0,59
Chronic kidney disease	14	3	0,13
Two and more comorbidites	93	36	0,01

F/M:Female/Male, DM: Diabetes Mellitus HT:Hypertension

the intensive care unit to the infection service was 4.28% of all patients who received iMv support.

A positive correlation was found between age and presence of HT and CAD. (P: 0.00, r: 0.18) and (p: 0.01, r: 0.17), respectively. There was a positive correlation between 2 or more diseases and age (p: 0.00, r: 0.19). There was a positive correlation between age and death (p: 0.00, r: 0.25). A positive correlation was found between age and imv support (p: 0.00, r: 0.25).

A positive correlation was found between length of stay and discharge (p: 0.03, r: 0.14)

There was a positive correlation between the presence of 2 or more diseases and death (p: 0.01, r: 0.17). There was no correlation between other parameters and death.

Discussion

The effects of the COVID-19 pandemic on mortality rates and the health system have been discussed for a long time. The 1-year mortality rate has been estimated to be between 4 and 46% [7]. It is known that factors such as hypertension, diabetes mellitus, presence of chronic disease, male gender play a role in COVID-19 infections [8]. In a study examining mortality rates in people infected with covid-19 in centers such as nursing homes, advanced age and people in need of social care indicate an increase in both the incidence and mortality rates of this infection [9-10].

In our study, it was observed that the average age of the patients who were followed up in the anesthesia intensive care units of our hospital during a 1-year period was above 65. In addition, the average age of the patients who died was found to be higher in the group. When we assume that covid 19 is more severe in patients receiving IMV support; IMV support with age and positive correlation with death may indicate that the severity of the disease and mortality increase as the age gets older.

The female to male ratio was similar between the groups. However, the number of female patients admitted to intensive care units was 84, while the number of male patients was 120. This situation may indicate that the disease is more severe due to the greater need for intensive care in male patients.

In some studies, it is known that the presence of chronic pulmonary heart and neurological diseases brings the need for IMV support in the intensive care units of the patients. (11th) . In our study, the most common comorbidities were Diabetes mellitus, hypertension, chronic heart disease, and chronic lung disease, respectively. Additional diseases of the groups were similar between the groups. However, the presence of two or more additional diseases in the patients was statistically higher in group 1 patients compared to group 2 patients. In addition, a positive correlation was found between having 2 or more diseases and death. Therefore, we can think that the increase in the comorbidities of the patients increases the risk of death.

In our study, it was observed that most of the patients who received IMV support lost their lives. It was observed that the need for intubation and mechanical ventilation increased in patients infected with Covid 19 and most of these patients

died [12]. ARDS that develops in severe patients and the development of inflammatory response associated with it are shown. [13] Pulmonary edema, alveolar damage and Atelectasis causes high mortality. [14-15-16] In our study, it was observed that critical covid-19 patients were taken into intensive care and 134 out of 204 patients who were taken into intensive care units lost their sickness. We think that the factors that cause this cause of mortality are the fact that our patients are elderly and only severe covid 19 patients are taken into intensive care. In addition, only 7 patients (4.28%) who needed IMV support were discharged from mechanical ventilation and were discharged to the service. In other studies, the mortality rate in patients who received IMV support was high [12]. Similar results were obtained in our study. It is important to know that these patients who receive IMV support have more severe disease.

Conclusion

During the Covid 19 pandemic, many studies have been added to the literature, and many studies have emphasized that advanced age, additional disease and male gender affect the severity and mortality of the disease, and patients who receive IMV support have a more mortal course. The results of our study were found similar to those studies. It was observed that the results did not change in patients who were followed for a year. Still comorbid disease poses a risk for male gender and advanced age Covid 19.

Referencess

1. *Williamson EJ, Walker AJ, Bhaskaran K, et al. Factors associated with COVID-19 death in 17 million patients using OpenSAFELY. Nature. 2020; 584(7821): 430-436. doi:10.1038/s41586-020-2521-4*

2. *Huang C, Wang Y, Li X, et al. Clinicalfeatures [publishedcorrectionappears in Lancet. 2020 Jan 30:]. Lancet. 2020; 395(10223): 497–506.*

3. *Inglis R, Ayebale E, Schultz MJ. Optimizing respiratorymanagement in resource-limitedsettings. CurrOpinCritCare, 2019; 25: 45–53.*

4. *Chen N, Zhou M, Dong X, et al. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptivestudy. Lancet. 2020; 395(10223): 507–513.*

5. *Cheng Y, Luo R, Wang K, et al. Kidney disease is associated with in-hospital death of patients with COVID-19. Kidney Int. 2020; 97(5): 829–838. doi:10.1016/j.kint.2020.03.005*

6. *Raoof S, Nava S, Carpati C, Hill SN, High-Flow, NoninvasiveVentilation and Awake (Nonintubation) Proning in Patients With Coronavirus Disease 2019 With Respiratory Failure CHEST 2020; 158(5): 1992-2002.*

7. *Banerjee A, Pasea L, Harris S, Gonzalez-Izquierdo A, Torralbo A, et al. Estimating excess 1-year mortality associated with the COVID-19 pandemic according to underlying conditions and age: a population-based cohort study. Lancet. 2020 May 30; 395(10238): 1715-1725. doi: 10.1016/S0140-6736(20)30854-0. Epub 2020 May 12. PMID: 32405103; PMCID: PMC7217641.*

8. *Mikami T, Miyashita H, Yamada T, Harrington M, Steinberg D, Dunn A, Siau E. Risk Factors for Mortality in Patients with COVID-19 in New York City. J Gen Intern Med. 2021 Jan; 36(1): 17-26. doi: 10.1007/s11606-020-05983-z. Epub 2020 Jun 30. PMID: 32607928; PMCID: PMC7325642.*

9. *Oliver D. David Oliver: let's be open and honest about covid-19 deaths in care homes. BMJ 2020; 369: m2334. doi:10.1136/bmj.m2334 pmid:http://www.ncbi.nlm.nih.gov/pubmed/32554433*

10. *Guan WJ, Liang WH, ZhaoY, et al. Comorbidity and its impact on 1590 patients with COVID-19 in China: a nationwide analysis [manuscript published online ahead of print 26 March 2020] .Eur Respir J 2020 .*

11. *Thibodeaux K, Speyrer M, Raza A, Yaakov R, Serena TE. Hyperbaric oxygen therapy in preventing mechanical ventilation in COVID-19 patients: a retrospective case series. Journal of wound care, 2020; 29(Sup5a): S4-S8.*

12. *Cheung TM, Yam LY, So LK, et al. Effectiveness of noninvasive positive pressure ventilation in the treatment of acute respiratory failure in severe acute respiratory syndrome. Chest 2004; 126: 845–850.*

13. *Lentz S, Roginski MA, Montrief T, Ramzy M, Gottlieb M, Long B. Initial emergency department mechanical ventilation strategies for COVID-19 hypoxemic respiratory failure and ARDS. The American Journal of Emergency Medicine. 2020.*

14. *Poston JT, Patel BK, Davis AM, Management of critically ill adults with COVID-19 JAMA (2020); 10.1001/jama.2020.4914*

15. *COVID-19 Treatment Guidelines Panel Coronavirus Disease 2019 (COVID-19) Treatment Guidelines National Institutes of Health (2020) Available at https://www.covid19treatmentguidelines.nih.gov/ (Accessed June 15, 2020)*

16. *Alhazzani W, Møller MH, Arabi YM, Loeb M, Gong MN, Fan E, et al. Surviving Sepsis Campaign: guidelines on the management of critically ill adults with Coronavirus Disease 2019 (COVID-19) Intensive Care Med (2020), 10.1007/s00134-020-06022-5*

Corresponding Author:
Ulku Ince,
Unye State Hospital,
Anesthesiology and reanimation department,
Ordu,
Turkey,
E-mail: ulku84ince@yahoo.com

A new gene mutation of PRKAR1A was found in a Carney complex case

Li Yang[1], Hai-Xuan Ding[2], Yue Jiang[2], Li-Ping Chen[1], Juan Luo[1], Lang-Bo Li[1], Kai Chen[1], Ling-Yun Huang[1], Han-Ying Luo[1], Xin-Lan Zhao[1]

[1] Department of Endocrinology, Hunan Provincial People's Hospital, (The First Affiliated Hospital of Hunan Normal University), Changsha, Hunan, China,

[2] Department of Endocrinology, The First Affiliated Hospital of Hunan Normal University, (Hunan Provincial People's Hospital),Changsha, Hunan, China.

Abstract

Purpose: Primary Pigmented Nodular Adrenocortical Disease (PPNAD) is a rare bilateral adrenocortical hyperplasia, inherited in an autosomal dominant fashion, resulting in a pro-adrenocorticotropic non-dependent Cushing's syndrome. PPNAD may be isolated or associated with Carney complex (CNC). For the diagnosis of PPNAD and CNC, a search for PRKAR1A mutations may be recommended in addition to hormonal and imaging tests. The purpose of this study was to investigate the clinical features, diagnosis and treatment of the new pathogenic mutations in the PRKAR1A gene causing Carney complex.

Methods: We report here a case of a patient whose clinical data were retrospectively analyzed.

Results: The 13-year-old patient was diagnosed with Carney complex through a series of tests and a new causative gene mutation locus (C.1-2942G>A) was identified.

Conclusio:n Carney complex is usually more difficult to be diagnosed at an early stage in the clinic, and it is beneficial for clinicians to raise awareness of the disease for early recognition and timely intervention.

Key words: Carney complex, Cushing's syndrome, PPNAD, PRKAR1A

Introduction

Carney complex (CNC) is a rare multiple tumor syndrome characterized by patchy pigmentation of the skin and mucous membranes associated with a variety of non-endocrine and endocrine tumors, including Primary Pigmented Nodular Adrenocortical Disease (PPNAD).Carney complex is an autosomal dominant multiple tumor syndrome [1], which mainly presents clinically as skin and mucosal punctate pigmentation with various endocrine and related endocrine tumors, which can present in various forms, such as cardiomyoma, skin and other tissues, and various other endocrine and endocrine tumors, including pituitary tumors, adrenocortical tumors, thyroid tumors, sarcoid melanoma schwannoma testicular cancer, breast cancer, ovarian lesions, and bone lesions [2], and skin pigmentation or skin hyperplasia in CNC patients usually occurs early in life and can be located anywhere on the body, usually on the face, lips, and genitalia [3].It has been reported that most PPNAD or Carney syndrome is associated with mutations in the PRKAR1A gene, in addition to mutations in the PDE11A and PDE8B genes [4, 5].A 13-year-old boy was referred for suspected Cushing's syndrome. On physical examination, he showed signs of hypercortisolism and hyperpigmentation.Biochemical studies showed pro-adrenocorticotropic hormone-dependent Cushing's syndrome. Enhanced computed tomography (CT) scan of the abdomen showed multiple small nodules in the left adrenal inner branch and body, which were considered as adenoma or adrenal tuberculosis.He subsequently underwent a left laparoscopic adrenalectomy with histopathology consistent with PPNAD.Genetic testing identified a novel transcoding oncogene C.1-2942G>A in the PRKAR1A gene. the mutation was associated with Primary Pigmented Nodular Adrenocortical Disease (PPNAD).This is a novel mutation that has not been previously publicly clinically reported to be associated with the disease, and the evaluation of other clinical features of the syndrome has not been disclosed.We report a case of PPNAD-associated Cushing's syndrome diagnosed as CNC due

to a novel genetic causative locus in PRKAR1A.It is associated with PPNAD. This is a novel mutation that has not been publicly reported because of its association with the disease.

Case Presentation

A 13-year-old boy presented 2 years ago with facial rounding and hyperpigmentation of the face, eyelids and lips. Growth was slow, approximately 3 cm/2 yr. Six months ago, the patient developed acne on the face. Half a month ago, the patient felt pain in the lower back and was affected by activity. Past history: postural lithotripsy was performed in August 2017 and April 2018. Family history: The family complained of hyperpigmentation on the face and lips of the father, aunt and grandmother, who did not have a similar obese body type, but they could live a normal life. Physical examination: height 148 cm, weight 70 kg (BMI 31.95 kg/m2, BP 120/80 mmHg, full moon face, obese body type, upper body measurement 66 cm, lower body measurement 82 cm, finger spacing 142 cm, patchy pigmentation visible on mouth, lips and eyelids, facial acne (Figure 1 BCD), acanthosis nigricans visible on neck and axillae, breast Tanner stage 3 (Figure 1 E). The respiratory sounds of both lungs were clear, no dry and wet sounds, the heart border was not large, the heart rate was 96 times/min, no pathological murmur was heard. The abdomen was soft, no purple lines, no pressure pain, rebound pain, muscle tension, pubic hair growth, short penis, normal testicular development, Tanner stage 3, red rash was seen in the groin, and the toes became rough and grayish white. No obvious abnormalities were found in the heart, lungs and abdomen.

Laboratory findings showed hypercortisolism, and cortisol levels remained high after a 1 mg dexamethasone suppression test (Table 1). This suggests that Cushing's syndrome is not related to ACTH and that the grandmother, father and aunt all had patchy hyperpigmentation.

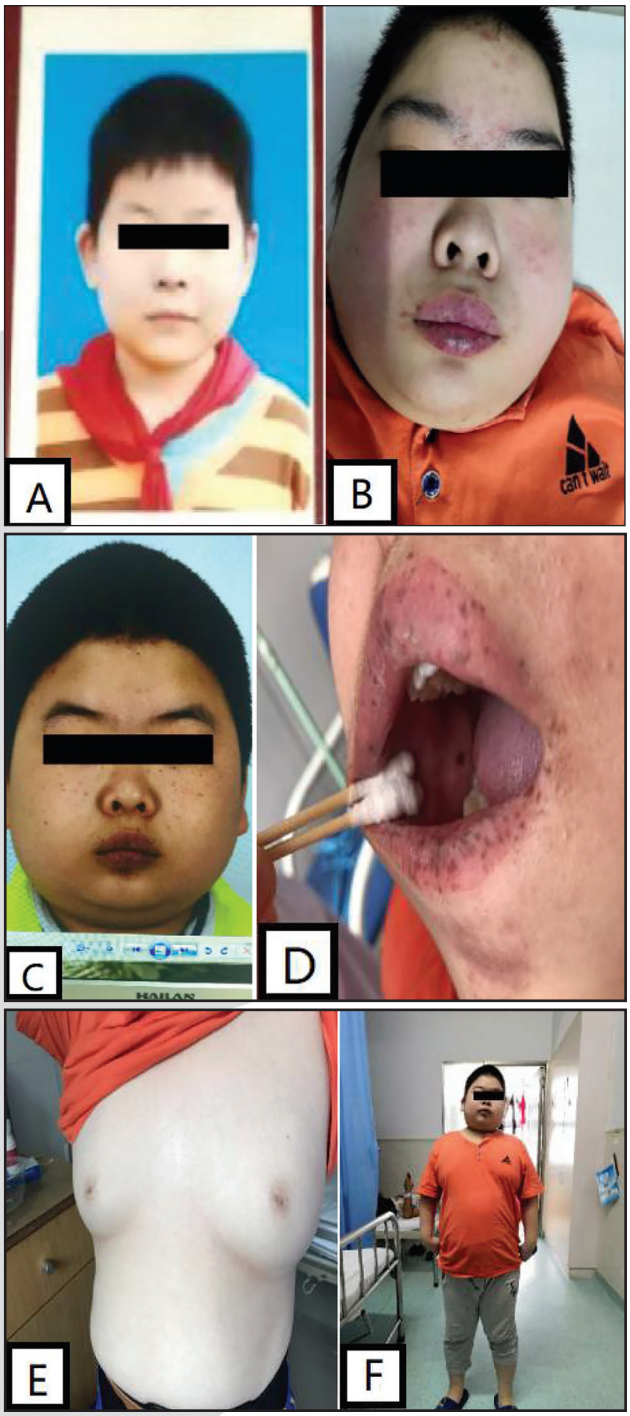


Figure 1. (ABCDEF) Physical signs of the patient before adrenalectomy. Cushing-like features include moon face before surgery (BC), central obesity (F), breast development (E), spots on the face, lips, oral mucosa and skin pigmentation (CD).

Table 1. Patient laboratory parameters

	0 AM	8 AM	4AM	1mg dexamethasone inhibition test
ACTH	0.392pg/ml (7-64)	0.958pg/ml (3-32)	0.71pg/ml (0-32)	0.714pg/ml (7-64)
Cortisol	25.96ug/dl (4.26-24.85)	24.32ug/dl (2.926-17.3)	24.75ug/dl (0-6.72)	25.79ug/dl (4.26-24.85)

Endocrine hormone tests showed a marked increase in cortisol, rhythm disturbances, and marked suppression of ACTH levels. The deceptive dexamethasone suppression assay could not be suppressed. Adrenal computed tomography (CT) showed multiple small nodules seen in the left adrenal inner branch and body (Figure 2 A), considering adenoma or adrenal tuberculosis; enhanced CT of the pituitary gland did not show any abnormality; magnetic resonance imaging of the thoracic spine showed a compression fracture of the thoracic spine (T11), and whole-body bone SPECT showed an increased radiological uptake shadow visible in the 11th thoracic spine, considering a compression fracture; echocardiography did not show any cardiac mucosal The echocardiogram did not show any cardiac mucosal tumor. Combined with the patient's history and physical examination of ancillary tests, small adrenal nodular hyperplasia not dependent on ACTH hyperplasia is currently considered.

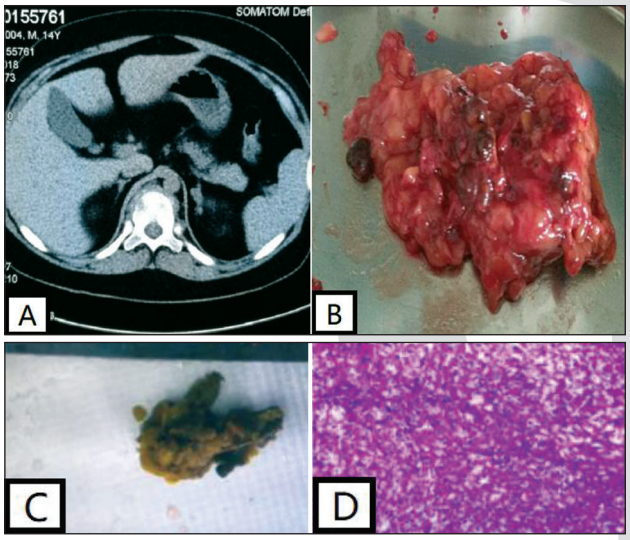


*Figure 2. Computed tomography of the patient's adrenal gland showed multiple small nodules in the left adrenal inner branch and body (Figure A), considering adenoma or adrenal tuberculosis. The patient's left adrenal gland macroscopically showed a piece of grayish-yellow tissue measuring 8*6*3.5 cm, including an adrenal gland measuring 6.5*2.5*0.3 cm, with multiple small nodules of 0.2-0.7 cm in diameter attached to the surface (C). Microscopic examination of the patient's left adrenal gland showed multiple nodules in the adrenal cortex, without envelope, partially protruding from the adrenal gland, with clear cytoplasm and eosinophilic cells (D).*

One week after the patient entered urology, the left adrenal lesion was removed by laparoscopic surgical team and sent for pathological examination (Figure 2 B), the left adrenal gland, a piece of grayish yellow tissue, size 8*6*3.5 cm, of which the size of the adrenal gland was 6.5*2.5*0.3 cm, with multiple small nodules of 0.2-0.7 cm in diameter attached to the surface, the cut surface was grayish brown, solid, soft in texture, partly with adrenal Pathological examination showed multiple nodules in the adrenal cortex, without envelope, partially protruding from the adrenal gland, with transparent cytoplasm, eosinophilic, special staining, and PSA (-) (Figure 2 D). Genetic analysis of the patient, using peripheral blood and DNA sequencing with specific equipment, revealed the mutant gene PPKAR1A variant locus C.1-2942G>A (Figure 3); associated disease: Cushing syndrome (primary pigmented nodular adrenocortical disease type 1, PPNAD1).

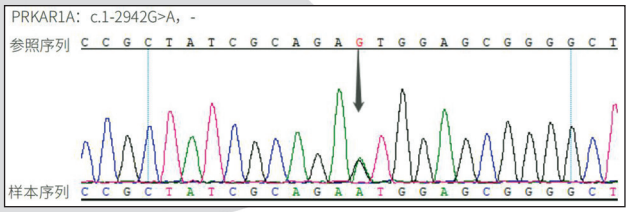


Figure 3. DNA sequence detection: variant gene PPKAR1A variant locus C.1-2942G>A, associated disease: Cushing's syndrome (primary pigmented nodular adrenocortical disease type 1, PPNAD1).

This patient was diagnosed with Carney syndrome through a series of tests and a new mutant locus for the causative gene was identified. The patient's ACTH was 0.488 ↓ pg/ml (7-64) and plasma cortisol was 14.38 ug/dl (4.26-24.85) on a recheck at 8 am on the fourth postoperative day. The patient was discharged on the eighth postoperative day (Figure 4 AD) and was treated with prednisone 20 mg Qd after discharge.At 10 months postoperatively, we followed up with the patient, who had grown 5 cm taller and lost 5 Kg of weight compared to admission (Figure 4 BE). At 18 months postoperatively, the patient's ACTH and plasma cortisol had normalized on retest, and he had reached a height of 158 cm and a weight loss of 68 Kg (Figure 4 C).

The patient and her parents provided informed consent for the release of this case report and images.

Laboratory findings showed excess cortisol, and cortisol levels remained high after a 1 mg dexamethasone suppression test (Table 1), indicating pro-adrenocorticotropic non-dependent Cushing's syndrome.

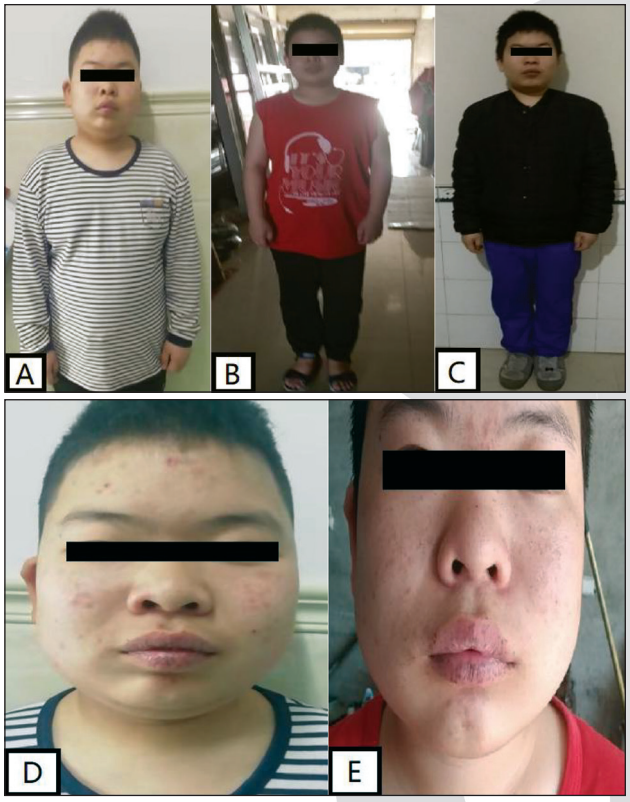


Figure 4. The patient on the eighth day after surgery (AD). The patient has grown 5 cm in height and lost 5 Kg in weight at 10 months postoperatively (BE). The patient has reached a height of 158 cm and weight loss of 68 Kg at 18 months postoperatively (E).

Discussion

In the above case report, we describe a patient with typical features such as patchy pigmentation of the face, lips, and oral mucosa, compression fractures of the thoracic spine leading to osteoporosis and Cushing's syndrome of primary pigmented nodular adrenocortical disease (PPNAD), and genetic detection of the variant gene PPKAR1A, which meets the diagnostic criteria for CNC (Figure 3).

Primary pigmented nodular adrenocortical disease is a rare non-adrenocorticotropic hormone-dependent Cushing's syndrome [6], affecting up to 60% of individuals with a gender preference, 70% of whom are female [7, 8]. It has a characteristic histological appearance with multiple small (< 1 cm) dark brown nodules scattered throughout the cortex, but it is difficult to make a diagnosis without histological examination, as the imaging presentation of PPNAD, including irregularly outlined and well-defined hypodense lesions, may be lost due to the small size of the pigmented nodules, and computed tomography sections should be 3 mm or less thick for optimal evaluation [9], and the adrenal glands are most commonly normal or even small in adrenal imaging [10].However, in our patient the left adrenal gland showed on CT multiple small nodules in the inner branches and body, the recommendations for the treatment of PPNAD vary, many authors recommend bilateral adrenalectomy [11-14], others believe that in some cases clinical and biochemical improvement can be achieved by unilateral adrenalectomy, and when cortisolism recurs, the removal of a second adrenal gland should be considered [11 ,15,16]. Meanwhile, the Endocrine Society's 2015 clinical practice guideline recommends one-stage surgical resection for bilateral adrenal disease [17], but our patient opted for resection of the left adrenal gland due to consideration of being in the growth phase, and was given a postoperative hormone replacement regimen, and the patient continued to be followed up at a later stage and underwent contralateral adrenalectomy if necessary. PPNAD is one of the manifestations of Carney complex (CNC), which was first reported by JA Carney in 1985 [1].CNC is a rare multiple tumor with additional clinical features of skin pigmentation, cardiac mucinous tumor, neurological and endocrine tumors can be diagnosed from the patient's clinical presentation, laboratory findings and/or genetic examination in a 13-year-old boy patient with histological confirmation of PPNAD in resected left adrenalectomy and inactivated PRKAR1A alterations in genetic sequencing Carney complex. Pathogenic variants in the PRKAR1A gene are present in more than 70% of CNC patients and up to 80% of PPNAD patients with combined Cushing's syndrome [7], the PRKAR1A gene is located on chromosome 17q24.2, and there are at least 140 known types of PKAR1A pathogenic

mutations (httP://prkar1a.nichd.nih.gov/ hmdb/ intro.html), this patient was detected with a variant in the PRKAR1A gene at locus c.1-2924G > A. A 1-locus variant occurred, consistent with primary pigmented nodular adrenocortical disease type 1, which is autosomal dominant, and a heterozygous locus variant was detected in its associated PRKAR1A gene, which is rare and The pathogenicity of this variant is unclear because it is rarely studied. A search of public databases such as ClinVar showed that the c.1-2924G＞A variant is located in the UTR region, and this variant is not included in the Chinese population of the Thousands Project, the East Asian population of the EXAC database, the East Asian population of the gnomAD database, or local databases.Groussin L et al [18] reported this locus and 11 patients with carney complex participated in the study, all of whom had symptoms of primary pigmented nodular adrenocortical disease of Cushing's syndrome. They were genetically tested and the locus was detected in 1 patient and in 190 healthy patients, and this paper indicates that the variant forms a new start codon.Gene sequencing revealed a new pathogenic variant in the PRKAR1A gene due to sequencing, our patient was found to have a new shifted code pathogenic variant (c.1-2942G>A) resulting in premature termination codons, he had PPNAD and some scattered hyperpigmentation, but the current clinical history and examination did not match other features of CNC, and even then should be considered in all PPNAD CNC should be considered in all patients with PPNAD, and timely diagnosis and regular monitoring of CNC manifestations may help to prevent complications of the disease,In particular, complications from cardiac tumors, cardiac mucinous neoplasms affect 20-40% of CNC resulting in embolic stroke, heart failure and arrhythmias.Recommendations for CNC screening tests include echocardiography (annually or every two years depending on the history of cardiac mucinous neoplasms), skin assessment, thyroid ultrasound, pituitary MRI, testicular/ovarian ultrasound, and growth hormone, insulin-like growth factor 1 and prolactin serum measurements [19].

Conclusion

Our case increases the number of reported CNCs, the possibility of late development of cardiac mucinous neoplasms in this disease, and the necessity to clinically evaluate these patients followed by long-term follow-up; also our current CNC diagnosis in cases of Cushing's syndrome is established due to a novel predicted inactivating pathogen in the PRKAR1A gene, increasing the knowledge of the disease, but the early diagnosis of endogenous cortisolism remains a diagnostic challenge. The novel mutations presented in this article are considered causative factors of PPNAD, and timely diagnosis of CNC and careful surveillance could help prevent potentially fatal complications of the disease.

References

1. *Carney JA, et al. The complex of myxomas, spotty pigmentation, and endocrine overactivity. Medicine (Abingdon). 1985; 13(1): 19-26.*

2. *Kirschner LS, Sandrini F, Monbo J, et al. Genetic heterogeneity and spectrum of mutations of the PRKAR1A gene in patients with the carney complex.[J] .Hum Mol Genet, 2000; 9: 3037-3046.*

3. *Carney JA, Hruska LS, Beauchamp GD, et al. Dominant inheritance of the complex of myxomas, spotty pigmentation, and endocrine overactivity.[J] .Mayo Clin Proc, 1986; 61: 165-172.*

4. *Horvath A,Boikos S, Giatzakis C, et al. A genome-wide scan identifies mutations in the gene encoding phosphodiesterase 11A4 (PDE11A) in individuals with adrenocortical hyperplasia.[J] .Nat Genet, 2006; 38: 794-800.*

5. *Horvath A, Giatzakis C, Tsang K, et al. A cAMP-specific phosphodiesterase (PDE8B) that is mutated in adrenal hyperplasia is expressed widely in human and mouse tissues: a novel PDE8B isoform in human adrenal cortex.[J] .Eur J Hum Genet, 2008; 16: 1245-1253.*

6. *De Venanzi A, Alencar GA, Bourdeau I, et al. Lacroix A. Primary bilateral macronodular adrenal hyperplasia. Current Opinion in Endocrinology Diabetes & Obesity. 2014; 21(3): 177-184.*

7. *Jerome B, Anelia H, Lionel G, et al. Mutations in Regulatory Subunit Type 1A of Cyclic Adenosine 5_-Monophosphate-Dependent Protein Kinase (PRKAR1A): Phenotype Analysis in 353 Patients and 80 Different*

Genotypes. J Clin Endocrinol Metab. 2009; 94(6): 2085-2091.

8. *Courcoutsakis NA, Tatsi C, Patronas NJ. The complex of myxomas, spotty skin pigmentation and endocrine overactivity (Carney complex): imaging findings with clinical and pathological correlation. Insights Imaging. 2013; 4(1): 119-133.*

9. *Doppman JL, Travis WD, Nieman LK, et al. Cushing syndrome due to primary pigmented nodular adrenocortical disease: Findings at CT and MR imaging. Radiology. 1989; 172(2): 415-420.*

10. *Rockall AG, Babar SA, Sohaib SAA, et al. CT and MR imaging of the adrenal glands in ACTH-independent cushing syndrome. Radiographics A Review Publication of the Radiological Society of North America Inc. 2004; 24(2): 435-452.*

11. *Groussin L, Cazabat L, Ren&eacute, et al. Adrenal pathophysiology: lessons from the Carney complex. Horm Res Paediatr. 2005; 64(3): 132-139.*

12. *Sikorska D, Bednarek-Papierska L, Mojs E, et al. Samborski W Bilateral primary pigmented nodular adrenal disease as a component of Carney syndrome - case report. Endokrynol Pol. 2017; 68(1): 70-72.*

13. *Lowe KM, Young WF, Lyssikatos C, et al. Cushing Syndrome in Carney Complex: Clinical, Pathologic, and Molecular Genetic Findings in the 17 Affected Mayo Clinic Patients. Am J Surg Pathol. 2016; 41(2): 171-181.*

14. *Jerome B. Carney complex (CNC). Orphanet J Rare Dis. 2006; 1(1).*

15. *Sarlis NJ, Chrousos GP, Doppman JL, et al. Primary pigmented nodular adrenocortical disease: reevaluation of a patient with carney complex 27 years after unilateral adrenalectomy. J Clin Endocrinol Metab. 1997; 82(4): 1274-1278.*

16. *Wei Q, Jin XL, Zhu YB, et al. Primary pigmented nodular adrenocortical disease: a report of 5 cases. Journal of Diagnostics Concepts & Practice. 2006; 119(9): 782-785.*

17. *Nieman LK, Biller BMK, Findling JW, et al. Treatment of Cushing's Syndrome: An Endocrine Society Clinical Practice Guideline. J Clin Endocrinol Metab. 2015; (8): 2807-2831.*

18. *Groussin L, Kirschner L S, Vincent-Dejean C, et al. Molecular Analysis of the Cyclic AMP-Dependent Protein Kinase A (PKA) Regulatory Subunit 1A (PRKAR1A) Gene in Patients with Carney Complex and Primary Pigmented Nodular Adrenocortical Disease (PPNAD) Reveals Novel Mutations and Clues For Pathophysiology:[J].American Journal of Human Genetics, 2002; 71(6): 1433-1442.*

19. *Correa R, Salpea P, Stratakis CA. Carney complex: an update. Eur J Endocrinol. 2015; 173(4): M85-97.*

Corresponding Author
Xin-Lan Zhao,
Department of Endocrinology,
Hunan Provincial People's Hospital,
(The First Affiliated Hospital of Hunan Normal University),
Changsha,
Hunan,
China,
E-mail heyhaixuan@sina.com

Instructions for the authors

All papers need to be sent to e-mail: healthmedjournal@gmail.com

Preparing Article for HealthMED Journal

First Author[1], Second Author[2], Third Author[3]

[1] First affiliation, Address, City, Country,
[2] Second affiliation, Address, City, Country,
[3] Third affiliation, Address, City, Country.

Abstract

In this paper the instructions for preparing camera ready paper for the Journal are given. The recommended, but not limited text processor is Microsoft Word. Insert an abstract of 50-100 words, giving a brief account of the most relevant aspects of the paper. It is recommended to use up to 5 key words.

Key words: Camera ready paper, Journal.

Introduction

In order to effect high quality of Papers, the authors are requested to follow instructions given in this sample paper. Regular length of the papers is 5 to 12 pages. Articles must be proofread by an expert native speaker of English language. Can't be accepted articles with grammatical and spelling errors.

Instructions for the authors

Times New Roman 12 points font should be used for normal text. Manuscript have to be prepared in a two column separated by 5 mm. The margins for A4 (210×297 mm2) paper are given in Table 1.

Table 1. Page layout description

Paper size	A4
Top margin	20 mm
Bottom margin	20 mm
Left margin	20 mm
Right margin	18 mm
Column Spacing	5 mm

Regular paper may be divided in a number of sections. Section titles (including references and acknowledgement) should be typed using 12 pt fonts with **bold** option. For numbering use Times New Roman number. Sections can be split in subsection, which should be typed 12 pt *Italic* option. Figures should be one column wide. If it is impossible to place figure in one column, two column wide figures is allowed. Each figure must have a caption under the figure. Figures must be a resolution of 300 DPI, saved in TIFF format, width 10 cm min. For the figure captions 12 pt *Italic* font should be used. (1)

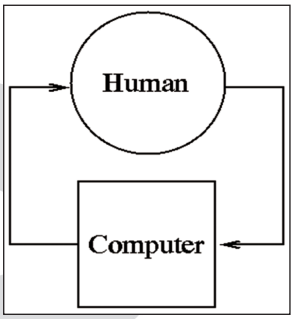


Figure 1. Text here

Conclusion

Be brief and give most important conclusion from your paper. Do not use equations and figures here.

Acknowledgements (If any)

These and the Reference headings are in bold but have no numbers.

References

1. *Sakane T, Takeno M, Suzuki N, Inaba G. Behcet's disease. N Engl J Med 1999; 341: 1284–1291.*
2. *Stewart SM, Lam TH, Beston CL, et al. A Prospective Analysis of Stress and Academic Performance in the first two years of Medical School. Med Educ 1999; 33(4): 243- 50.*

Corresponding Author
Name Surname,
Institution,
City,
Country,
E-mail: