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Gabrijel Jurkić (1886-1974), "A winter morning", 1950, oil on cardboard, 300x400 mm. Courtesy of the National Gallery of Bosnia and Herzegovina.

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The Influence of Gender on the Cortical Width of the Lower Border of the Mandible and the Mandibular Cortical Index

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Key words: Mental Index ▪ Mandibular Cortical Index ▪ Gender.

Objective. To evaluate the influence of gender on the mental index (MI) and the mandibular cortical index (MCI). **Methods.** In this study, there were 120 subjects (43 male and 77 female subjects), who had undergone a dental panoramic radiograph examination for the needs of diagnosis and future treatment planning. MI and MCI were determined by orthopantomograph. **Results.** There was a statistically significant difference in MI dependent on gender. Male patients demonstrated significantly higher values for MI than female patients (right: t=4.127; P=0.0001, left: t=3.110; P=0.002). No statistically significant difference was observed for MCI dependent on gender (right: χ^2=2.36 P=0.308, left: χ^2=3.85 P=0.146). **Conclusion.** MI is affected by gender, but MCI is not.

Introduction

The cortical thickness of the lower border of the mandible is a useful parameter for assessment of the bone quality of the mandible. Since the cortical thickness of the lower border of the mandible may be easily seen on a panoramic radiograph, with no need for specialized facilities, it is the index most-commonly used (1, 2). The cortical width below the mental foramen (mental index) (MI), at the gonion (gonion index) and antegonion (antegonion index) have often been measured. There is a relationship between these parameters and bone mineral density (3-6). The reproducibility and repeatability of digital panoramic images have been found to be high for measurements of MI (7).

The mandibular cortical index (MCI) has been used to assess the status of the mandibular bone and to determine signs of resorption. Some authors have found that the mandibular cortical index makes it possible to identify reduced bone mineral density and to distinguish normal and osteoporotic bones (8-10). The MCI is based on Klemetti's classification of changes in the inferior cortex of the mandible on panoramic imaging (11). In postmenopausal women, the MCI was found to be significantly correlated with maxillary and mandibular bone mineral density (12). Von Wowern found that the average bone mineral content (BMC) loss (%) in the bones of the mandible seems to be higher in older women (1.5 and 1.4% per year) than in older men (0.9 and 0.7% per year) (13). Thus, it seems important to monitor the sex- and age-related bone mineral content loss in the mandible separately. The results of bone mineral content exami-

nations indicated a significant difference between the two sexes. With advancing age, the values of BMC measured in male mandibles tended to increase slightly, and in female the mandibles tended to decrease (14).

The aim of this study was to evaluate the influence of gender on MI and MCI.

Methods

Subjects

In this study, there were 120 subjects (43 male and 77 female subjects), with an age range from 21 to 80 years, who had undergone a dental panoramic radiograph examination for the needs of diagnosis and future treatment planning. The purpose of the research was presented to all the participants, and they provided written consent. The research was conducted at the Prosthetic Department of the School of Dental Medicine, University of Sarajevo.

Inclusion criteria were: subjects aged 21 years or above, who underwent a dental panoramic radiograph examination for the needs of diagnosis and future treatment planning, and the inferior mandibular cortex and both mental foramina should be noticeable on the radiograph. Exclusion criteria were: the presence of systemic disorders which affect bone mineral density, metabolic bone diseases, cancer with bone metastasis, use of medications that affect bone metabolism (corticosteroid, heparin, calcium, calcitonin, vitamin D, bisphosphonates).

Methods

Dental panoramic radiographs were made using an Orthopantomograph OP 100. The same cephalostat was used during exposure, so that the Frankfurt horizontal plane (tragion-orbitale) was parallel to the horizontal plane, and the mediosagittal plane was perpendicular to the horizontal plane. All films were processed in an automatic dark chamber processor (XR 24 Nova, Dürr Dental) for 7 minutes. Images were processed using Kodak film. The dental panoramic radiographs were viewed using a flat view box, in a room with subdued light.

Two examiners assessed indices on all dental panoramic radiographs. The cortical thickness below the mental foramen (MI) was measured on each radiograph on the right and left sides of the mandible (15): We drew a line parallel to the long axis of the mandible and tangential to the inferior border of the mandible, and constructed a dotted line perpendicular to this tangent intersecting the inferior border of the mental foramen, along which the mandibular cortical width was measured. The distance between the two parallel solid lines is the cortical width. Measurements of mental index were made using a magnifying loupe (x4, Gethaldus, Zageb, Croatia) and precise digital calliper, to precision of a 0.01 mm (version 05/09, model No. 1112-150, Conrad Electronic International, Germany). The mandibular cortical shape was determined on the dental panoramic radiographs by observing the mandible distally from the mental foramen bilaterally, according to the method of Klemetti et al. (11) as follows: C1- normal cortex, the endosteal margin of the cortex is even and sharp on both sides, C2- mildly to moderately eroded cortex, the endosteal margin shows semilunar defects (lacunar resorption) or appears to form endosteal cortical residues on one or both sides, C3- severely eroded cortex, the cortical layer forms heavy endosteal cortical residues and is clearly porous. The results demonstrated good intra-observer ($r=0.86$ on the right side, $r=0.95$ on the left side; $P<0.01$) and inter-observer correlations ($r=0.81$ on the right side, $r=0.86$ on the left side; $P<0.01$).

Ethics Statement

The study was approved by the Ethical Committee of the Faculty of Dentistry, University of Sarajevo, Bosnia and Herzegovina.

Statistical Analysis

The data were analysed using the SPSS 13.0 (IBM Co., NY, USA) statistical package. Categorical variables (sex and MCI) were presented as numbers and proportions (%). Quantitative variables were presented as means and standard deviations (SD). Differences between groups for categorical variables were evaluated using the χ^2 test. Differences for quantitative variables were evaluated using the student's t test. P values less than 0.05 were considered statistically significant. The normality of the variance distribution was verified using the Kolmogorov-Smirnov test. The one-sample Kolmogorov-Smirnov test revealed that all the variables of MI on both sides were distributed normally.

Results

One hundred and twenty subjects participated in this study aged from 21 to 80 years (46.83±15.96 years). According to dental status, there were 42 subjects who had all their teeth, 38 subjects who were partially dentate (Kennedy Class I) and without antagonistic contacts in the posterior regions, and 40 subjects who were completely edentulous. According to gender, there were more female subjects (77 subjects, 64.2%) than male subjects (43 subjects, 35.8%). The mean and standard deviation of the MI on both sides are presented in Table 1. The mean MI value measured on the right side was higher than MI measured on left side of the mandible, but there was no statistically significant difference.

Table 1. Values of Mental Index on Different Sides of the Mandible

MI	$\bar{x}$±SD	CI (95%)	Min.	Max.
Right	4.42±0.91	4.25- 4.58	2.19	7.05
Left	4.36±0.91	4.19-4.52	2.14	6.75

MI=Mental Index; t=1.032; P=0.304.

The mean and standard deviation of the MI according to gender are presented in Table 2. Considering gender, the mean MI values were lower in females than in males on both sides of the mandible. The t-test demonstrated a statistically significant difference for MI between the gender groups.

Table 2. Difference for the Mental Index Between Gender Groups

Gender	Right*	Left†
	$\bar{x}$±SD	$\bar{x}$±SD
Male (N=43)	4.85±1.01	4.69±1.02
Female (N=77)	4.18±0.75	4.17±0.79
Total (N=120)	4.42±0.91	4.36±0.91

MI=Mental Index; *t=4.127; P<0.00; †t=3.110; P=0.002 on the left side.

The distribution of categories of MCI according to gender on both sides are presented in Table 3.

Table 3 Distribution of Categories of MCI According to Gender

Categories	Gender			
	Male	Female	Male	Female
	*Right		Left†	
	N (%)	N (%)	N (%)	N (%)
C1	8 (18.6)	19 (24.7)	6 (14.0)	23 (29.9)
C2	29 (67.4)	41 (53.2)	28 (65.1)	40 (51.9)
C3	6 (14.0)	17 (22.1)	9 (20.9)	14 (18.2)

MCI=Mandibular Cortical Index; C1=Normal cortex; C2=Mildly to moderately eroded cortex; C3=Severely eroded cortex; *χ^2=2.36, P=0.308; †χ^2=3.85, P=0.146.

The distribution of categories of MCI (C1, C2, C3) according to gender is similar. On the right side, most participants presented as C2, and also on the left side. Differences for MCI between the gender groups are not statistically significant for the right side and the left side.

Discussion

In the present study, the MCI and cortical width were used for assessment of the bone quality of the mandible. In recent decades many authors have investigated the relationship between these indices and different factors (systemic and local) such as age, gender, number of teeth, hormonal status (menopause) etc. The majority of studies on the MCI and cortical width have considered only the elderly female population, with or without signs of systemic osteoporosis. Our study group represented a typical range of female and male patients with a need for prosthodontics or periodontal treatment, with an age range of 21 to 80 years.

None of measurements taken in this study were corrected for the magnification inherent in panoramic radiography. All the radiographs were produced using the same type of panoramic equipment with a nominal magnification factor of 1.2. The results of our study revealed significant differences between males and females ($P<0.001$) in the measured values of the cortical width of the lower border of the mandible - below the MI. The females demonstrated lower values of MI measurements than the males. This finding is in agreement with the study of Musa et al. (16), who measured values of cortical width in participants aged 15 to 87 years. In Knezović-Zlatarić´s study (17), MI showed a general downward trend for both genders with age until 75 years, when the mean values began to fall sharply for females compared to males, but the difference between the gender groups did not reach a statistically significant level for MI. Dutra et al. (18) found that MI values were significantly lower in older females, whereas they were greater in older males. Knezović-Zlatarić et al. (1) found that there was no significant difference in any linear radiomorphometric indices between boys and girls younger than 18 years. This could be attributed to the fact that this study group represented a typical range of young boys and girls, with no signs of any hormonal dysbalance. The influence of different sex-hormone metabolisms on bone structure and bone quality in those subjects had not yet reached the level of significance (1). Hastar et al. (19) found that there was a statistically significant difference in the measured MI between males and females older than 60 years. Yüzügüllü et al. (20) concluded that severe erosion of the endosteal margin of the mandible was seen more frequently in women over 60 years in age. While the mean mandibular cortical width values were stable in men over 60 years, the mean mandibular cortical width values decreased significantly in women of the same age group (20). The results of Kalinowski´s study (21) showed that when age and gender were discussed simultaneously, the highest values of MI were observed in the 30–39 years age group in both genders, followed by a gradual decrease with age, but this decrease was more pronounced in females. The possible difference between males and females for MCI ratio could be explained by occlusal forces, because men have greater occlusal force than women (22-24). Al-Dwairi et al. found a positive correlation between MCI ratio and occlusal forces, so they reported that the average occlusal force in subjects with Klemetti class 3 was less than occlusal force in Klemetti class 1 subjects (25).

In evaluation of MCI on both sides of the mandible, the majority of males and females presented as C2. We found no significant difference for MCI between males and females.

Uysal et al. concluded that when the effects of age and gender are evaluated together, women may be expected to have a more porous mandibular cortex (26). Also, many authors found that MCI was affected by gender (17, 19, 26, 27). They found significantly more C2 and C3 in women than in men. In

contrast, Gulsahi et al. concluded that MCI was not affected by gender (28).

Conclusion

The cortical thickness of the lower border of the mandible below the mental foramen, and the mandibular cortical index are important and simple indices for assessment of the bone quality of the mandible. No significant difference was found between the right and the left sides of the mandible for MI (P>0.05). MI is affected by gender. Male patients demonstrated significantly higher values for MI than females. The mandibular cortical index is not affected by gender.

What is already known on this topic

The mandibular cortical index (MCI) and cortical width are indices for assessment of the status of the mandibular bone and for determining signs of resorption. They are important due to the relationship between these indices and bone mineral density. With advancing age, the cortex of the lower border of the mandible in women becomes thinner and more porous.

What this study adds

This study did not detect any difference between the right and the left sides of the mandible in terms of the cortical width of the mandible. Previous studies on the mandibular cortical index (MCI) and cortical width have mainly taken an elderly female population into consideration. This study included participants of both genders, with an age range of 21 to 80 years.

Authors' contributions: Conception and design: AKĆ and MA; Acquisition, analysis and interpretation of data: AKĆ, ADĐ, AG and MA; Drafting the article: AG and SSP; Revising it critically for important intellectual content: SSP, LB, LK and EB; Approved final version of the manuscript: AKĆ and ADĐ.

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Original Article
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Depressive Symptoms Among Sarajevo University Students: Prevalence and Socio-Demographic Correlations

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Objectives. The aim of this research was to detect the presence of depressive symptoms among the student population at a Faculty of Medicine, as well to determine the correlation between the socio-demographic characteristics and students' lifestyle and depressive symptoms. **Subjects and Methods.** Of 800 students enrolled and asked to participate, 412 responded to the survey. The study included students from all 6 years of studies. The degree of depressive symptoms was measured by a 21-item revised form of the Beck Depression Inventory (BDI). We built bivariate logistic regression models to study whether age, gender, housing accommodation, year of medical training, and school success status (Grade Point Average - GPA) were associated with depressive symptoms. The results are reported as odds ratios (OR) with 95% confidence intervals (CI). **Results**. The study revealed that almost one third of students reported BDI >16 (30.1%). The present study did not find any association between BDI scores and study year or age difference, but we found that there was an association between housing accommodation and depressive symptoms. Students who lived with their parents had lower BDI scores than those who lived in a dormitory. The results of this study showed there is a negative correlation between physical activity and depressive symptoms in students, as well as that there is a positive correlation between depressive symptoms and substance abuse. **Conclusion**. Overall, our study confirms that the factors associated with an increase in medical students' depressive symptoms are housing accommodation, a lack of physical activity and substance abuse. Regarding failing a year of study at the medical school, as well as gender and age differences, we did not find any significant difference between students with higher compared to those with lower depressive symptoms.

Introduction

Depressive disorders are one of the most common mental disorders, with a lifetime prevalence of 16.2% and 12-month prevalence of 6.6% in the general population (1). Depression affects people of all ages, from all walks of life, in all countries. It causes mental anguish and impacts people's ability to carry out even the simplest everyday tasks, with sometimes devastating consequences for relationships with family and friends, and the ability to earn a living. At worst, depression can lead to suicide, which is now the second leading cause of death among 15-29 year-olds (2).

It is known that females are more likely to suffer than males, given the complex interaction of females' biological, psychological and social-cultural vulnerability. There is a significant increase in the incidence of depressive symptoms during pregnancy and especially postpartum. Other risk factors include: a positive family history for depression, the existence of a physical illness that causes disability or pain, and other mental disorders, such as dementia. Depression is also increased by stress and poor socio-economic conditions of life (3).

However, depression can be prevented and treated. A better understanding of what depression is, and how it can be prevented and treated, will help reduce the stigma associated with the condition, and lead to more people seeking help (3). It is estimated that more than 450 million people suffer from mental disorders, and every fourth person may have some mental health problems in their lifetime. 350 million people (5%) of the world's population suffer from depressive disorders (4). Depression will be the second greatest global burden by 2020, but also a leading health issue in developed countries. Treatment costs for depression by 2030 will increase so much that it will become a major problem for the financial stability of health care systems (4).

According to a WHO-led study (5), which calculated treatment costs and health outcomes in 36 low-, middle- and high-income countries for the 15 years from 2016-2030, low levels of recognition of and access to care for depression, and another common mental disorder, anxiety, will result in a global economic loss of a trillion US dollars every year. The losses are incurred by households, employers and governments. Households lose financially when people cannot work. Employers suffer when employees become less productive and are unable to work. Governments have to pay higher health and welfare costs.

In research published last year by the Journal of the American Medical Association (6), based on an international survey, 27% of medical students reported symptoms of depression. Another problem is that students training to care for the mental and physical health of others do not have time to tend to their own health (6). In 2016, in the region of the Sarajevo Canton, 7.28 persons per 1,000 inhabitants (7) had some kind of mental disorder, including depression, but there are no records that include the representation of mental health disorders in the student population for the Federation of Bosnia and Herzegovina (BH) or Sarajevo Canton (7).

Recently there have been a number of studies on the prevalence of depressive symptoms in university students worldwide (8-11). A study about depressiveness among Chinese university students showed that the prevalence of depressive symptoms was 11.7%, and 4.0% of the sample was experiencing a Major Depressive Disorder (1). Bayram & Bilgel reported that depressive symptoms of moderate severity or above were found in 27.1% of Turkish university students (9), while Bostanci reported out of all university students in Denizli, 26.2% had a Beck Depression Inventory (BDI) score of 17 or higher, and also that no differences in depressive symptoms were observed between male and female students (10). Among other things, this study showed that senior students had higher BDI scores compared with freshmen (11). Moreover, students with learning disabilities, as well as those who were dissatisfied with their major study course, the quality of the educational system, their living arrangements, their social life and the university facilities available, were more likely to report clinical depressive symptoms (11).

The aim of this research was to detect the presence of depression and depressive symptoms among the student population at

the Faculty of Medicine, University of Sarajevo, as well to determine the correlations between the students' socio-demographic characteristics and lifestyle and depressive symptoms, and compare the results with major studies conducted around the world.

Methods

Study Population

The Faculty of Medicine is an organizational unit of the University of Sarajevo. In total, there were 800 students enrolled in regular classes in the academic year 2016/2017. Students attending medical studies in English were not included in this research due to language restrictions and the possibility of the influence of the different socio-demographic characteristics of the sample (the countries from which they come from, the amount of income, their lifestyle and customs). The total number of students who responded to the survey was 412. The study included students from all 6 years of studies.

The Questionnaire

The research was designed as a cross-sectional study and it was conducted by means of a questionnaire consisting of two parts: the first part examined the sociological characteristics and student's lifestyle, and the second part examined depressiveness in students, using Beck's scale, adapted to this research and translated into the official languages of Bosnia and Herzegovina (12).

The degree of depressive symptoms was measured by a 21-item revised form of the Beck Depression Inventory (BDI) (12). The BDI statements were ranked from 0 to 3, with 0 representing the least serious and 3 the most serious symptoms. The questionnaire contained 18 questions in the first part and 21 groups of items divided into 8 thematic units in the second part. Each statement in this inventory had a possible score range of 0 to 3, with the total score being 63. A referral BDI score value of 0 to 4 is considered as normal, 5 to 13 represents borderline clinical depression, 14 to 20 moderate depression, and 21 to 63 severe depression (13). We used a BDI score cutoff of 16 to be able to compare it with other studies (10) and because a score of 17 or more is used as the conventional cutoff for clinical depression. After prior approval had been granted by Dean of the Faculty, the research was conducted from 23.3.2017 to 31.3.2017. The students filled out the questionnaires by themselves online. The socio-demographic variables analyzed were: age, gender, year of studies, mean grade point average (GPA), duration of studies, failing a year of studies, accommodation, physical activity – running, jogging or gym, time spent weekly on physical activity, time spent on computer/laptop per week, having hobbies, visits to a psychologist/psychiatrist, use of psychoactive substances – light and heavy drugs in recent years.

Statistical Analysis

Logistic regression was used to assess the relationship between the socio-demographic variables and the symptoms of depression. A bivariate logistic model was calculated by taking each correlate at a time. We built bivariate logistic regression models to study whether age, sex, housing accommodation, year of medical training and study success status (grade point average - GPA) were associated with depressive symptoms. The results are reported as odds ratios (OR) with 95% confidence intervals (CI). Between-group comparisons for categorical and binary data were computed by means of the chi square test and $P \leq 0.05$ was considered to be statistically significant. The SPSS statistical package (SPSS Inc., Chicago, IL, USA) was used for data analysis.

Results

The total number of respondents was 412 students, of which 115 (27.9%) were men and 297 (72.1%) were women. The mean (±standard deviation) age of the participants was 21.6±2.8 (range 17-41 years). Most of the respondents were 20-21 years old (32.8%), then 18-19 years old (25.2%), 24 and older (22.1%) and 19.9% were 22-23 years old. The largest number of the respondents were students in their 1st year of medical studies, 34.0% of all students included (n=140), followed by 21.6% respondents from the 2nd year of medical studies (n=89), 12.9% respondents (n=53) from the 5th year, 12.6% (n=52) from the 3rd year, 11.9% (n=49) from the 6th year and 7.0% (n=29) respondents in their 4th year of medical studies.

The majority of the respondents were within the referral BDI value range, 195 of them (47.3%). Mild depressive symptoms were found in 93 of the respondents, which is 22.6%, borderline clinical depressive symptoms were present at 40 respondents (9.7%), moderate depressive symptoms in 65 cases (15.8%), severe depressive symptoms in 15 (3.6%) respondents, and, finally, 4 respondents had scores that showed severe depression symptoms, with scores above 47 (1.0%).

The average BDI score was 21.63 (SD= ±2.77) while 30.1% of students had BDI >16 (n=124) (Table 1). The referral BDI value was found in 58 men (50.4%) and 137 women (46.1%). Mild depressive symptoms were found in 21 male respondents (18.3%) and 72 female respondents (24.2%). Borderline clinical depressive symptoms were found in 18 male students (15.7%) and 22 (7.4%) female students. Moderate depressive symptoms were found in 13 men (11.3%) and 52 women (17.5%), severe depressive symptoms in 4 (3.5%) men and 11 women (3.7%). Severe depressive symptoms with score above 47 were evaluated in 1 man (0.9%) and 3 women (1.0%). Table 2 shows the results of bivariate logistic regression models for the association between students' BDI scores and different socio-demographic characteristics. According to the bivariate logistic model, the odds of having depressive symptoms are insignificantly higher in students group who have GPA less than 8.00, have no hobby, as well as for students who live in their own apartment and spend more than 90 minutes on computer/laptop per week. The odds of having depressive symptoms were significantly higher in students, who live in a dormitory, do not undertake any physical activity, and who have used psychoactive substances or ever visited a psychologist/psychiatrist.

The distribution of the respondents in relation to gender (sex) and depressive symptoms was not statistically significant (χ^2 (5.412)=9.494, P=0.091). BDI >16 varied between different age groups with a range from 28.8% (the lowest value) to 31.7% (the highest value) and distribution of the respondents in relation to gender (sex) and depressive symptoms was not statistically significant (P=0.979).

Students with less successful academic performance (mean GPA less than 8.00) had higher occurrence of depressive symptoms (32.7% students in this group had BDI >16), compared to students with better school performance (mean GPA 8.00-10.00) with 28.2% of students with BDI >16 in this group, but there was a non-statistically significant difference in the occurrence of depressive symptoms between less and more successful students (P=0.323).

29.7% of students had failed a year during their studies and had BDI >16, while 30.7% students that had not failed a year had BDI >16. There was no statistically significant difference in the occurrence of depressive symptoms between students who had failed and those who had not failed a year of studies.

Table 1. Socio-Demographic Characteristics of Students in Relation to Depressive Symptoms

Socio-demographic characteristics	Percent of students with BDI ≤16*	Percent of students with BDI >16†	Statistical analysis‡	
	N (%)	N (%)	χ^2 test	P
Sex				
Both sexes	288 (69.9)	124 (30.1)		
Male	79 (68.7)	36 (31.3)	0.111	0.740
Female	209 (70.4)	88 (29.6)		
Age group (year)				
18-19	74 (71.2)	30 (28.8)		
20-21	94 (69.6)	41 (30.4)	0.191	0.979
22-23	56 (68.3)	26 (31.7)		
24 and more	64 (70.3)	27 (29.7)		
Year of studies				
1st	100 (71.4)	40 (28.6)		
2nd	58 (65.2)	31 (34.8)		
3rd	38 (73.1)	14 (26.9)	4.159	0.527
4th	24 (82.8)	5 (17.2)		
5th	35 (66.0)	18 (34.0)		
6th	33 (67.3)	16 (32.7)		
Mean GPA				
6.00-6.99	1 (100.0)	0 (0.0)		
7.00-7.49	30 (68.2)	14 (31.8)		
7.50-7.99	84 (66.7)	42 (33.3)	5.032	0.412
8.00-8.49	113 (68.1)	53 (31.9)		
8.50-8.99	45 (80.4)	11 (19.6)		
9.00-10.00	15 (78.9)	4 (21.1)		
Duration of studies				
1 year	76 (71.7)	30 (28.3)		
2 years	42 (61.8)	26 (38.2)		
3 years	41 (68.3)	19 (31.7)		
4 years	21 (80.8)	5 (19.2)	9.395	0.153
5 years	28 (59.6)	19 (40.4)		
6 years	46 (80.7)	11 (19.3)		
More than 6 years	34 (70.8)	14 (29.2)		
Failing a year of studies				
Yes	114 (70.8)	47 (29.2)	0.103	0.749
No	174 (69.3)	77 (30.7)		
Accommodation				
With his/ her parents	101 (67.3)	49 (32.7)		
Rented apartment	106 (67.1)	52 (32.9)	2.840	0.417
Their own apartment	18 (64.3)	10 (35.7)		
Dormitory	46 (60.5)	30 (39.5)		

Table 1. Socio-Demographic Characteristics of Students in Relation to Depressive Symptoms

Socio-demographic characteristics	Percent of students with BDI ≤16*	Percent of students with BDI >16†	Statistical analysis‡	
	N (%)	N (%)	χ^2 test	P
Physical activity§				
Yes	185 (73.7)	66 (26.3)	4.414	0.036
No	103 (64.0)	58 (36.0)		
Time spent weekly on physical activity				
Less than 30 min	135 (64.9)	73 (35.1)	5.214	0.157
30-60 min	66 (76.7)	20 (23.3)		
60-90 min	30 (73.2)	11 (26.8)		
More than 90 min	38(51.9)	29 (26.0)		
Time spent on computer/laptop per week				
Less than 90 minutes	128 (72.7)	48 (27.3)	1.165	0.280
More than 90 minutes	160 (67.8)	76 (32.2)		
Do you have hobby				
Yes	188 (72.0)	73 (28.0)	1.532	0.216
No	100 (66.2)	51 (33.8)		
Have you ever visited a psychologist/psychiatrist				
Yes	39 (59.1)	27 (40.9)	4.367	0.037
No	249 (72.0)	97 (28.0)		
Do you use any psychoactive substances‖				
Yes	20 (51.3)	19 (48.7)	7.100	0.008
No	268 (71.8)	105 (28.2)		

*Beck depression inventory; †BDI scores were dichotomized using 17 as the cut-off point. This column shows the percentage of the people with BDI scores 17 or higher; ‡Pearson's chi-squared test; §Running, jogging or gym; ‖Use of psychoactive substances – light and heavy drugs in recent years.

According to the bivariate logistic model, the odds of having depressive symptoms were higher in students who lived in a dormitory compared to ones who lived with their parents.

Assessing activity and depressive symptoms, 26.3% active students had BDI >16 in the active group, and 36.0% students with no activity and BDI >16 in the inactive group. There was a statistically significant difference in the occurrence of depressive symptoms between active and inactive students (P=0.036). The prevalence of depressive symptoms was not significantly different between those who spent more than 90 minutes on a laptop per week, and those who spent less time (P=0.280).

63.3% students answered positively regarding having a hobby while 36.7% had no hobbies. 28.0% students with hobbies and 33.8% students with no hobbies had BDI >16.

Comparing students who had visited a psychologist/psychiatrist (16.0%) and those who had not done so at any time in their lives (84.0%), the students from the first group presented with a higher prevalence of depressive symptoms than students who had never visited a psychologist/psychiatrist (BDI >16 40.9% vs. 28.0%, P=0.037, respectively). A small number of students admitted using psychoactive substances (9.5% vs. 90.5%). A statistically significant difference was noted in the prevalence of depressive symptoms with regard to substance abuse. In the group of students with substance

Table 2. Description of the Sample and Association of Depressive Symptoms with Socio-Demographic Characteristics in University Students

Socio-demographic characteristics	Bivariate model*	
	OR†	95% CI‡
Sex		
Female	Reference group	-
Male	0.92	0.58-1.47
Age group (year)		
18-19	Reference group	-
20-21	0.93	0.53-1.63
22-23	0.87	0.47-1.64
24 and more	0.96	0.52-1.78
Year of studies		
1st - 3rd	Reference group	-
4th - 6th	1.04	0.66-1.63
Mean GPA§		
8.00 and more	Reference group	-
Less than 8.00	1.24	0.81-1.90
Failed a year of studies		
Yes	Reference group	-
No	0.93	0.60-1.44
Accommodation		
With his/ her parents	Reference group	-
Rented apartment	1.05	0.65-1.69
Their own apartment	1.21	0.50-1.69
Dormitory	1.68	0.89-3.19
Physical activity‖		
Yes	Reference group	-
No	1.58	1.03-2.42
Time spent weekly on physical activity		
More than 60 min	Reference group	
Less than 60 min	1.30	0.81-2.09
Time spent on computer/laptop per week		
More than 90 minutes	Reference group	-
Less than 90 minutes	0.79	0.51-1.21
Do you have hobby		
Yes	Reference	-
No	1.31	0.85-2.02
Have you ever visited a psychologist/psychiatrist		
No	Reference group	
Yes	1.78	1.03-3.06
Do you use any psychoactive substances¶		
No	Reference group	-
Yes	2.43	1.24-4.73

*The bivariate model comes from a backward stepwise logistic regression analysis; †Odds ratio; ‡Confidence interval; §Grade Point Average; ‖Running, jogging or gym; ¶Use of psychoactive substances – light and heavy drugs in recent year.

abuse, 48.7% had BDI <16 while 28.2% students who did not use psychoactive substances had BDI <16 (P=0.008). According to the bivariate logistic model, the odds of having depressive symptoms were significantly higher in students who had visited a psychologist/psychiatrist (OR of depressive symptoms was 1.78, 95% CI, 1.03-3.06) and who had used psychoactive substances in recent years (OR of depressive symptoms was 2.43, 95% CI, 1.24-4.73).

Discussion

The primary scope of the present study was to provide an estimate of the prevalence of depressive symptoms among university students at the Faculty of Medicine of the University of Sarajevo. Furthermore, the study explored depressive symptoms and their association with individual, academic and social characteristics. The study revealed that almost one third of students reported BDI>16 (30.1%) which is more that measured in other countries, such as Turkey (26.2%) (2) and China (22.91%) (1). We did not perceive any gender differences in depressive symptoms in our study. We hypothesize that this situation originates from the fact that female students at our university, and in general, are strongly opinionated, more self-assured, and are aware of having equal or more rights compared with the situation in the past. Similar observations were made in other studies (10). Contrary to our results, significantly more depressive symptoms were found in female students than in male students in two different studies (11, 14).

The present study did not find any association between BDI scores and study year. Dogan et al. also found no difference in relation to study year in terms of depressive symptoms, as there was no positive correlation between study year and increased average BDI scores (14). On the other hand, several studies did find an association between BDI scores and study year (8, 10) with freshmen being less depressed. In the present study, we found that there was no significant association between academic success and depressive symptoms. However, we must add that students who were more successful and had better mean GPA, had lower BDI scores than those who were less successful. The odds of having depressive symptoms were significantly higher in students who lived in a dormitory compared to students who lived with their parents. We hypothesize that this is a result of having security and support while living with parents rather than in dormitory with other students.

The results of this study showed there is a negative relationship between physical activity and depressive symptoms in students. There are several possible mechanisms of how physical activity can influence depressive symptoms. Exercising may have a physiological effect on depressiveness with an increased release of β-endorphins and neurotransmitters such as serotonin and dopamine (15). Another presumed explanation is that exercise decreases psychological stress and acts as a shield against traumatic incidents. In addition, participation in regular exercise programs may express a sense of prowess and improved self-esteem. Participation in exercise programs or exercise groups can also provide social connections and increase the participants' social skills. Furthermore, students who participate in after-class physical activities in the "natural" environment, recreational areas, parks, and playgrounds, may improve their mental health (16). Other studies (17, 18) also identified an inverse relationship between physical activity, including participation in sports, and depressive symptoms among students, which is in accordance with the present study.

It was also found that there is a positive relationship between depressive symptoms and substance abuse. Alcohol and

some other substances actually increase the stress response by stimulating production of stress hormones. Alcohol directly activates the hypothalamus-pituitary-adrenal axis to produce excess cortisol. Substance abuse produces physiological stress and the body's responses to this kind of stress are similar to its responses to other stressors. Nevertheless, some individuals abuse substances to alleviate stress, wrongly thinking that it will help them deal with stress.

In the comparison of students who have visited a psychologist/psychiatrist and those who never have in their lifetime, it was found that students from the first group showed a higher prevalence of depressive symptoms than students who had never visited a psychologist/psychiatrist. This could suggest that medical students with more severe depressive symptoms either have better access to psychological support or/and perceive it better and seek help.

Limitations of the Study

There were several limitations to the present study. The first limitation is the potential for sampling bias, as the sample in the study was randomly selected from only the Faculty of Medicine. It is hard to generalize our findings to all Sarajevo University students. However, we had a moderate sample size and used Beck's scale to diagnose depressive symptoms. The second point is that we only surveyed the depressiveness distribution in university students and did not consider other psychological problems, such as anxiety. The end sample size is small, and further longitudinal, more accurate studies are needed in order to confirm this merely preliminary report. Another limitation of our study is that we did not consider family history of depressiveness and stressful events. A future study may be required to examine the factors related to genetic and/or other environment variables. Slightly more than 50% of the eligible population responded to the survey. Students who did not respond to the survey could be completely different to those who were included in the study and this could introduce substantial selection bias. Our data were collected cross-sectionally and it is not possible to establish any temporal link between the individual socio-demographic characteristics, school performance and lifestyle and depressive symptoms. Therefore, it is possible that the link observed is reverse, i.e. it is possible that students who are more depressed use more psychoactive substances, and also that those who use psychoactive substances become more depressed. It is also possible that students who are depressed do less physical activity, but also that those who do less physical activity become more depressed. Cross-sectional design could be one of the limitations when interpreting associational results.

Conclusion

The prevalence of depressive symptoms in Sarajevo University students was relatively high throughout our study, reaching almost one-third (30.1%). This indicates that a need for knowledge concerning depressive symptoms still exists and should be addressed by depressiveness-related health education programs. The factors associated with the increase in medical students' depressiveness were: housing accommodation, lack of physical activity and substance abuse. Regarding the years of study at the medical school, as well as gender and age differences, we did not find any significant difference between students. Access to psychological care and support is very important because students with mood problems are part of society and we have a moral and ethical responsibility to help them.

What is already known on this topic

Depressive disorder is one of the most common mental disorders. Depression affects people of all ages, from all walks of life, in all countries. It is known that women are more likely to suffer than males, given the complex interaction of women's biological, psychological and social-cultural vulnerability. Depression is also increased by stress and poor socio-economic conditions in life.

What this study adds

The prevalence of depressiveness in Sarajevo University students was relatively high. The factors associated with the increase in medical students' depressiveness were: academic success, the lack of physical activity, and substance abuse. Regarding the years of study at the medical school, as well as sex and age differences, there were no significant differences between students.

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The Veil of Obscuration: Additional Radiographic Sign of Posterior Shoulder Dislocation

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Objective. To describe a new radiographic sign, "veil of obscuration", associated with posterior glenohumeral joint (shoulder) dislocations and determine its incidence and validity compared to other known classic radiographic signs. **Methods.** Four-year retrospective study identified 30 acute posterior shoulder dislocation patients. Radiographs reviewed in consensus by 2 musculoskeletal radiologists for the "veil of obscuration", seen on AP shoulder radiographs and representing a comminuted fracture of the lesser tuberosity projecting over the humeral head or glenohumeral joint. Incidence of this radiographic sign of posterior glenohumeral joint dislocation in addition to other previously described classic radiographic signs, and association with other fractures, surgery, and mechanism of injury were evaluated. Continuous data was analyzed with student t-test and categorical data with Chi-Square test. **Results.** There were 20 right and 10 left posterior shoulder dislocations. Majority of injuries resulted from vehicle crash (44%). In most cases, reverse Hill-Sachs lesion (83%) and fixed internal rotation of the humeral head (76%) were present, followed by trough line (43%) and "veil of obscuration" (40%). Trough line was seen in significantly more major trauma and vehicle crashes (78% and 46%; P=0.015), while "veil of obscuration" was seen in more seizures (86%; P=0.037) and in all surgical patients. No significant difference in presence of other classic radiographic signs in regards to surgery. **Conclusion.** The newly described radiographic sign of posterior shoulder dislocations named the "veil of obscuration" has comparable incidence as other classic radiographic signs and may be useful in the recognition and diagnosis of these injuries.

Introduction

The shoulder, or glenohumeral joint is a ball and socket construct allowing a wide range of motion. Both static and dynamic elements provide stability for this joint (1). The humeral head is significantly larger compared to the glenoid, which contributes to instability of the glenohumeral joint. Shoulder dislocations are common, accounting for 50% of all joint dislocations (2, 3), although posterior shoulder dislocations comprise less than 2-5% of all shoulder dislocations (2-4). A posterior shoulder dislocation is defined as posterior displacement of the humeral head in relation to the glenoid (Figure 1). These dislocations most frequently occur in male patients between 20 and 49 years of age

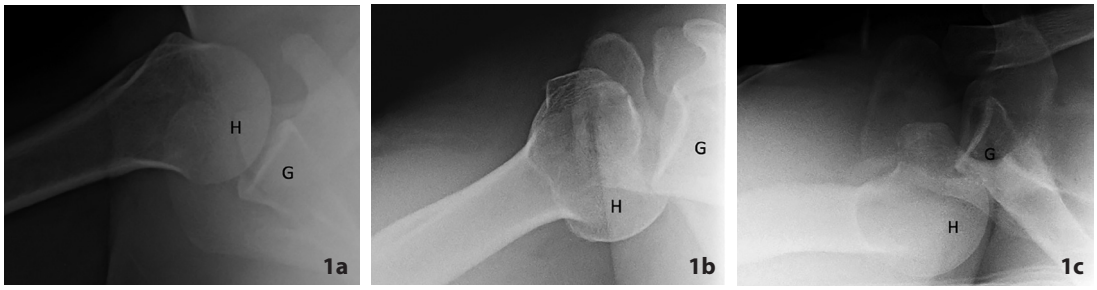

Figure 1. Axillary radiographs of the normal and posteriorly subluxed or dislocated glenohumeral joint. In (a) note normal anatomic alignment of the glenohumeral joint, with the humeral head well seated in the glenoid fossa compared to (b) which shows posterior subluxation of the glenohumeral joint, with the humeral head partially posteriorly displaced in relation to the glenoid, and (c) which demonstrates posterior dislocation of the glenohumeral joint, with the humeral head displaced completely posterior to the glenoid. H=humeral head, G=glenoid.

in addition to elderly patients over 70 years old (2). The most common mechanisms of injury include traumatic accident, seizures, and electrocution (2).

Management of posterior shoulder dislocations varies with each patient. Nonsurgical treatments include closed reduction techniques or even rarely leaving the shoulder in a chronic dislocated state (5, 6). Surgical treatment options include open reduction, McLaughlin or modified McLaughlin procedures for significant reverse Hill-Sachs lesions, anterior approach and bone grafting of the Hill-Sachs lesion, posterior open Bankart procedure, arthroscopic posterior Bankart repair, and arthroplasty (5, 6).

Although posterior shoulder dislocations are not very common, Robinson and collaborators (2011) showed that almost 18% of subjects with these injuries went on to develop recurrent instability within the first year (2). They also showed that those at highest risk for recurrent instability included age less than 40 years, large reverse Hill-Sachs lesion, and seizure as the mechanism of injury.

Imaging Work-up of Posterior Shoulder Dislocations

Routine radiologic shoulder examination usually consists of anteroposterior (AP) radiographs in internal and external rotation and either axillary or scapular "Y" views (5, 7) (Figure 2). While an axillary view can confirm the diagnosis, there can be limitations in obtaining this view in patients with posterior shoulder dislocations due to pain and difficulty with arm abduction (4). In these cases where it is difficult to obtain an axillary radiograph, a scapular "Y" view is recommended (8). Computed tomography (CT) may be performed to clarify or confirm the findings if clinically indicated. In addition to CT, magnetic resonance (MR) imaging and MR arthrography may help to further characterize associated bone and soft tissue injuries, but is not indicated in the acute clinical setting and may not be readily available in many academic institutions worldwide (9, 10).

Posterior shoulder dislocations can be overlooked on radiographs due to the subtlety of the imaging findings and difficulties in patient positioning, as well as the relative rarity of posterior shoulder dislocations (3, 7). If missed, the untreated cases can progress to chronic instability or lead to open reduction (2, 5).

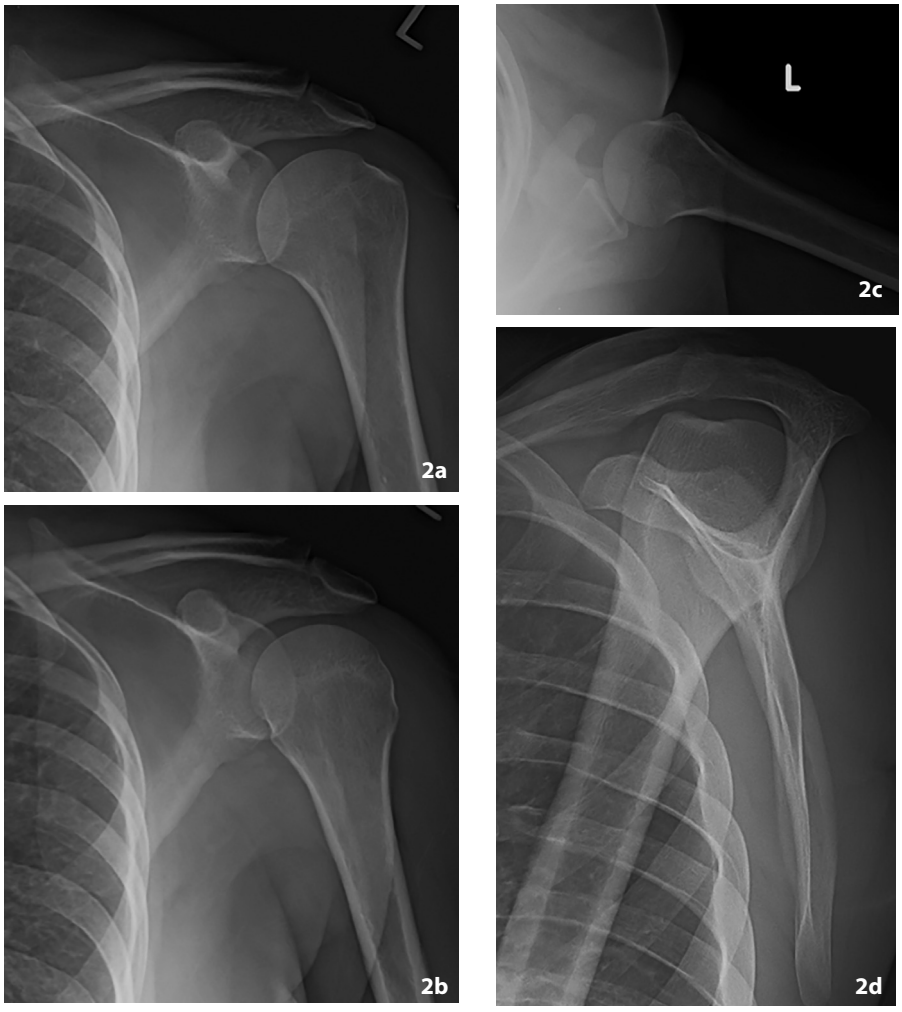

Figure 2. Routine shoulder radiographs. The complete radiographic examination of the shoulder consists of anteroposterior (AP) radiographs in (a) external rotation and (b) internal rotation and (c) an axillary view. When an axillary view cannot be obtained due to pain and difficulty with arm abduction, (d) a scapular "Y" view may be obtained.

Classic Radiographic Findings of Posterior Shoulder Dislocations

Knowledge and awareness of the radiographic findings which facilitate the diagnosis of posterior shoulder dislocations are required. These include fixed internal rotation of the humeral head (Figure 3a-b), impaction fracture at the anteromedial aspect of the humeral head (reverse Hill-Sachs lesion) (Figure 3c), widening of the glenohumeral joint space with lack of humeral head and glenoid overlap in AP projection (Figure 3d), and the "trough line" (Figure 3e), a vertical line of cortical bone seen at the edge of a compression fracture at the anterior superomedial aspect of the humeral head (3, 4, 11, 12).

The "Veil of Obscuration" – An Additional Radiographic Finding Associated with Posterior Shoulder Dislocations

Imaging studies are a common part of a patient's Emergency Department visit. How-

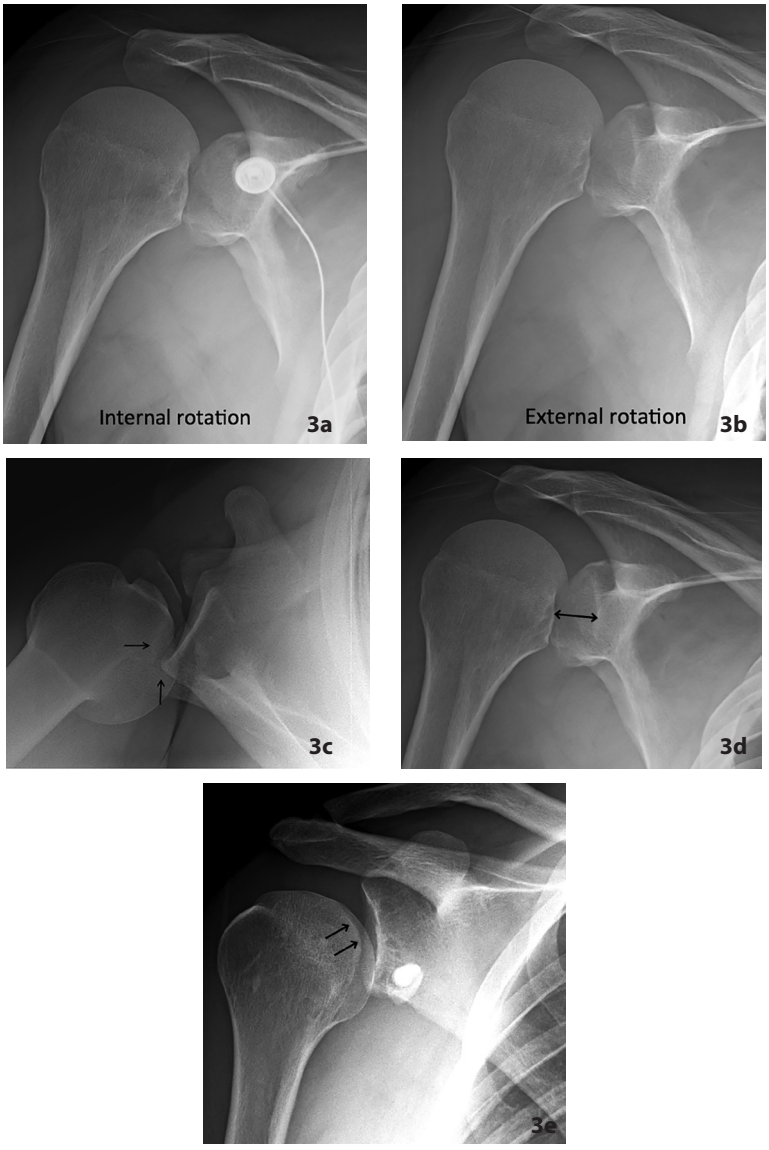

Figure 3. Classic radiographic findings of posterior shoulder dislocation. In (a) AP internal rotation and (b) attempted AP external rotation radiographs of the right shoulder, the humeral head remains in fixed internal rotation on both imaging projections. (c) Axillary radiograph of the right shoulder in a different patient shows an impaction fracture at the anteromedial aspect of the humeral head (arrows) consistent with a reverse Hill-Sachs lesion. In (d), internal rotation AP radiograph of another patient, note a widened glenohumeral joint space (arrow) measuring 1.8 cm with inadequate overlap between the humeral head and glenoid. (e) AP radiograph of the right shoulder in another different patient shows a vertical line of cortical bone projecting over the superomedial aspect of the humeral head (arrows) corresponding to the trough line sign created by the margin of the humeral head impaction fracture. Surgical hardware projects over the inferior glenoid from prior screw fixation.

ever, in many cases the initial imaging interpretation falls upon the emergency physician, with the final interpretation by the radiologist occurring after patient disposition and treatment plans have been made or not at all. In addition, in many academic institutions, attending radiology interpretation may not be readily available overnight.

To further assist the emergency physician in identification of posterior shoulder dislocations, we describe an additional radiographic sign of posterior shoulder dislocation that we refer to as the "veil of obscuration" (Figures 4 and 5). This sign is seen on AP shoulder radiographs and represents a frequently comminuted fracture of the lesser tuberosity projecting over the humeral head or glenohumeral joint creating a "veil" of bone density that may obscure the underlying posterior dislocation. It is well known that the lesser tuberosity of the humeral head is susceptible to fracture in association with posterior dislocations of the glenohumeral joint. Fractures of the lesser tuberosity may be sizable, and much larger than anticipated on radiographs.

We believe that the "veil of obscuration" sign may aid in the detection of posterior

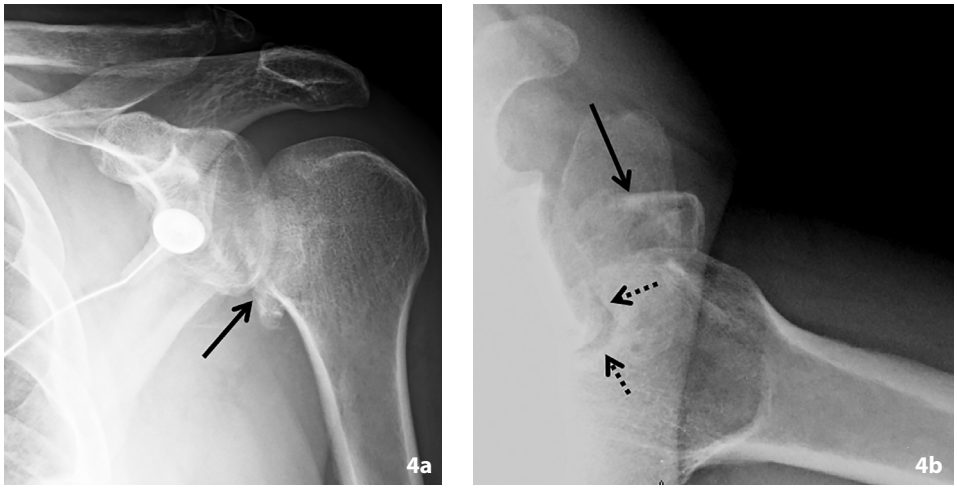

Figure 4. The "veil of obscuration" radiographic sign. (a) AP internal rotation radiograph of the left shoulder shows a displaced comminuted lesser tuberosity fracture (solid arrow) creating the "veil of obscuration" radiographic sign. (b) Axillary radiograph of the same shoulder demonstrates the displaced fracture of the lesser tuberosity (solid arrow). Also note posterior dislocation of the humeral head in relation to the glenoid with large reverse Hill-Sachs lesion at the anteromedial aspect of the humeral head (dashed arrows).

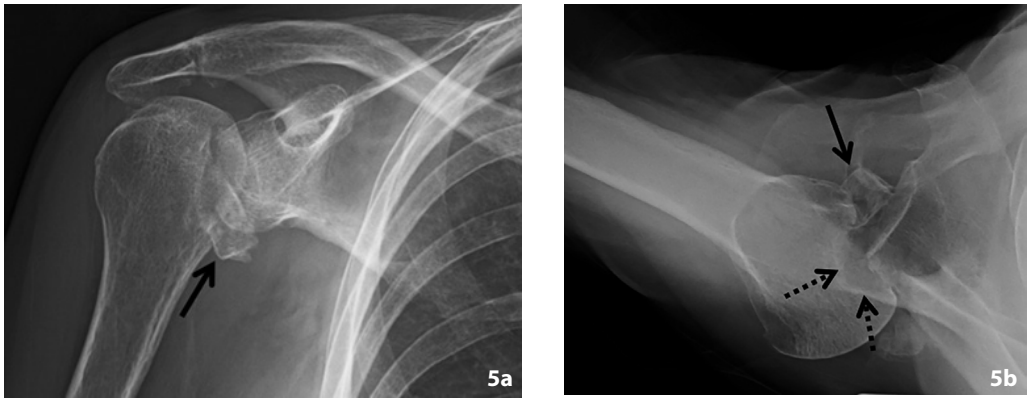

Figure 5. Sharply defined "veil of obscuration" radiographic sign. (a) AP internal rotation radiograph of the right shoulder shows a comminuted lesser tuberosity fracture (solid arrow) creating the sharply demarcated "veil of obscuration" radiographic sign. (b) Axillary radiograph of the same shoulder demonstrates a displaced fracture of the lesser tuberosity (solid arrow). Also note the humeral head is dislocated posteriorly in relation to the glenoid with large reverse Hill-Sachs lesion at the anteromedial aspect of the humeral head (dashed arrows).

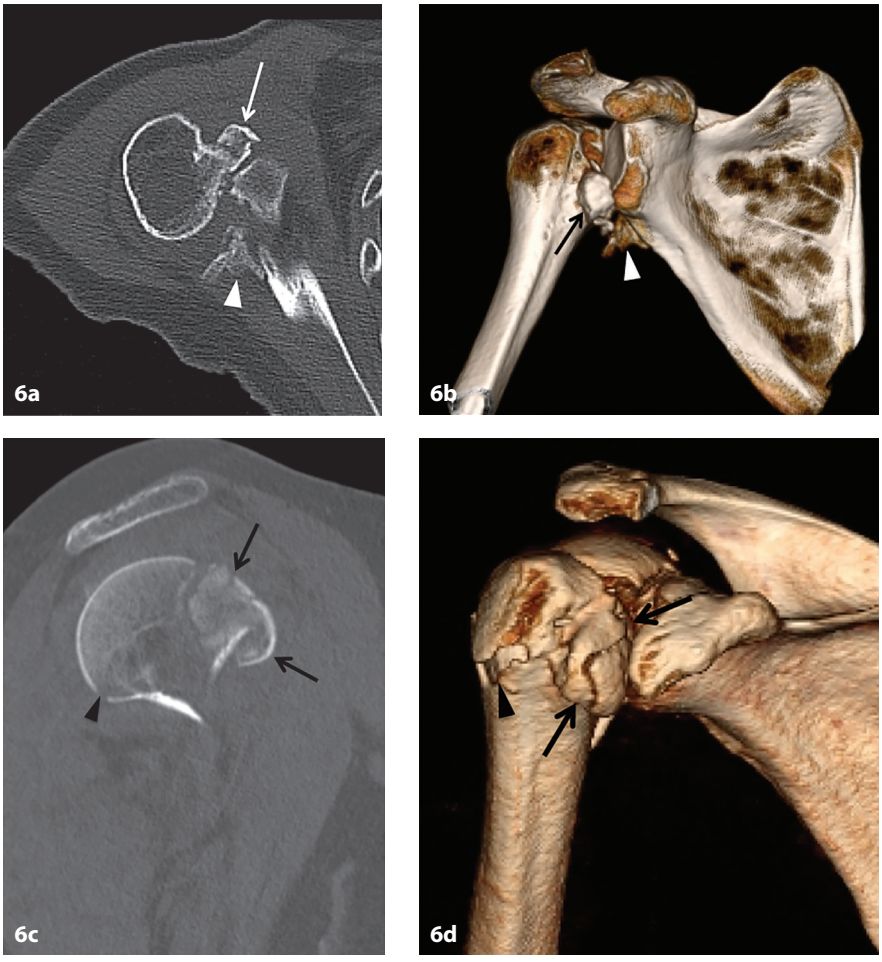

Figure 6. CT images of the "veil of obscuration" in the setting of posterior shoulder dislocations. (a) Axial and (b) 3D CT reconstruction images of the right shoulder clearly demonstrate a mildly displaced lesser tuberosity fracture fragment consistent with the "veil of obscuration" sign (arrow) and a displaced reverse bony Bankart lesion of the posterior glenoid (arrowhead). The humeral head is posteriorly subluxed. (c) Sagittal and (d) 3D CT reconstruction images of the right shoulder in another patient clearly demonstrate a mildly displaced comminuted lesser tuberosity fracture consistent with the "veil of obscuration" (arrows). Also note an associated comminuted humeral surgical neck fracture (arrowheads) as well as additional comminution of the humeral head. The humeral head is posteriorly subluxed, which was better seen on the axial CT images (not included).

glenohumeral joint dislocations. The principle fracture fragment is flat and disc-like shaped. It is typically displaced inferiorly and medially with respect to the humeral head and seen en-face on AP radiographs (Figures 4 and 5). In this projection, the fragment is usually poorly defined and appears as a veil or cloud-like density which obscures underlying bony detail (Figure 4). The "veil of obscuration" was so named because the "veil" created by the overlying displaced bone fragments often obscures the underlying posterior dislocation. Rarely, the fragment is more sharply defined on the AP projections (Figure 5). The true nature of the bone fragment is best visualized on CT images with 2D and 3D reconstruction (Figure 6) which may not be available in routine emergency department practice.

The purpose of this study was to describe and determine the incidence and validity of the "veil of obscuration" radiographic sign in posterior shoulder dislocations.

Methods

Subjects

Institutional review board approval was obtained with waiver of consent for this retrospective study. Consecutive patient records were obtained for patients diagnosed with posterior shoulder dislocation in our institution from January 1, 2011 to January 1, 2015. Inclusion criteria were (a) patients with diagnosis of acute posterior glenohumeral joint dislocation confirmed by radiographs and (b) patients with available diagnostic imaging on our Picture Archiving and Communication System (PACS) in a major regional university hospital which demonstrates the posterior glenohumeral joint dislocation. Exclusion criteria were patients without available radiologic images or with shoulder arthroplasty.

Radiographic images of the affected shoulder were reviewed by two fellowship trained musculoskeletal radiologists with more than 30 and 3 years of experience in consensus for presence of the "veil of obscuration" representing a displaced lesser tuberosity fracture fragment and other previously described classic radiographic signs for posterior shoulder dislocation including fixed internal rotation of the humeral head, widened glenohumeral joint space, and trough sign in the AP projections, and posterior subluxation or dislocation of the humeral head in relation to the glenoid, as well as reverse Hill-Sachs lesion at the anterior superomedial aspect of the humeral head and reverse bony Bankart lesion in the axillary and/or scapular "Y" projections. The electronic medical records were also reviewed to obtain information regarding patient demographics and any correlation with a specific type of trauma or other factors. The incidence of each of the radiographic findings/signs of posterior shoulder dislocations was calculated.

Statistical Analysis

Descriptive statistical analyses were performed. Mechanism of injury, prevalence of radiographic findings/signs, other fractures, and surgery were evaluated. Associations between the radiographic signs, other fractures, and surgery as a function of gender, age, and mechanism of injury were evaluated. Any significant differences in the radiographic signs and surgery were explored as well. Continuous data was analyzed with a student t-test and categorical data with a Chi-Square test.

Results

During the 48-month time period, there were 34 patients diagnosed with acute posterior shoulder dislocation at our busy emergency department which serves a population of at least a million people and approximately 100 or more patients with spectrum of shoulder injuries per week. Of these, 30 patients (26 males and 4 females) had available radiologic imaging pertaining to the diagnosis and were included in the study. All diagnoses of posterior glenohumeral joint dislocations were confirmed with radiographs, with 5 of these subjects also undergoing subsequent CT study and 1 subject undergoing subsequent MR imaging study. Females were significantly older than male patients (P=0.0115); 4 females (mean age, 62.25 years; age range 53-69 years) and 26 males (mean age, 40.80 years; age range, 20-68 years). Twenty posterior dislocations were of the right shoulder and 10 of the left. The majority of posterior glenohumeral joint dislocations occurred as a result of a vehicle crash (44%). Other mechanisms of injury included seizure, other major trauma (such as a fall), and minor trauma (such as tripping or lifting a tray). There was no significant difference (X^2=1.11, P=0.775) in

Table 1. Mechanism of Injury of Glenohumeral Joint Dislocations as a Function of Laterality

Mechanism	Left Side	Right Side	Total
	% (n)	% (n)	% (n)
Vehicle crash	40 (4)	45 (9)	44 (13)
Seizure	20 (2)	25 (5)	23 (7)
Other major trauma	40 (4)	25 (5)	30 (9)
Minor trauma	0 (0)	5 (1)	3 (1)
Total	100 (10)	100 (20)	100 (30)

Table 2. Prevalence of Radiographic Signs of Posterior Shoulder Dislocation

Radiographic Sign	% (n)
Widened joint space	37 (11)
Trough line	43 (13)
Veil of obscuration	40 (12)
Reverse Hill-Sachs	83 (25)
Other fractures	23 (7)
Fixed internal rotation of humeral head	76 (22)

mechanism of injury as a function of laterality (Table 1).

Table 2 demonstrates the prevalence of the radiographic signs of posterior shoulder dislocation. In most cases, a reverse Hill-Sachs lesion (83%) and fixed internal rotation of the humeral head (76%) were present, followed by the trough line (43%), and then the "veil of obscuration" (40%).

Twenty-five patients with posterior glenohumeral joint dislocations had reverse Hill-Sachs fractures. In 7 cases, other fractures were also present. These included 1 of the humeral surgical neck, 1 of the greater tuberosity, 1 of the posterior rim of the glenoid (reverse bony Bankart lesion), 2 of the humeral head, and 2 of the distal clavicle or acromion.

Table 3 demonstrates significant differences in the radiographic signs as a function of mechanism of injury. The trough line was seen in significantly more cases of other major trauma and vehicle crashes (78% of all other major trauma cases and 46% of all vehicle crashes; P=0.015), while the "veil of obscuration" sign was seen in significantly more cases of seizure activity (86% of all seizure cases; P=0.037). There was no significant difference found regarding a widened glenohumeral joint space, reverse Hill-Sachs lesion, reverse bony Bankart lesion, other fractures, or fixed internal rotation of the humeral head as a function of mechanism of injury. Fixed internal rotation of the humeral head could not be evaluated in one patient due to lack of AP external rotation view on initial radiographic evaluation. The presence of the other classic radiographic signs of posterior shoulder dislocation or other fractures did not differ as a function of age or gender.

Four patients (2 males and 2 females) required surgery following attempted unsuccessful or contraindicated closed reduc-

Table 3. Radiographic Signs in Posterior Glenohumeral Joint Dislocations as a Function Mechanism of Injury

Radiographic sign	Vehicle crash	Seizure	Other major trauma	Minor Trauma	P
	% (n)	% (n)	% (n)	% (n)	
Widened joint space (n=11)	64 (7)	18 (2)	18 (2)	0 (0)	NS
Trough line (n=13)	46 (6)	0 (0)	54 (7)	0 (0)	0.015
Veil of obscuration (n=12)	25 (3)	50 (6)	25 (3)	0 (0)	0.037
Reverse Hill-Sachs (n=25)	44 (11)	28 (7)	28 (7)	0 (0)	NS
Other fractures (n=7)	29 (2)	29 (2)	29 (2)	14 (1)	NS
Fixed internal rotation of humeral head (n=22)	36 (8)	27 (6)	32 (7)	5 (1)	NS

NS=not significant.

tion of posterior shoulder dislocation, usually related to complex injuries. There was a significant difference in gender, with 50% of females undergoing surgery versus 8% of males (P=0.021). There was a trend towards significance when looking at surgery and mechanism of injury, with 43% of patients with seizures leading to surgery (P=0.058). All surgical patients had reverse Hill-Sachs lesions and two of them presented with additional humeral head fractures.

In addition, all surgical patients had the "veil of obscuration" radiographic sign. Thirty-three percent of those with the "veil of obscuration" sign went on to surgery while no patients without this sign went on to surgery (P=0.0085). There was no significant difference in the presence of the other radiographic signs in regards to surgery.

Discussion

Posterior glenohumeral joint dislocations can often pose a diagnostic problem. Rowe et al. (1982) reported that 79% of posterior shoulder dislocations were missed on the clinical exam by the initial treating physician (13). Another study demonstrated that more than 50% of posterior shoulder dislocation cases can be initially missed on radiographs (7). Delays in diagnosing posterior dislocation are common, especially in older patients and those with concomitant injuries or fractures of the ipsilateral arm (7). Several reasons for delay in diagnosis have been reported which include failure of initial clinical evaluation to suspect the correct diagnosis, lack of or inadequate radiographic imaging and misinterpretation by inadequately trained physicians (7). If missed, the untreated posterior shoulder dislocations can progress to instability and/or lead to operative treatment (2, 5). However, in many instances these complications can be prevented by early diagnosis and prompt closed reduction.

Knowledge of radiographic signs associated with posterior shoulder dislocations are required to avoid delay in diagnosis and facilitate prompt diagnosis and timely treatment. Cisternino et al. (1977) previously described the frequency of the radiographic signs of posterior shoulder dislocation (11), not including the reverse Hill-Sachs lesion. In this study, the humeral head was held in internal rotation in 100% of posterior shoulder dislocations, followed by trough line (75%), and a widened joint space (55%). Similarly, when we excluded the reverse Hill-Sachs lesion, our study also demonstrated that the most frequent radiographic sign was fixed internal rotation (76%), followed by the trough line (43%), and then the widened joint space (37%). Another more recent study in 2010 (12) showed the frequency of the trough line sign to be 64%, followed by widened joint space (45%), although the presence of the humeral head fixed in internal rotation was not evaluated.

Our study demonstrates that the "veil of obscuration" is an additional likely reliable radiographic sign of posterior shoulder dislocation in addition to the other classic radiographic findings. While the "veil of obscuration" is only seen in cases of a posterior glenohumeral joint dislocation with concomitant comminuted fracture of the lesser tuberosity, its prevalence is similar to that of the "trough line" (40% versus 43%), and is slightly more common than a widened glenohumeral joint space (37%). The recognition of the "veil of obscuration" may be an indication for additional CT imaging for tri-dimensional evaluation of possible more complex injuries. Interestingly, the "veil of obscuration" appears to indicate a more severe case of posterior glenohumeral joint dislocation as all our patients who went on to have surgery demonstrated this radiographic sign. Additionally, in our subjects, the "veil of obscuration" is seen in significantly larger number of cases of seizures.

In line with previously published data (2), posterior dislocations were more commonly seen in men than women in our study. Robinson et al. (2011) reported a prevalence of 1.2 per 100,000 posterior dislocations per year in men versus 0.6 per 100,000 per year in women during their study period. A portion of this discrepancy which is even more apparent in our study may be due to differences in types of activity or occupation between the male and female genders.

We also described fractures associated with posterior shoulder dislocations. Similar to a study in 2012 by Rouleau and collaborators, the reverse Hill-Sachs lesion was the most common fracture type associated with posterior shoulder dislocations (83%), although we saw them in a greater number of cases than previously reported (29%) (14).

In contrast to prior reported numbers, only one case of posterior shoulder dislocation was initially missed in our study. In this case, the patient had sustained a vehicle crash, with the dislocation initially overlooked by the treating clinician in the emergency department. Humerus radiographs instead of dedicated shoulder radiographs were initially obtained. Although, the posterior shoulder dislocation was missed on the initial humerus radiographs, it was seen on follow-up dedicated shoulder radiographs a few days later. The radiographic signs present were a widened glenohumeral joint space and trough line. The "veil of obscuration" was not present in this case.

Conclusion

In conclusion, we described an additional radiographic sign associated with posterior shoulder dislocation called the "veil of obscuration" which has a comparable incidence as previously described classic signs including the widened joint space or trough line. This radiographic sign is frequently seen with seizure activity and in general suggests the presence of a more severe injury. We conclude that the "veil of obscuration" sign may be an additional useful aid in the recognition and diagnosis of posterior glenohumeral joint dislocations.

What is already known on this topic

Posterior shoulder dislocations can be overlooked on radiographs due to the subtlety of imaging findings and difficulties in patient positioning, as well as the relative rarity of posterior shoulder dislocations. If missed, the untreated cases can progress to chronic instability or lead to open reduction. Knowledge and awareness of the radiographic findings which facilitate the diagnosis of posterior shoulder dislocations are required. These include fixed internal rotation of the humeral head, impaction fracture at the anteromedial aspect of the humeral head (reverse Hill-Sachs lesion), widening of the glenohumeral joint space with lack of humeral head and glenoid overlap in AP projection, and the "trough line", a vertical line of cortical bone seen at the edge of a compression fracture at the anterior superomedial aspect of the humeral head.

What this study adds

We describe an additional radiographic sign of posterior shoulder dislocation that we refer to as the "veil of obscuration" to further assist the emergency physician. This sign is seen on AP shoulder radiographs and represents a frequently comminuted fracture of the lesser tuberosity projecting over the humeral head or glenohumeral joint creating a "veil" of bone density that may obscure the underlying posterior dislocation. We described and determined the incidence and validity of the "veil of obscuration" radiographic sign in posterior shoulder dislocations. This sign has a comparable incidence as previously described classic radiographic signs, is frequently seen with seizure activity, and in general suggests the presence of a more severe injury. The "veil of obscuration" sign may be an additional useful aid in the recognition and diagnosis of posterior glenohumeral joint dislocations.

Authors' contributions: Conception and design: LG, MT, and LR; Acquisition, analysis and interpretation of data: ZR, LG, LR, and EK; Drafting the article: LG, MT, and LR; Revising the article critically for intellectual content: MT and TC; Approved final version of the manuscript: MT and LG

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Evaluation of Physical Parameters of Novel Licorice Varnish Versus Fluoride and Combination Varnish: An In-Vitro Study

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Key words: Dental Varnish ▪ Early Childhood Caries ▪ Licorice ▪ Prevention of Tooth Decay ▪ *Streptococcus Mutans*.

Objectives. The aim of this study was to evaluate the physical properties of locally prepared Licorice varnish (LV), commercially available Fluoride varnish (FV) and a Combination of both Varnishes (CV). **Material and Methods.** LV was prepared using authenticated licorice roots. Commercially available FV (Bifluorid 12) was used as a positive control and CV was prepared in six different concentrations of both varnishes. Conventional antibacterial activity assessment, employing disc diffusion and broth dilution methods, was inconclusive. Therefore a novel assessment method was used, whereby the varnish was directly added to a mixture of Brain Heart Infusion broth with *Streptococcus mutans* and incubated. Physical parameters such as pH, rate of evaporation, viscosity, film forming ability, and cost incurred for preparation were assessed and compared. **Results.** FV, LV and CV (except the combination of LV 80% + FV 20%) showed antibacterial activity against *Streptococcus mutans*. All three varnishes formed films on the tooth surface as confirmed by Scanning Electron Microscopy. Mean pH was in the range of 4-4.5, viscosity 48-52 centipoise (cP), rate of evaporation was 150-160 seconds. They were comparable to each other in the physical parameters tested, except for the shelf life of LV. **Conclusion.** All three varnishes showed antibacterial activity against *Streptococcus mutans* which was established using an innovative method of antibacterial activity assessment. LV was most economical of all but had a shorter shelf life. The results of this study need to be evaluated through an in vivo study.

Introduction

Dental caries is the most common chronic infectious disease in childhood (1). Early Childhood Caries (ECC) is a devastating form of dental disease affecting the youngest members of society. Children's quality of life can be seriously affected by severe caries because of pain and discomfort which could lead to disfigurement, acute and chronic infections, and altered eating and sleeping habits, as well as the risk of hospitalisation, high treatment costs, and the loss of school days, with the consequent diminished ability to learn (2). The knowledge about dental caries has increased, but dentists worldwide are struggling to prevent ECC. Community-based preventive programs have to be developed and implemented urgently to achieve the World Health Organization (WHO) goals, and to improve oral health, health in general and the quality of life in particular (3).

The foremost of all caries preventive tools is Fluoride which can favourably al-

ter demineralisation and remineralisation processes, thus preventing caries (4). Long-lasting pharmaceutical formulations in the form of varnishes have been developed for the prevention of dental caries (5).Varnishes are easy to apply, have a high concentration of fluoride, and can be applied in a moist environment, and thus can be considered as the best preventive tool against ECC (6). The remineralising capacity and antibacterial activity of Fluoride against *Streptococcus mutans* have been reported and time tested, however, the cost and manpower required for fluoride varnish application necessitate the search for other alternative preventive tools. The gap in the knowledge base in this regard remains a topic for exploration, as in the present study.

Recently, there has been an increasing interest in herbal dentistry to overcome drawbacks of modern medicine such as the development of resistance to antibiotics, and side effects such as vomiting, diarrhoea, alteration of taste sensations, etc. (7). There has been growing interest in biologically active compounds, derived from natural products, which may have potential therapeutic uses in dentistry (8). Ayurveda has a wide range of medicinal plants which have been used to alleviate human suffering and promote general health and well being. Among the various medicinal plants used, Licorice – *Glycyrrhizaglabra* is one such plant. Licorice, known as the "Grandfather of Herbs," has been used by various cultures and is time tested. It is 50 times sweeter than sucrose, has been successfully used to relieve sore throat and gastric problems, and enhance memory in children. It is easily available, inexpensive, approved by the US FDA as GRAS (generally regarded as safe as per 21 CFR section, 21CFR 184-1408) and LD_{50} of *Glycyrrhizin* is 1.94 g /kg subcutaneously (9) indicative of a good safety profile.

Isolated use of fluoride has proved to be insufficient to prevent progressive mineral loss and consequent lesion formation in children at high risk for caries development (10). Hence the combination of fluoride with licorice varnish was undertaken with the idea that the combination may control plaque formation with reduced acidogenicity, and may also help in remineralization of initial lesions.

Thus the objective of the study was to compare the physical properties of all three varnishes. We also compared the cost incurred for preparation of the varnish.

Materials and Methods

The present study was carried out from Jan 2016 to April 2016 at the Dr. Prabhakar Kore Basic Science Research Centre, Belagavi. Ethical clearance was obtained from the Institutional Ethics Committee. Authenticated Licorice roots were used to prepare Licorice extract using the cold maceration method. The extract was filtered using a muslin cloth and Whatman No.1 filter paper. The filtrate was concentrated using an IKA Rotary evaporator at 40°C, and the resultant residue was kept in a refrigerator until further use. The extract obtained was assessed for its antimicrobial activity against *Streptococcus mutans* ATCC 25175 (procured from PGI Chandigarh) using the broth dilution method.

Licorice Varnish (LV)

The Faculty of Pharmacy guided the preparation of Licorice Varnish. All ingredients of *IP* (*Indian Pharmacopeia)* grade, were used for preparing the varnish (Table 1). A manual of operations was prepared, and the Good Laboratory Practices (GLP) guidelines were followed for the varnish preparation. LV was prepared by the addition of ethyl acetate to licorice extract in a sterile glass container. The extract was dissolved by keeping a glass container in a bath sonicator for 30 minutes. When the extract was completely dissolved,

Table 1. Ingredients Used for Preparing Licorice Varnish Along with Their Functions

Ingredient	Function	Manufacturer
Iso amyl propionate purchased from Sigma	Plasticizer	Sigma Aldrich, SAPC
Ethyl acetate	Solvent	Sigma Aldrich, SAPC
Collodion solution, gift sample from Sigma	Lacquer	Omatek Laboratories,Indore.
Fumed silica-Gift sample, Aerosil 200	Thickening agent	Pharma from Evonik Industries,Germany
Licorice extract	Antimicrobial activity	Indigenously prepared

Collodion solution, along with Iso Amyl Propionate was added. It was centrifuged again and fumed silica was added to this mixture. All the contents were centrifuged for 30 seconds and the mixture was transferred to an amber colored sterile bottle and labeled.

Fluoride Varnish (FV)

Commercially available Bifluorid12 varnish (VOCO Company, Germany. Lot no.1523310) was used as a positive control.

Combination Varnish (CV)

This was initially prepared by mixing 80% LV with 20% FV but when it failed, other combinations were tested. Combination varnish was prepared by mixing various concentrations of licorice varnish and fluoride varnish as described below: 50% LV + 50% FV; 60% LV + 40% FV; 75% LV + 25% FV; 60% FV + 40% LV; 75% FV + 25% LV. All the three varnishes were assessed for their antimicrobial activity and physical parameters.

Antimicrobial activity – The antimicrobial susceptibility test was performed according to the Agar diffusion method. *Streptococcus mutans ATCC 25175* was cultivated in Brain Heart Infusion (BHI) broth, and it was transferred after 18 hours to BHI agar containing 5% sucrose.

Disc diffusion method – The direct colony suspension method for the preparation of inoculums was followed. The inocula of *Streptococcus mutans* was prepared by collecting 3-4 colonies grown on agar after 24 hours and the number of microorganisms was calculated based on the standard turbidity of 0.5 McFarland, corresponding to $1.0x10^8$ colony forming units/ml. All the three varnishes, FV, LV and CV, were diluted to concentrations ranging from 100%, 50%, 25%, 12.5% and 6.25% with the help of distilled water. Twenty micro liters of the respective varnishes were transferred onto sterile filter papers (6.4 mm diameter) and placed on the agar plate. The plates were then incubated at 37°C for 48 hours anaerobically. The varnishes, being alcoholic mixtures, evaporated and did not diffuse through the agar plates (Figure 1).

Broth dilution method – The broth dilution method was attempted next. As a

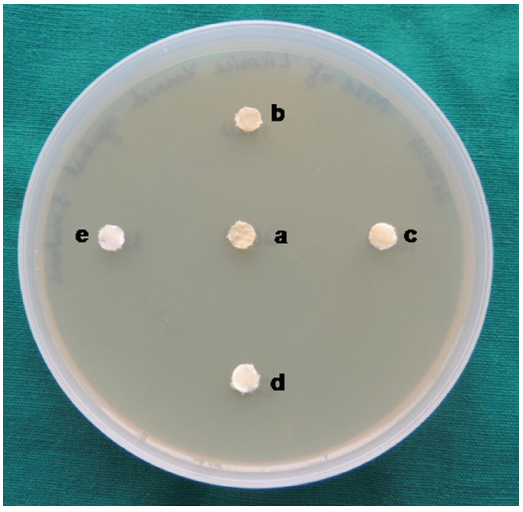

Figure 1. Disk diffusion method showing failure of varnishes (various dilutions: a=100%, b=50%, c=25%, d=12.5% and e=6.25%) to diffuse through agar medium.

procedural step, varnish was added to BHI broth, but as soon as the varnish was mixed with BHI broth a precipitate formed immediately annulling the chance of any further investigation. Since varnish is made up of resins, as soon as it was mixed with broth, a precipitate occurred (Figure 2). Since the result was inconclusive, this method was also discarded. The routine tests employed for testing the MIC of varnish failed and, hence there was a need to develop a novel method to assess the MIC of varnish.

Novel method – In this method, 0.5 ml of varnish was added directly to a mixture of 0.5 ml of BHI broth and *Streptococcus mutans*. One loop of this mixture was then spread over agar gel and incubated for 48 hours. A similar procedure was repeated with LV and CV and the results obtained are shown in Figure 3. As can be seen clearly, CV in a ratio of 80% LV and 20% FV, failed to show antimicrobial activity. All three varnishes were tested for physical properties by the principal investigator who was trained at KLE Dr. Prabhakar Kore Basic Science Research Centre.

Color matching – The freshly prepared LV was compared with the shade guide and the shade number was noted, along with the date of preparation. This helped us to assess the shelf life of the varnish. When performing the color matching, the investigator was wearing a vision aid, clear spectacles which are normally worn every day. The test area had the artificial natural daylight fluorescent illumination. The specimen was held at a distance of 25cms and was observed at perpendicularly. Color matching was done between the shade guide and the specimen. The intra observer agreement was calculated as the mean value of the highest percentage of identical scores for 6 specimen of the same shade, performed twice at an interval of one week: 1) Rate of evaporation – A sterile glass slide was taken and its weight was noted down. One hundred micro liters of varnish was then dispensed on it and evenly distributed, and kept on a digital weighing scale. A stop-watch was used to assess the time taken for the slide to return to its original weight. Viscosity was assessed using a CAP 2000 + Viscometer, Brookfield. Two ml of the varnish was placed on the viscometer plate and the test was run according to the manufacturer's instructions and values noted. 2) Film forming ability – Human Tooth samples of 3 mm thickness were obtained using hard tissue microtome. Fifty micro liters of the respective varnishes were applied us-

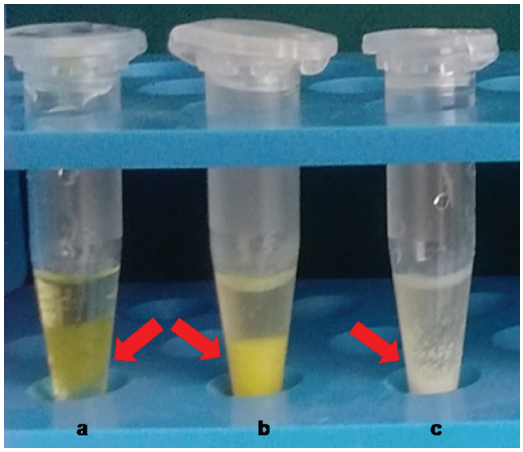

Figure 2. The broth dilution method showing the formation of precipitate upon addition of varnishes to Brain Heart Infusion broth: a=Licorice varnish; b=Fluoride varnish; c=Combination varnish.

Figure 3. New method for assessing the MIC of all three varnishes. Combination varnish (80% Licorice varnish and 20% Fluoride varnish) failed to show antibacterial activity.

ing the applicator tip. After the samples were completely dried, they were observed under a Scanning Electron Microscope (SEM). The morphology of the formed films on the tooth surface was studied using a JOEL Scanning Electron Microscope, Model JSM- 6360LV, operating in 15 kV acceleration voltage. 3) The safety of the LV was assessed by comparing the lethal doses of all the ingredients used with the actual concentration used for preparing the varnish (11-13).

Statistical Analysis

The data was analyzed using SPSS software version 20 (SPSS Inc Chicago, USA). The level of significance was set at 0.05. Intra examiner reproducibility was assessed using Cohen's Kappa for color matching. Triplicate values were used to determine the mean value for rate of evaporation and viscosity of the varnishes.

Results

Intra examiner Cohen's Kappa (k) for color matching was 0.86, confirming good reproducibility. The licorice extract, along with LV and FV, showed antimicrobial activity (Table 2). CV showed antimicrobial activity in all the tested permutations except 80% LV and 20% FV (Figure 4). All the combination of varnishes, that is (60% FV+40% LV), (40%FV+60%LV), (25%FV+75%LV), (75%FV+25%LV) and (50%FV+50%LV), were equally effective with regard to antibacterial activity. The combination varnish in the concentration of (50%FV+50%LV) was easier to prepare in terms of time and cost. Hence the physical parameters were assessed using this proportion and the results obtained are shown in Table 3. All the varnishes were acidic in nature.

Table 2. Results of Minimal Inhibitory Concentrations of Licorice Extract and the Three Varnishes Against *Streptococcus Mutans*

Test group	Antibacterial activity against *Streptococcus mutans*
Licorice extract	Positive - 2.0 mg/ml
Licorice varnish	Positive
Fluoride varnish	Positive
Combination varnish	
80% Licorice Varnish + 20% Fluoride Varnish	Negative
50% Licorice Varnish + 50% Fluoride Varnish	Positive
60% Licorice Varnish + 40% Fluoride Varnish	Positive
75% Licorice Varnish + 25% Fluoride Varnish	Positive
60% Fluoride Varnish + 40% Licorice Varnish	Positive

Table 3. Comparison of the Physical Parameters of All Three Varnishes

Parameters	Fluoride varnish	Licorice varnish	Combination varnish
Rate of evaporation (second)	150	156	160
pH	4	4.5	4.5
Viscosity (Pa*s)	48	52	49
Shelf life	Stable for 2 years	Shelf life 35 days	Shelf life 2 months
Cost	Rs 4500 per bottle*	Rs 700 per bottle; 6-7 times cheaper†	Approximately Rs 2500 per bottle

Pa*s=Pascal seconds; *Biflurid 12 Voco product; †Indigenously prepared; Rs=Indian Rupees.

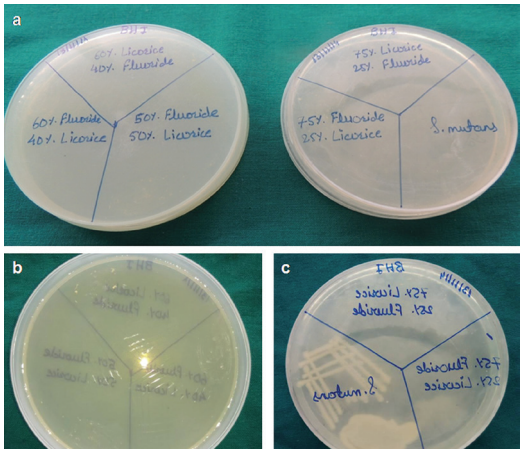

Figure 4: a) The combination varnish showed antimicrobial activity in all the tested permutations; b) No growth of *Streptococcus mutans* was seen in any of the combination varnishes; c) *Streptococcus mutans* growth was seen in the control group.

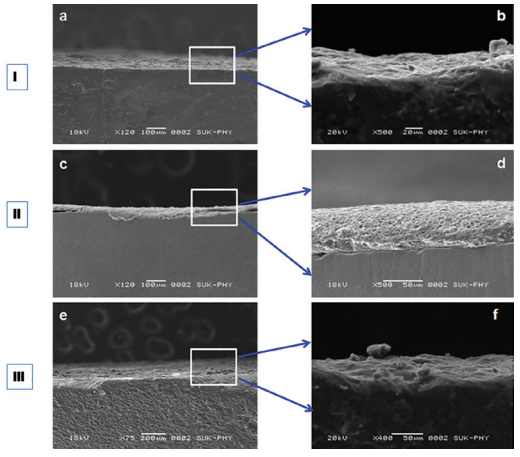

Figure 5. Morphological characterization of films formed on the tooth surface after application of varnishes. SEM images of I=Licorice varnish; II=Fluoride varnish; III=Combination varnish (a, c, e side view; b, d, f expansion view).

The safety profile of various components used in preparing LV is presented in Table 4.

Scanning Electron Microscopy (SEM) results - SEM images are presented in Figure 5. The images reveal the uniform film formation of all the three varnishes. The films were in intimate contact with the tooth. However, the compactness of the varnishes differed from one another.

Discussion

This study describes the development of a novel LV, as well as a new method to assess the MIC of varnish. The dental profession is currently faced with an enormous task of how to manage the huge burden of the consequences of the caries process amongst the world population (14). Providing care for preschool children can be stressful and troublesome (5). Hence, the focus is currently on minimally invasive approaches which can arrest caries progression. Fluoride is the most essential chemical agent used for dental caries prevention, and various topical fluoride interventions have been supporting this, with over six decades of experimental research (15). However, an increased resistance to caries from fluoride has been reported (16).

The present study compared locally prepared LV with FV and their combination. The antimicrobial activity was assessed using a novel method for LV. An extensive literature review showed that there were no

Table 4. Comparison Between the Toxic Values of Varnish Ingredients and the Actual Concentrations Used per Milliliter of the Varnish

Ingredient	Toxicity profile	Concentration*
Licorice extract	Animal studies – it does not cause genotoxicity, cytotoxicity or cellular toxicity. 1.94 gms/kg (29)	8 mg
Iso amyl propionate	Approximately 5 ml/kg (12)	0.1 ml
Aerosil	>3160 mg/kg body weight (Evonik MSDS datasheet)	10 mg
Ethyl acetate	11.3 g/kg body weight (12)	0.2 ml
Collodion solution	10 mg/kg (12)	0.2 ml

*Concentration used per milliliter of licorice varnish.

reports on licorice varnish and our study seems to be the first one. In the present study, licorice extract was found to have an effective antibacterial activity against *Streptococcus mutans,* and this result is in concordance with other studies (17, 18). Licorice contains alkaloids, flavonoids, saponins like *glycyrrhizic acid, glycyrrhizin* and stilbenes – *gancaonin G* which have antimicrobial and anti-adherent properties against *Streptococcus mutans* and thus can help in caries control (19). The minimum inhibitory concentrations (MIC) of licorice varnish provide evidence that, even when the licorice extract was mixed with the other constituents of varnish, the extract was able to sustain its antimicrobial activity. The licorice varnish can be considered as a pragmatic option to prevent dental caries.

Though *in vitro* studies have made it clear that licorice has good antimicrobial activity against *Streptococcus mutans* and other organisms, it has not been used in a therapeutic form which is practical and feasible in a field trial involving preschool children. MIC is considered the 'gold standard' for determining the susceptibility of organisms to antimicrobials and is therefore used to judge the performance of all other methods of susceptibility testing (20). Varnishes, being alcoholic mixtures, evaporated and failed to diffuse through the agar plates. Hence, the conventional tests employed for testing MIC of varnish did not give any results, and a new technique which could overcome this problem was needed.

The inability of the varnish to diffuse through agar medium was overcome by the novel method, and the varnish acted directly on *Streptococcus mutans,* thus demonstrating the antimicrobial potential of the varnish. Antimicrobial testing of propolis varnish has been reported (21) where the authors diluted propolis varnish in an ethanol-water solution at 20% in a proportion of 1:1 (75 mg/ml) to reduce the viscosity of the varnish. This technique though it provided satisfactory results, actually camouflages the inherent antimicrobial activity of the varnish. Thus this particular technique was not followed in the present study.

When the cost factor was compared, LV proved to be more economical compared to FV. It is about 6-7 times cheaper than FV (Bifluorid 12). A comparison of the three varnishes revealed that licorice and CV were comparable to FV in most of the parameters assessed. However, when shelf life was assessed, LV had a shorter shelf life. When the rate of evaporation was assessed, it was found to be slightly longer for LV, although the difference was not statistically significant. This could be attributed to the lower viscosity of LV.

Combination varnishes, such as fluoride with chlorhexidine, fluoride with cervitec, and chlorhexidine with xylitol, have been used in dentistry, as the combinations have been shown to increase the suppression period of *Streptococcus mutans* (22-24). Both Cervitec F and fluoride varnish performed similarly when their antimicrobial activity against *Streptococcus mutans* was compared (24). Contrary to this, MI varnish, a newer combination varnish with CPP-ACP and fluoride, was compared against plain fluoride varnish and chlorhexidine varnish, but chlorhexidine showed significantly better results than a combination of CPP-ACP and fluoride varnish for antibacterial activity against *Streptococcus mutans* (25). On the other hand, Gedalia (26) reported that when *Glycyrrhizin (Licorice)* was added to the APF solution, fluoride uptake increased and enamel solubility was reduced. To test this hypothesis, a CV was tested in the present study. In the present study, CV prepared by mixing 80% LV with 20% FV failed to show antimicrobial activity. This may be due to the high concentration of licorice (80%) varnish in the CV which probably antagonized the effect of fluoride varnish present

in a lower concentration (20%). Further, the interaction between the active constituents of licorice varnish with the sodium and calcium fluoride present in fluoride varnish may have resulted in the annulling of each other's antimicrobial activity. However, the exact reason why the combination varnish with 80% LV with 20% FV failed to show any antimicrobial activity remains unclear. An interaction study between licorice and fluoride varnish is probably needed to find the answer, however it was beyond the scope of the present research. FV has multiple effects such as remineralization of initial enamel lesions and inhibition of *Streptococcus mutans*. We can predict that when licorice is mixed with FV it probably enhances the antibacterial activity of FV. The inhibition of plaque biofilm formation is the key to successful control and prevention of dental caries (27). This may indirectly enhance the remineralizing potential of CV and at a cost much lower than FV. Will CV improve the efficiency of the Gold standard "FV "in preventing ECC? This question needs to be answered in future studies.

As shown by SEM analysis, varnish formulations formed a uniform layer on the tooth structure. FV (Bifluorid 12) contains 5.6% F, and both sodium fluoride and calcium fluoride, which could penetrate the tooth surface more effectively (28). Hence, this was used as a positive control in the present study. Both sodium and calcium ions are positively charged ions, and have a high affinity to the fluoride ion. This affinity makes CaF and NaF crystals more stable, thus enabling the compact nature of the varnish. However, it has been reported that since Bifluorid 12 has higher viscosity, it formed a thicker layer on the acrylic surface to which *Streptococcus mutans* adhered easily (29). On the other hand, LV had lower viscosity, and we can speculate that it would penetrate the enamel tags to a greater depth. Whether these properties make any significant impact on caries progression or biofilm formation needs to be assessed through *in-vivo* studies.

Safety Issues

Licorice has been used by various cultures for thousands of years and many previous studies have shown that it is a safe medicinal herb (30). Ames test using *S Typhimurium* TA 1535 revealed no genotoxicity; a cytotoxicity study with Promega's CellTiter-Glo Assay, using cell lines of Jurkat HOK68 CHO and BHK, revealed no cellular toxicity. A single dose acute toxicity test with mice confirmed *Glycyrrhiza glabra* to be non-toxic (30). All the ingredients used in the present study were of *IP* (Indian Pharmacopeia) Grade, and GLP (Good Laboratory Practices) guidelines were followed during the preparation of LV, thus ensuring the safety of LV and CV.

Dental caries is a multifactorial disease and many organisms cause this disease. However, in the present study, a single organism was used, that is, *Streptococcus mutans*. It would be interesting to find out if LV has broad spectrum antibacterial activity in future studies, by assessing its antibacterial activity against other oral pathogens. Nevertheless, such an investigation was beyond the scope of the present study. The shelf life of LV was found to be shorter than FV, and further studies with respect to optimization of methods for preparation of the varnish are required to improve the product.

Conclusion

LV, FV and CV (except 80% LV + 20% FV) showed antimicrobial activity against the standard strain of *Streptococcus mutans.* The viscosity, rate of evaporation, pH, and film forming ability of all three varnishes were comparable to each other. LV was the most economical of the three but had a shorter

shelf life. Future studies with *in vivo* study design are required to confirm these findings.

What is already known on this topic

ECC is pandemic in prevalence and is amenable to prevention. The Cochrane database recommends the use of fluoride varnish for the prevention of dental caries in young children. However, varnish is an expensive preventive tool, especially for developing countries where the prevalence of the disease is high, and resources to tackle it are limited and hence there is a need to search for an alternative indigenous product. Licorice has been used for various ailments for centuries and has been used in dentistry as a mouthwash and lollipop for its anti caries activity against Streptococcus mutans.

What this study adds

Although the anti-cariogenic properties of licorice have been suggested for over 30 years, it has not been tested in a dosage form that can be used in public health programs. Hence this study presents the details of licorice varnish its preparation and its comparison with fluoride varnish. A combination varnish may provide more benefits by suppressing the acidogenic bacteria in addition to accelerating the remineralization process of white spot lesions. The present research work also describes a novel way of assessing the MIC of a viscous substance such is "dental varnish".

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Authors' contributions: Conception and design: RS and AA; Acquisition, analysis and interpretation of data: RS, KB and UB; Drafting the article: RS and MR; Revising it critically for important intellectual content: KB, UB and MR; Approved final version of the manuscript: RS, AA, KB, UB and MR.

Conflicts of interests: The authors declare that they have no conflict of interest.

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Non-Recurrent Laryngeal Nerve and Concurrent Vascular Variants: A Review

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Key words: Thyroidectomy ▪ Recurrent Laryngeal Nerve ▪ Variant ▪ Aberrant Right Subclavian Artery.

Objective. The purpose of this paper is to review the current data on the coexistence of non-recurrent laryngeal nerve (RLN) and vascular variations. **Methods.** A systematic literature search was conducted on MEDLINE for case reports, original articles and reviews regarding the presence of non-RLN and coexisting vascular variants. **Results.** From the literature search, 104 cases of non-RLN with confirmed vascular variants were reported. More specifically, 97.7% (n=101) of cases involved a right and 2.3% (n=3) a left non-RLN. The most common concurrent vascular variant reported with a right non-RLN was an aberrant right subclavian artery (97%; n=98). One case report (0.9%) of an intrathyroidal right common carotid artery was noted and 2 cases (1.9%) were associated with normal vascular anatomy. Furthermore, all 3 cases of a left non-RLN were associated with a right aortic arch, while 2 of them were also accompanied with situs inversus. **Conclusions.** The presence of vascular variations of the great vessels must prompt the surgeon to search for a non-RLN. Intraoperative neuromonitoring increases the detection rate of non-RLN. Further research is required to determine anatomic landmarks for the perioperative identification of a non-RLN, allowing its protection from potential injury.

Introduction

Surgery is indicated for the treatment of both benign and malignant thyroid diseases. Thyroidectomy is a common procedure, as reflected in the 72,344 total thyroidectomies performed in the United States in 2011 (1). In the late 19th century, the work of Kocher revolutionized the surgical management of thyroid disease, thus converting an operation with unacceptably high morbidity to a safe procedure (2). A bloodless field and thorough understanding of the regional normal and variant anatomy are crucial for an efficient and safe operation.

The recurrent laryngeal nerve (RLN) originating from the cervical vagus (cranial nerve X) provides sensory and motor function to the larynx. Sensory function involves the subglottic region while all the laryngeal muscles, except for the cricothyroid are innervated by the RLN. This nerve is responsible for both vocal cord abduction and adduction.

Damage to the RLN during thyroidectomy is responsible for vocal cord paralysis. On the right, the RLN courses posterior to

the right subclavian artery and ascends superiorly to the lateral trachea located in the tracheoesophageal groove before entering the larynx at the level of the first tracheal ring. On the left, the RLN courses posteriorly to the aortic arch at the level of the ligamentum arteriosum, traveling along the tracheoesophageal groove superiorly before entering the larynx. Non-recurrent laryngeal nerve (non-RLN) is a rare anatomic variant with a reported incidence of 0.3-0.8% on the right and 0.004% on the left side (3). In that case, the nerve enters the larynx directly after its origin from the cervical vagus. The risk of injury to the RLN is 1-2%. On the other hand, the risk of injury to a non-RLN skyrockets to 12.9%, with the first report of such an injury in 1932 given by Pemberton (4, 5). Furthermore, non-RLN has been observed with concurrent variants of the great vessels. The presence of an aberrant right subclavian artery (ARSA) or arteria lusoria originating from the aortic arch is associated with the presence of a right non-RLN. The purpose of this study is to review current evidence on the coexistence of vascular variants and non-RLN to raise surgeons' awareness, thus preventing potential injury to the nerve.

Materials and Methods

A systematic search of international literature indexed in MEDLINE was conducted. In June 2018, the PubMed search engine was accessed for original articles, cadaveric reports, case reports and reviews regarding non-RLN and confirmed concurrent vascular variations. The search terms thyroid, thyroidectomy, non-recurrent laryngeal nerve,

Table 1. The Number of Non-Rlns Reported in the International Literature, Grouped as Right and Left Side Nonrlns and their Associated Vascular Variant

Study	Non-RLN cases (n)	Right non-RLNs (n)	Left non-RLNs (n)	Associated vascular variant
Mahmodlou et al. (3)	1	1	-	ARSA
Toniato et al. (4)	31	31	-	ARSA (only 5 cases verified)
Morais et al. (9)	2	2	-	ARSA+ common trunk of common carotids
Hong et al. (11)	15	15	-	ARSA
Natsis et al. (12)	6	6	-	ARSA
Baker et al. (13)	1	1	-	Intrathyroidal CCA
Obaid et al. (14)	1	1*	-	Normal anatomy
Sagayaraj et al. (15)	3	3	-	ARSA
Masuoka et al. (16)	1	-	1	Right-sided aortic arch + Aberrant left SCA
Niu et al. (18)	26	26	-	ARSA
Tateda et al. (19)	1	1	-	Normal anatomy
Henry et al. (20)	33	31	2	ARSA (right non-RLN), Right aortic arch + situs inversus (left non-RLN)
Marchesi et al. (21)	7	7	-	ARSA
Patron et al. (22)	1	1	-	ARSA
Iorgulescu et al. (23)	1	1	-	ARSA
Total	104	101 (97.1%)	3 (2.9%)	Right non-RLN:ARSA (97%, n=98); Normal anatomy (1.9%, n=2); Intrathyroidal CCA (0.9%, n=1); Left non-RLN: Right aortic arch (100%, n=3)

*List of abbreviations: non-RLN= right non-recurrent laryngeal nerve; ARSA= aberrant right subclavian artery; CCA= common carotid artery; SCA= subclavian artery

vascular variants, vascular variations and aberrant right subclavian artery were used. No restrictions were taken regarding the year the articles were published, owing to the rarity of the non-RLN. Cases of non-RLN were recorded and analyzed for concurrent vascular variants. In the event of confirmed coexisting vascular variations, cases were further grouped as right and left non-RLNs, and the incidence of specific vascular variants was calculated using Microsoft Excel version 2016 MSO (16.0.9330.2124) 32-Bit (Microsoft Corporation).

Results

From the literature search, 15 articles met the criteria to be included in our review. Extraction of data from these studies identified 104 cases of non-RLN in living and cadaveric specimens with confirmed concurrent vascular variations. Statistical analysis of the data (summary of the results shown in Table 1) revealed the following: 97.1% (n=101) cases regarded a right, while 2.3% (n=3) a left non-RLN. What is more, the majority of right non-RLN were accompanied with an ARSA in 97% of cases (n=98). One case of right non-RLN involved an intrathyroidal right common carotid artery (CCA) (0.9%), while in 2 cases, normal vascular anatomy was reported (1.9%). Furthermore, all left non-RLNs were associated with a right aortic arch, while two of them were also related with situs inversus (Figure 1).

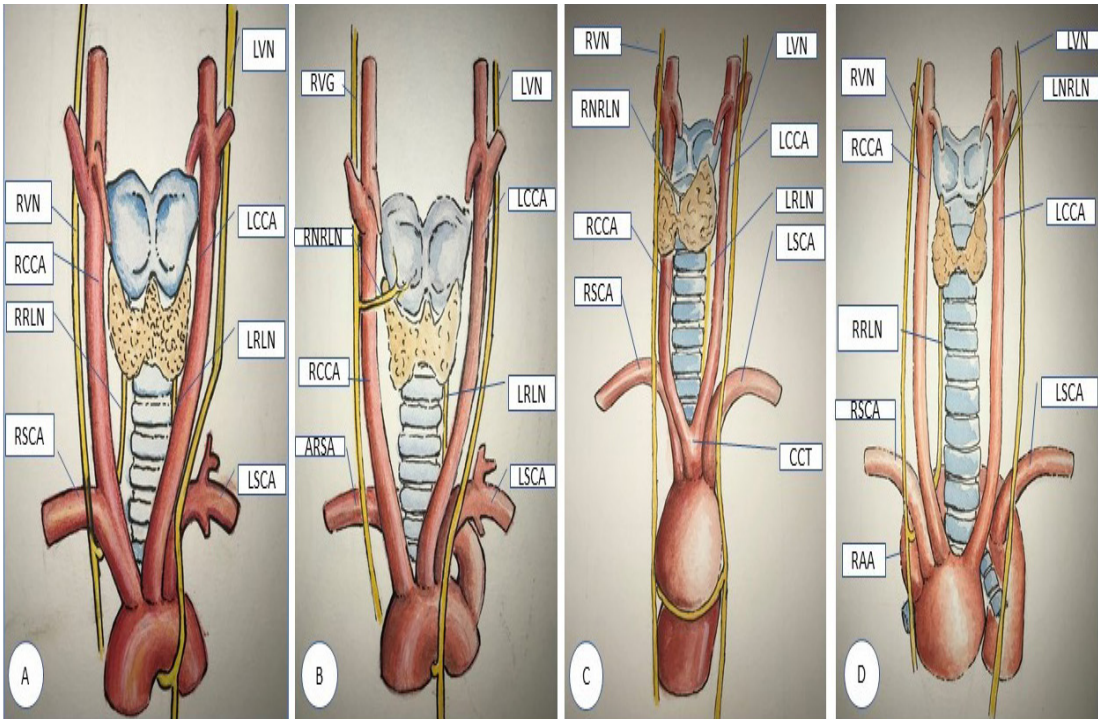

Figure 1. Schematic presentation of the recurrent laryngeal nerve (RLN) and vessel anatomy. A=Normal anatomy; B=Right non-RLN and ARSA; C=Right non-RLN and Intrathyroidal right common carotid artery [Adapted from Baker et al. (12)]; D=Left non-RLN and Right-sided aortic arch; RVN=right vagus nerve; LVN=Left vagus nerve; RRLN=Right recurrent laryngeal nerve; LRLN=Left recurrent laryngeal nerve; RCCA=Right common carotid artery; LCCA=Left common carotid artery; RSCA=Right subclavian artery; LSCA=Left subclavian artery; RNRLN=Right non recurrent laryngeal nerve; ARSA=Aberrant right subclavian artery; LNRLN=Left non recurrent laryngeal nerve; CCT=Common carotid trunk.

Discussion

Prevention of the dreaded complication of vocal cord paralysis from RLN damage during thyroid gland surgery requires an in-depth knowledge of the regional anatomy and its variants. Non-RLN is a rare variant, with a reported incidence of 0.3-0.8% on the right and 0.004% on the left side, and was first described in 1823 by G.W Stedman (3, 6). Data from studies evaluating the intraoperative use of neuromonitoring for prevention of RLN injury suggest a higher incidence of non-RLN,, as high as 6% (7). The risk of injury to the RLN is 1-2%, while in contrast the risk of injury to a non-RLN skyrockets to 12.9%, with the first report of such an injury in 1932 given by Pemberton (4, 5).

A brief review of thyroid and regional vasculature embryology may help elucidate the development of such anatomic variations. The arteries of the head and neck derive from six pairs of aortic arches, formed by the fifth gestational week. Each vessel follows a course along the axis of the pharyngeal arches and is accompanied by a cranial nerve. The third aortic arch forms the common and part of the internal carotid artery, while the fourth arch forms the aortic arch to the left and the proximal part of the subclavian artery to the right. The RLN, a branch of the vagus nerve (cranial nerve X), derives from the sixth pharyngeal arch and accompanies the sixth aortic arch. Because the right sixth aortic arch degenerates during fetal development, the right RLN is translocated superiorly, coursing around the right subclavian vein. In contrast, the left sixth aortic arch remains, hence the left RLN pivots around the ductus arteriosus, which in the neonate forms the ligamentum arteriosus of the aortic arch (8). From these data, we can extrapolate possible mechanisms responsible for the presence of a non-RLN. Anomalous regression of the distal dorsal aorta leads to the aberrant origin of the right subclavian artery from the aortic arch. As a result, the right RLN fails to loop around the right subclavian artery and becomes a right non-RLN. To the left, for a left non-RLN to occur, concurrent regression of the fourth and sixth aortic arches is required.

Observation of the course of the non-RLN allows its classification into two types: Type I and II (9,10). Type I non-RLN arises directly from the cervical vagus and travels along the superior thyroid pedicle, while type II travels along the inferior thyroid artery. Hong KH et al. proposed an alternative, more detailed classification based on their observations on 15 patients with right non-RLN. They classify them into four categories: descending, vertical, ascending and V-shaped, with an incidence of 33%, 27%, 20% and 20% accordingly. This group of patients consisted of 13 females and two males who were found to have a retroesophageal origin of the subclavian artery. The authors also noted a variable location of the inferior thyroid artery but could not compare its relationship to the non-RLN (11).

Identifying a non-RLN is almost always associated with variants of the great vessels. The most common vascular variant associated with a non-RLN is the ARSA, arising from the aortic arch, following a retroesophageal course. This subclavian artery variant, also known as arteria lusoria, may present with dysphagia in 5% of cases. A study of 237 Greek cadavers by Natsis et al. demonstrated six cases of ARSA (2.2%). In 2 cases the ARSA was also accompanied by a common trunk of the left and right common carotid arteries. A female predominance was noted, with a 2:1 ratio. All ARSAs were accompanied with a right non-RLN (12). In the study by Toniato et al. 31 cases of a right non-RLN were reported in a series of 6000 patients who underwent surgery for thyroid disease. However, not all reported cases were included in our review because only 5 of them had a confirmed concurrent vascular variant (4).

In our review, there were cases where a right non-RLN was accompanied by extremely rare vascular anatomic variants. In a case report by Baker et al. an intrathyroidal right common carotid artery with a non-RLN was described in a 23-year-old patient. Although medial displacement of the common carotid artery has been observed in other studies, this report is the first to describe such an aberrant, intrathyroidal course of the carotid artery (13). In contrast, Obaid et al. identified the extremely rare coexistence of a right non-RLN and a right RLN without any associated vascular variant, during a combined parathyroidectomy and thyroidectomy (14). Sagayaraj et al. propose a medially placed vagus in relation to the common carotid artery as an operative marker of a non-RLN. Their conclusions were based on the intraoperative findings of three patients, who were shown postoperatively to have aberrant subclavian artery anatomy (15).

The left non-RLN comprises an extremely rare variant, as has already been stated. When present, it is usually associated with situs inversus. Masuoka et al. attempted to clarify the etiology of left non-RLN. Their initial hypothesis, that the coexistence of a right-sided aortic arch and an aberrant left subclavian artery indicates a left non-RLN, was invalidated from their observations of 4 patients. From that sample, only one patient validated the initial hypothesis, thus demonstrating a left non-RLN. By examining the results of Magnetic Resonance Angiography of the aforementioned patients, the researchers recognized the presence of a descending aorta diverticulum at the point of origin of the aberrant subclavian artery in the three patients with RLNs. In contrast, the diverticulum was absent in the patient with the left non-RLN and the descending aorta traveled straight down after the aortic arch. The authors concluded that the combination of a right-sided aortic arch, an aberrant left subclavian artery and the absence of an aortic diverticulum suggests a left non-RLN (16).

Prevention of injury to a non-RLN is of utmost importance. As has been demonstrated in our review, non-RLN is almost always associated with vascular variations. Therefore, efforts should be focused on the preoperative identification of such variants. A preoperative neck and chest CT or MRI scan can accurately demonstrate vessel anatomy. However, this practice raises the question of increased healthcare costs for the identification of a rare anatomic variation and high radiation dosage in the case of a CT scan. Considering this, our proposal is the neck CT or MRI scan performed for thyroid cancer or large goiters. Another less expensive and more readily available approach is the use of ultrasound. This also has the advantage of no radiation. On the other hand, it is operator dependent.

Intraoperatively, careful dissection is mandatory. When the surgeon fails to identify the recurrent inferior laryngeal nerve in its predicted place, he should consider the presence of a non-RLN. Intraoperative neuromonitoring helps the surgeon to understand the anatomy and function of the nerve structures better and it does not add significantly to the cost of the operation. Donatini et al. identified and preserved a right non-RLN in 11 cases, in a series of 402 thyroidectomies utilizing constant neuromonitoring. In the absence of neuromonitoring devices, the surgeon should dissect the vagus nerve and recognize the non-RLN at its origin from the cervical vagus, and follow its course to the cricothyroid muscle (7). Another approach is to dissect the suspected non-RLN in a retrograde manner, starting from its insertion into the cricothyroid muscle, keeping track of it in the neck.

The results of our study are in accordance with the findings of Henry et al. In their meta-analysis, the prevalence of an ARSA

coexisting with a right non-RLN was 89.3%, after reviewing 136 cases of right non-RLN. Furthermore, 2 cases of left non-RLNs were associated with situs inversus (17).

Even though the prevalence of non-RLN is estimated to range between 0.3-0.8% and 0.004% for right and left non-RLN respectively, cadaveric studies suggest a higher prevalence of 2.2% (3, 11). In addition, intraoperative neuromonitoring may further increase those numbers up to 6% (7). Those discrepancies in prevalence suggest that even though non-RLN is a rare anatomic entity, it is rarely reported or there is a failure to recognize it. Therefore, the importance of proper and accurate preoperative imaging combined with intraoperative neuromonitoring is emphasized in increasing the detection rate of non-RLN. Furthermore, all cases of non- RLN and other rare anatomic variants need to be reported in nationwide registries.

Conclusions

Recurrent laryngeal nerve palsy is one of the complications of thyroid surgery with a reported incidence of 1-2%. A non-RLN may be a rare anatomic variant with an incident reaching 0.3-2.2%, but prediction and recognition of its presence can save the surgeon and the patient from potential injury to it, resulting in devastating results. This review aims to highlight the high degree of caution the surgeon must maintain when faced with anatomic variants of the great vessels, regarding the presence of a non-RLN. As shown in our review, the ARSA is almost always accompanied by a right non-RLN, with an incidence of 97%. In the case of the extremely rare left non-RLN, situs inversus or a right aortic arch is observed. Preoperative identification of vascular variants suggests the presence of a non- recurrent laryngeal nerve. Further research is needed to recognize specific anatomical landmarks for its preoperative and intraoperative identification. The role of preoperative imaging, such as ultrasound, computerized tomography and magnetic resonance imaging, needs to be thoroughly evaluated. Neck ultrasound is a readily available and inexpensive method to detect vascular variations related to a non-RLN as an adjunct to thyroid ultrasound. However, the results are operator dependent. CT and MRI scans may give more detailed anatomical information but have the disadvantage of higher cost as well as a high dose of radiation in the case of a CT scan. Careful dissection with the aim of identifying the RLN is imperative. Constant intraoperative neuro-monitoring helps the surgeon identify and preserve the recurrent laryngeal nerve, and is associated with a higher identification rate of non-RLN at nearly 6%. Although rare, the non-RLN in the hands of an unprepared surgeon may become their surgical Waterloo. It is a surgeon's responsibility to recognize the presence and preserve the anatomic integrity of such a rare neural entity. Further research is warranted for the identification of specific anatomic landmarks pointing to a non-RLN and the adoption of efficient preoperative and intraoperative methods to identify this elusive anatomic entity.

What is already known on this topic

Non-RLN is a rare anatomic variant of the inferior laryngeal nerve. Although rare, knowledge of its presence is fundamental in order to avoid injury to it during thyroid surgery.

What this study adds

This study aims to highlight the relationship between non-RLN and vascular variants. When a patient is shown to have anatomic variants of the great vessels, the surgeon should be aware of the presence of a non-RLN and opt to preserve it. As shown in our study, an ARSA is associated with a right non-RLN in 97% of cases, while the extremely rare left non-RLN is usually associated with a right aortic arch.

Author's contributions: Conception and design: EB; Acquisition, analysis and interpretation of data: EB, IM, TD and GT; Drafting the article: EB and IM; Figure design: EB; Revising it critically for important intellectual content: EB, PS and DF; Approved final version of the manuscript: EB, IM, TD, GT, PS and DF.

Conflict of interest: The authors declare that they have no conflict of interest.

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Case Report
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Relapsing Tumefactive Demyelination: A Case Report

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Objective. We present a case of relapsing tumefactive demyelination in a young female patient, that posed a real diagnostic challenge, with a heterogeneous clinical picture, atypical for multiple sclerosis (MS) presentation, and neuroradiological manifestations with a high suspicion of neoplastic diseases. **Case Report**. An 18-year old female patient presented to our Neurosurgical Out-patients' Clinic with symptoms atypical for multiple sclerosis, unremarkable neurological deficit, one tumefactive lesion on MRI, followed by relapse and another two lesions within a period of six months. We decided to perform biopsy of the tumefactive lesion with compressive effect. Serological and clinical data were negative for MS, and the patient did not respond well to corticosteroid therapy. Fresh frozen tumor tissue aroused a strong suspicion of gemistocytic astrocytoma, so total resection was done, but the definitive pathohistological examination confirmed tumefactive demyelination. **Conclusion**. For clinicians, it is important to consider demyelinating disease in the differential diagnosis of a tumor-like lesion of the central nervous system, in order to avoid invasive and potentially harmful diagnostic procedures, especially in younger patients.

Introduction

Tumefactive demyelination is rare atypical inflammatory demyelinating syndrome, predominantly affecting young people, with an estimated prevalence of 1-3/1000 cases and an annual incidence of 0.3/100,000 (1). Magnetic resonance imaging (MRI) usually specifies demyelinating brain lesions 2 cm or larger in size, often with perilesional edema, mass effect and incomplete ring enhancement, unlike the typical small, homogenous, well demarcated plaques of multiple sclerosis (2).

The clinical presentation may vary from a benign monophasic form to an acute fulminant variant with lethal outcome, presenting with atypical multiple sclerosis symptoms such as: headache, cognitive abnormalities, mental confusion, aphasia, apraxia and/or seizures (3). Literature data most commonly report sensory deficit, motor weakness and cognitive impairment as the initial clinical presentation (4).

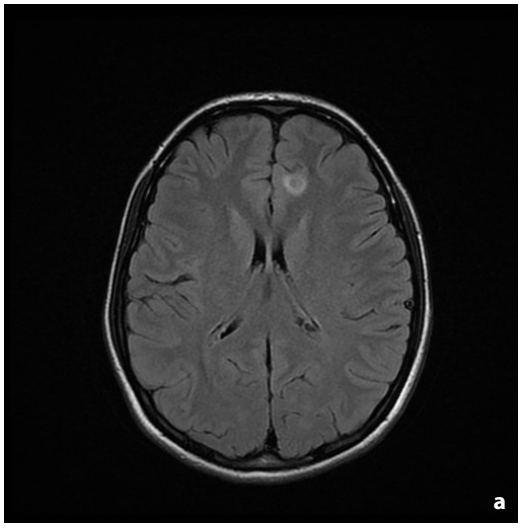
Tumefactive demyelination itself often represents a diagnostic challenge to neurologists and radiologists, with a misleading clinical picture, resulting in up to 10% incorrect diagnoses, mostly diagnosis of neoplastic diseases, infective diseases, other inflammatory disorders (5) or even a stroke (6). Therefore, histopathological confirma-

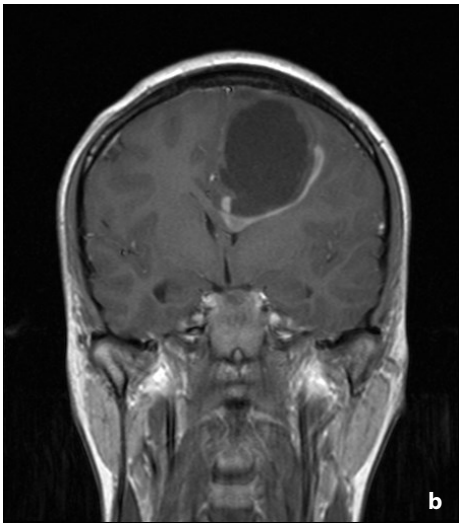
tion is sometimes unavoidable for confirmation of the diagnosis.

We present a case of relapsing tumefactive demyelination in a young female patient, that posed a real diagnostic challenge, with a heterogeneous clinical picture, atypical for multiple sclerosis presentation, and neuroradiological manifestations with a high suspicion of neoplastic diseases.

Case Report

An 18-year old female Bosnian patient presented to our Neurosurgical Outpatients' Clinic in November 2014 with a 2 month history of transient visual loss and headache. A head MRI (Figure 1a) showed a solitary lesion up to 11 mm in diameter in the right frontoparietal subcortical white matter, while the initial MRI scans of the brain and cervical spine, done two months earlier, were without pathological changes. At that time, she was admitted to the neurological ward, and she felt numbness followed by progressive weakness of her lower extremities. CSF examination showed elevated protein level (3.22 g/l, IgG index 63.7), EMNG findings showed severe generalized sensorimotor polyneuropathy of the axonal-demyelinating type, and she was diagnosed with acute polyradiculoneuritis and successfully treated with plasma exchange (5 cycles).





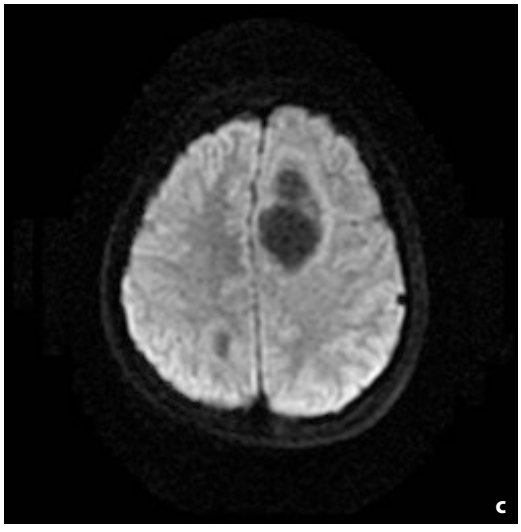
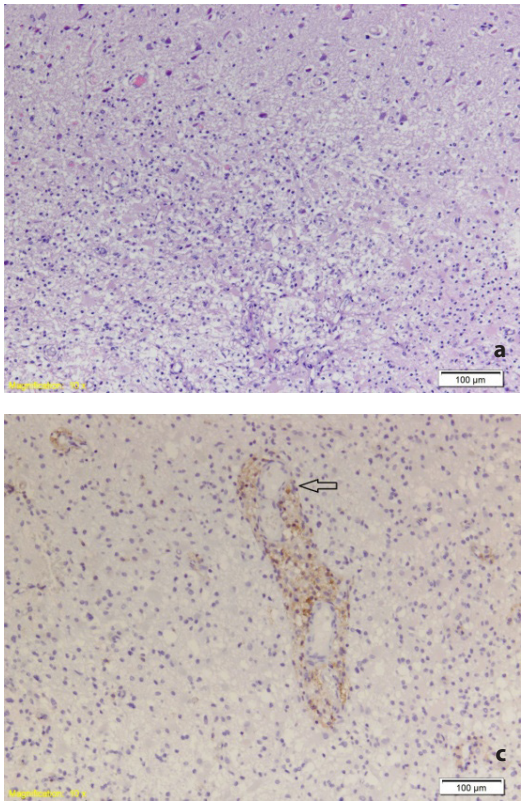


Figure 1. a) Brain MRI performed on 10th November 2014, Axial T2 showing a solitary lesion without contrast enhancement. (Flair Axial). b) Preoperative brain MRI showing enlargement of the lesion to more than 7 cm in AP diameter and its compressive effect on surrounding structures. c) The emergence of new zones of changed signal intensity in the left frontoparietal region immediately next to the extensive zone of signal intensity changes, with perifocal edema in the left frontoparietal supraventricular region, and right parietal parasagital region. There is an impression of discrete reduction in the peripheral edema extension, but also of the same extension of the tumefactive lesion to the left (DWI).

A follow-up MRI, done six months later, revealed enlargement of the lesion previously described to 57mm x 32mm, with post-contrast ring enhancement (Figure 1b). MRI of the cervical spine was normal. Serological findings were all negative. The IgG index was high and oligoclonal bands were negative. HIV status was not checked. The patient was tested for aquaporin 4 antibodies and they were negative. She was treated with pulse corticosteroid therapy, but 2 weeks after, follow-up MRI (Figure 1c) showed enlargement of the lesion previously described, it was now 70 mm in AP diameter with compressive effect and medio-sagittal shift, and there were two new lesions, located in the left frontoparietal and right parietal white matter, sized 10 mm in diameter.

We decided to perform a surgical procedure to achieve decompression and to take tissue for pathohistological diagnosis. The neurosurgeon (IO) performed frontoparietal craniotomy. Intraoperatively, we found a tumor-like formation with solid edges, a central cyst with a white reticular wall, partially well limited from the brain tissue, partially infiltrating the surrounding brain tissue. Fresh frozen tumor tissue biopsy showed a strong suspicion of gemistocytic astrocytoma, and gross total resection of the lesion was done, but the definitive pathohistological examination confirmed the diagnosis of demyelination (Figure 2a-c).

In September 2015 the patient was admitted again to the Neurological Department due to neurological deterioration (EDSS 6). A new MRI showed the progression of the changes previously described and the emergence of new ones (Figure 3a). After pulse corticosteroid therapy was administrated, there was complete withdrawal of the neurological deficit. She started interferon therapy, and the follow-up MRI (October 2016) showed almost complete resolution of



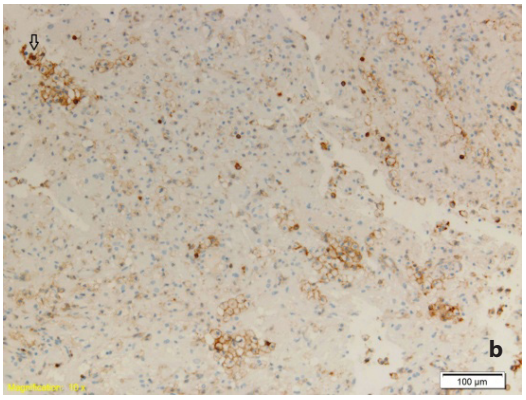


Figure 2. a) Hypercellular lesions with confluent demyelination, abundant foamy macrophages containing myelin debris, reactive astrogliosis, 'relative' axonal preservation and variable perivascular and parenchymal lymphocytic inflammation. JC virus chromogenic in situ hybridisation was negative. b) The results obtained from immunohistochemical analysis were used to determine demyelinating changes, central necrosis, macrophage infiltration, angiogenesis and perivascular lymphocytic cuffing (CD 4). c) Immunohistochemical staining for CD 163 (magnification x10). Perivascular cuffing inflammatory cells and macrophages contain myelin debris within their cytoplasm.

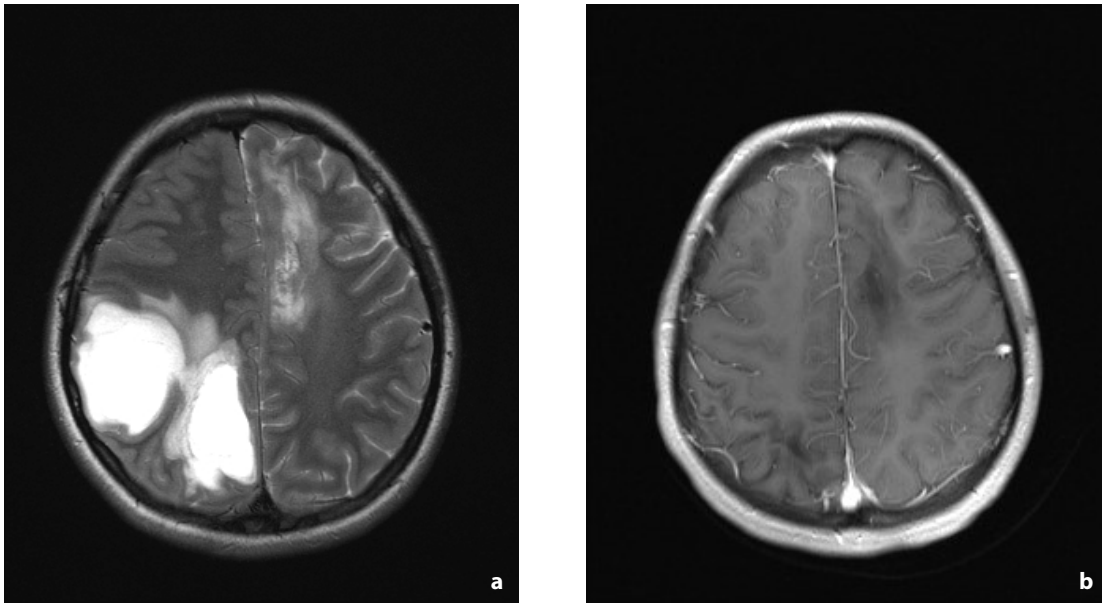


Figure 3. a) Brain MRI showing further evolution of the tumefactive lesions (T2 axial). b) Brain MRI showing resolution of multiple lesions (T2 axial).

the lesions previously described (Figure 3b). She has been stable since then and no further relapse has been reported.

Discussion

Tumefactive demyelination may occur as solitary or multiple intracranial masses larger than 2.0 cm in diameter, presenting as a distinct demyelinating disease or sustained in other demyelinating process, such as multiple sclerosis, acute disseminated encephalomyelitis, or neuromyelitis optica spectrum disorders (7). Gender predilection has not been well determined, although the incidence has been suggested to be higher in males (8). However, according to the literature review by Lucchinetti et al. (9), most of the reported patients were females with an average age of 37, and the typical localization of tumefactive lesions was in the frontal or parietal lobes, as in our case. In terms of location, lesions occur most frequently in the frontal or parietal lobes, with variable effects on the gray matter, and often adjacent spread into the corpus callosum (10).

Tumefactive demyelination can pose real diagnostic difficulties in cases of a high suspicion of neoplastic disease. Large tumefactive lesions may be indistinguishable from neoplasms on MRI, as both can lead to mass effect/edema, a hypo-intense rim on T2 weighted scans, venular enhancement, and a variable degree of ring-enhancement (3). DWI and ADC sequences might be crucial for correct diagnosis, as the changes on diffusion-weighted imaging evolve rapidly, unlike stable tumorous or abscess lesions with no apparent diffusion coefficient restriction (7). Additionally, the use of FDG-PET scanning can be useful, as the degree of hypermetabolism of acute demyelinating lesions appears to be smaller compared to neoplastic lesions, but in the case of the unavailability of FDG-PET, a combination of non-contrast brain CT in addition to MRI can improve the diagnostic accuracy of tumefactive demyelination (7). The CSF may be normal or have high levels of immunoglobulin G (IgG) index and oligoclonal bands. (11) Abnormal visual (VEPs) and somatosensory evoked

potentials may present in 33-60% of cases with tumefactive demyelination (9).

In a few cases biopsy is unavoidable, although frozen sections rarely suggest a diagnosis of a demyelinating disease. The target of biopsy should always be the wall of the tumefactive demyelinating lesion, unlike in tumors, where the central core of the lesion is more important (12). The histological features may mimic a tumor, including hypercellularity, astrocyte pleomorphism, variable nuclear atypia, a rare mitotic figure, and occasionally necrosis or cystic changes. The presence of Creuztfeldt-Peters cells may be mistaken for mitotic glial cells. However, the presence of large numbers of infiltrating macrophages in the setting of myelin loss and relative axonal preservation should confirm the diagnosis of an inflammatory demyelinating disease (13). With the development of neuroimaging, biopsy can be avoided; it is used mostly in patient without a pre-existing diagnosis of MS, with indecisive imaging, and negative oligoclonal bands, as it was in our case report.

Our patient was previously diagnosed with acute polyradiculoneuritis and successfully treated with plasma exchange, with complete withdrawal of neurological deficit. Although both acute polyradiculoneuritis and demyelinating diseases are of immune-mediated origin, their co-existence is very rare, which makes the diagnostic dilemma even greater. Two studies have reported that the prevalence of Guillain-Barre syndrome (GBS) was higher in the MS population than in a control group (14, 15), however, only one study had statistically significant findings (15). The diagnosis of GBS, at our center, was based on the well-established diagnostic criteria and the subsequent development of tumefactive demyelination may suggest a kinship between these two entities.

Literature data regarding the course of tumefactive demyelination and prognoses are insufficient. Acute treatment includes intravenous methylprednisolone and/or plasma exchange, rituximab and natalizumab, followed by immunomodulatory agents (16). Some patients have a monophasic self-limited course, but recurrence of the disease with new tumefactive lesions is not unusual (17). According to Lucchineti et al. (9), the median time interval was 4.8 years until the second relapse. The neuroanatomical sites of recurrent demyelinating lesions in the present case were the contralateral frontoparietal and the right parietal white matter. Khan et al. (17) reported a case of a 34 year old male with contralateral recurrence of tumefactive lesions, while some authors suggest that new tumefactive lesions occur most commonly at the site of the index lesion (10).

Due to the limited data available in the literature, the prognostic significance of recurrent tumefactive lesions remains undetermined. Many patients demonstrate a monophasic self-limited course, while others experience relapse despite identical imaging features (10). It has not been established whether the neuroanatomical mechanism of the recurrence represents a repercussion of different underlying pathogenesis, and whether it impacts patient's prognosis (9). It has been reported that lesions larger than 5cm were associated with greater disability at follow-up (9). On the other hand, Wattamwar and coauthors described the significant long-term functional recovery of 14 patients from their large demyelinating lesions (18). Some studies report clinical and radiological improvement of tumefactive demyelinating lesions, with no future development of typical recurrent relapsing MS (16). In contrast, a few authors report the development of clinically definitive MS (9).

Conclusion

For clinicians, it is important to consider demyelinating disease in the differential diagnosis of a tumor-like lesion of the central nervous system, in order to avoid invasive and potentially harmful diagnostic proce-

dures, especially in younger patients with atypical clinical or imaging features.

What is already known in this topic

Tumefactive demyelination is a rare entity among the demyelinating group of diseases as a leading cause of progressive neurological deficit in young adults. Although there are no pathognomonic signs to indicate tumefactive demyelination, advances in neuroimaging are often sufficient in recognition of this peculiar manifestation of inflammatory demyelinating diseases.

What this study adds

This study emphasis that many cases of tumefactive demyelination can be monitored simply, clinically and radiologically. However, in the case of atypical clinical or imaging features, surgical biopsy should not be delayed, in order to avoid diagnostic speculation, and to implement appropriate therapy.

Authors' contributions: Conception and design: IO and DL; Acquisition, analysis and interpretation of data: ADŽ, NM, MN, NB and DL; Drafting the article: ADŽ, NM and DL; Revising it critically for important intellectual content: IO and ES; Approved final version of the manuscript: IO and ES.

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Case Report

Case Report and Mini Review
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A Rare Branching Pattern of a Middle Mesenteric Artery Supplying the Head of the Pancreas and the Transverse Colon

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Key words: Inferior Pancreaticoduodenal Artery ▪ Middle Colic Artery ▪ Abdominal Aorta ▪ Superior Mesenteric Artery.

Objective. The appearance of a middle mesenteric artery is a rare branching variation, with an incidence lower than 0.1%. Our case reports such an anatomical artery pattern which was discovered in a male Caucasian cadaver during routine educational dissection. This alternation is seldom encountered and may trouble diagnostic and surgical interventions. **Case Report.** The case of a Middle Mesenteric Artery is described, as a vessel originating from the Abdominal Aorta 3.3 cm below the origin of the Superior Mesenteric and 3.8 cm above the origin of the Inferior Mesenteric Artery. The middle mesenteric artery, directed upwards, gives two branches for supplying blood to the head of the pancreas. We first mention the thinner branch, corresponding to the posterior one of the inferior pancreaticoduodenal artery, and second the thicker branch corresponding to the anterior branch of the Inferior Pancreaticoduodenal Artery. The main artery continues its course between the two sheets of the mesocolon to supply the transverse colon, thus substituting the normal colic artery. **Conclusion.** The occurrence of a Middle Mesenteric Artery constitutes a very rare anatomic variation. We present, to our knowledge, the first case described where the Middle Mesenteric Artery provides blood to the pancreas.

Introduction

The Middle Colic Artery (MCA) normally emerges from the Superior Mesenteric Artery, just inferior to the uncinate process of the pancreas, and anteriorly to the third part of the duodenum. The artery may branch either separately or as a common trunk with the Right Colic Artery (1-2). The Middle Mesenteric Artery (MMA) is defined as a vessel which originates directly from the abdominal aorta. In these cases, the vessel arises between the Superior (SMA) and the Inferior Mesenteric Arteries (IMA) and mainly supplies the transverse, and sometimes the descending or ascending colon (3-6). The MMA is considered to be a very rare variation, with an incidence lower than 0.1% (5).

The Inferior Pancreaticoduodenal Artery (IPA) arises more commonly from the SMA (posterior, left and right lateral or anterior side) and supplies the pancreatic head (1, 7). This artery may present with various anatomic points of emergence. Thus, it might emerge a) from a common trunk with the first jejunal branch (20-64.7% of cases), b) from a common trunk with the dorsal pancreatic artery (6-8% of cases), c) from a common trunk with the second jejunal artery (2% of cases), d) from the right acces-

sory hepatic artery (the incidence has not been estimated), e) more rarely from a common trunk with the first two or three jejunal arteries, f) from the transverse pancreatic artery, g) from the MCA and h) from an accessory MCA (7, 8).

Case Report

We report an anatomical variation of an MMA which was discovered in a male Caucasian cadaver (deceased at the age of 66), during routine educational dissection at our Anatomy Department. The cadaver derived from a body donation with informed consent, written and signed (with signature authentication) by the donor himself. For our review of the literature, we conducted a thorough search in the PubMed database, using the words "Middle Mesenteric Artery" and "Inferior Pancreaticoduodenal Artery" as key terms. In the present case report, we describe a MMA, which provides two branches to the head of the pancreas before its termination as an MCA.

The branches of the abdominal aorta were carefully dissected. The stomach and the pancreas were also dissected and mobilized to expose the celiac trunk, the SMA and their branches. The Inferior Pancreaticoduodenal Artery and the MCA were not detected as one of the branches of the Superior Mesenteric Artery, as expected. Then the transverse colon and mesocolon were retracted in order to reveal the IMA and its branches. An MMA was observed originating from the Abdominal Aorta between the Superior and Inferior Mesenteric Arteries, 3.3 cm distal to the SMA and 3.8 cm proximal to the inferior one. This artery supplied

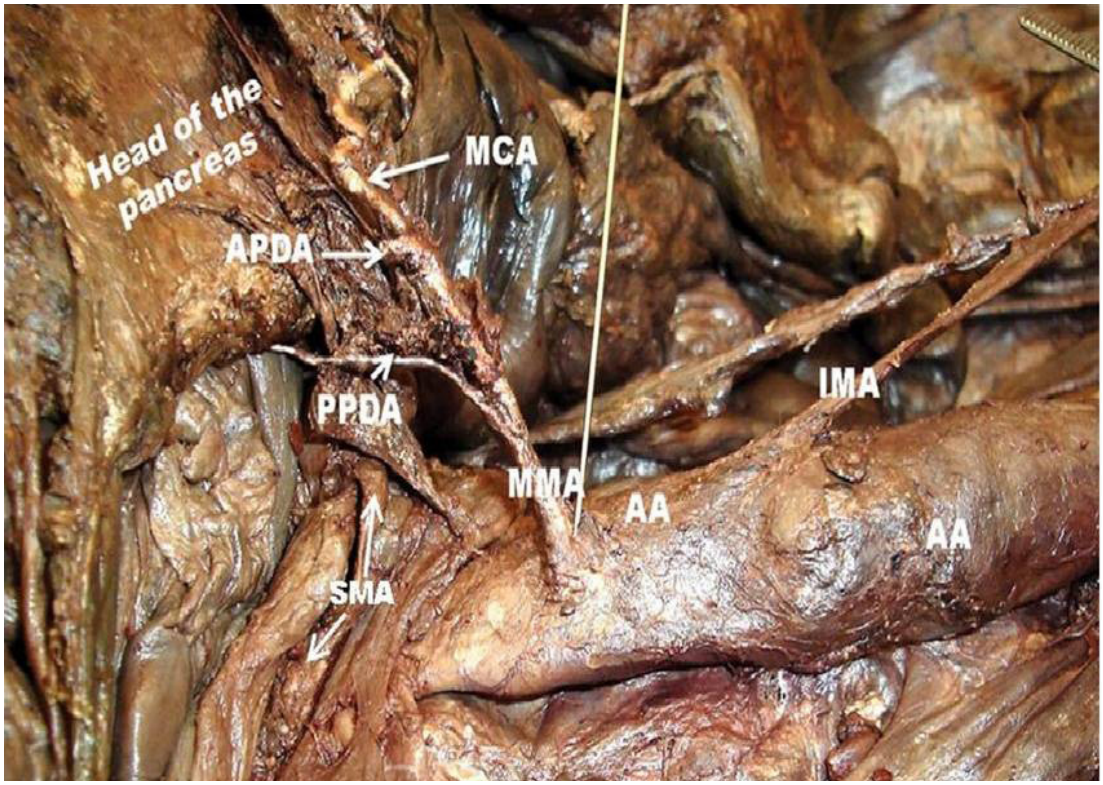

Figure 1. A rarely encountered Middle Mesenteric Artery. MMA=The Middle Mesenteric Artery; AA=Abdominal Aorta; IMA=Inferior Mesenteric Artery; APDA=Anterior Pancreaticoduodenal Artery; PPDA=Posterior Pancreaticoduodenal Artery; SMA=Superior Mesenteric Artery; MCA=Middle Colic Artery; IVC=Inferior Vena Cava.

the transverse colon as well as the head of the pancreas, as follows: It produced a rather thin (proximal) branch to the posterior surface of the head of the pancreas at first (after a course of 1.8 cm), then it coursed in close contact with the pancreatic head, supplying a second (rather thick) branch (distal), 2.6 cm after the proximal one (Figure 1). The first branch, after a short course, was anastomosed with branches of the Superior Pancreaticoduodenal Artery, while the second one entered the head of the pancreas from its anterior surface. Thereafter, it continued its route in the transverse mesocolon to reach the transverse colon, as the MCA does (Figure 1). The two branches thus detected were considered to substitute the anterior (the thick one) and posterior (the thin one) branches of the Inferior Pancreaticoduodenal Artery (Figure 1). The usual Colic and Pancreaticoduodenal Branches of the Superior Mesenteric Artery were absent, whereas it gave rise to the usual ileocolic, jejunal and ileal branches. The rest of the arterial pattern of the gut was normal, as anatomically expected.

Discussion

The mere existence of an unpaired arterial branch between the Superior and Inferior Mesenteric Arteries is occasionally reported as a case report and should therefore be considered as rare. This branch, whenever it exists, may be named either "Middle Mesenteric", from which the MCA emerges in most cases, or "Middle Colic" originating from the aorta (4). We prefer and propose the term "Middle Mesenteric", as more succinct: it indicates both the position of the artery and the rareness of its existence. Moreover, the term is more collective, as it encompasses all possible further variations. For example, this artery does not always provide a branch to the transverse colon, i.e. a Middle Colic Artery.

Nine such cases of an MMA were found in the literature (Table 1). According to the available data, the first report of such a variation was made by Benton and Cotter in 1963. They described an "anomalous mesenteric artery" in a cadaver, which emerged from the aorta between the superior and inferior mesenteric arteries. The artery was named as "a duplication of the Inferior Mesenteric Artery". In this case the middle colic branch of the SMA did not exist (9). In 1987, Lawdahl and Keller reported an angiogram, in which a similar artery was revealed and also had a similar course, supplying the splenic flexure of the colon. This time the middle colic branch of the SMA was present. The authors called it a "Middle Mesenteric Artery" for the first time and may claim its denomination (10). Yoshida et al. in 1993 described another case of an MMA, also revealed during an angiography. This one had two branches, one right branch anastomosed (within the mesentery) with the right colic artery, and one left branch that supplied the left part of the transverse colon, the splenic flexure and the proximal descending colon. Only its final and marginal branch communicated with the corresponding branch which derived from the left colic artery (from the inferior mesenteric) (3). Higashi and Hirai reported a cadaveric finding in 1998, in which "the second Superior Mesenteric Artery" (as they called it, although its origin was only 2.3 cm above that of the inferior mesenteric artery) had five small intestinal arteries supplying the inferior portion of the small bowel, and five large intestinal arteries supplying the cecum, the ascending colon, the transverse colon and the superior portion of the descending colon. The authors argued that this arterial pattern was the cause of a malformation in the nonrotation of the intestinal tracts, also observed in that cadaver (11). Another case of colon malrotation was presented by Kawai et al. in 2006. They also observed an MMA supplying the ascending and the transverse

colon, anastomosed with the SMA and IMA respectively, through the marginal arteries (12). Dirrigl et al. operated on a patient in 2009 with an inflammatory infrarenal aortic aneurysm and discovered a MMA replacing to a large extent both the SMA and a hypoplastic IMA, since it supplied the distal jejunum, the ileum and the colon (ascending, transverse and descending) (13). Kachlik et al. in 2009 described a case of an MMA supplying the left colic flexure and continuing as a left colic artery (4). Naito et al. in 2011 reported a very rare case where the MMA gave a left testicular artery and then supplied the transverse colon (5). Finally, Milnerowicz et al. in 2012 described a cadaveric specimen, in which they also performed arteriography with a MMA totally and exclusively supplying the transverse colon, behaving thus as an aberrant middle colic artery (6).

Our case describes a MMA, which gave off two branches to the head of the pancreas (anterior and posterior branches of the Inferior Pancreaticoduodenal Artery) and continues its course towards the transverse colon as a middle colic artery. Having in mind the arteries described above, we note that no such case seems to have been reported in the literature. The total number of MMAs revealed either through anatomical dissection or through arteriograms, or even during operations, is extremely small, and a reliable estimation of its frequency is not feasible. Milnerowicz et al. evaluated it as less than 0.1%. Moreover, no credible association of this rare variation with sex or race may be established (6).

The unpaired visceral branches derive from the ventral splanchnic arteries which develop initially as paired vessels (1). In a later stage of the embryonic development these arteries regress and anastomose usually to three main trunks, the Celiac, Superior Mesenteric and Inferior Mesenteric Arteries (1, 6). The branches of these arteries develop afterwards, as the viscera descend into the abdomen. The MMA, according to the literature, seems to be an example of additional unpaired artery supplying the midgut and the hindgut (4, 6). In our case, the MMA replaces the MCA and gives also rise to the "absent" Inferior Pancreaticoduodenal Artery, which normally supplies the head of the pancreas and usually emerges from the SMA below the MCA. We assume that during embryonic development this persistent additional branch replaced both the two first branches of SMA, supplying not only the gut but the head of the pancreas also. Milnerowicz et al. as well as Kachlik et al. proceeded to a description of any clinical implications present. It was concluded that routine morphological examination of the arterial pattern of the celiac aorta by either convention-

Table 1. Cases of a Middle Mesenteric Artery

MMA* reference	MMA Description
Benton and Cotter in 1963	Emerge from the aorta...a duplication of the inferior mesenteric artery
Lawdahl and Keller in 1987	Emerge from the aorta a middle mesenteric artery
Yoshida et al. in 1993	A MMA with two branches
Higashi and Hirai reported in 1998	The second superior mesenteric artery
Kawai et al. in 2006	A MMA anastomosed with the SMA† and IMA‡
Dirrigl et al. in 2009	A MMA replacing to a large extent both the SMA and a hypoplastic IMA
Kachlik et al. in 2009	A MMA supplying the left colic flexure and continuing as a left colic artery
Naito et al. in 2011	The MMA gives a left testicular artery
Milnerowicz et al. in 2012	A MMA as an aberrant middle colic artery

*Middle mesenteric artery; †Superior mesenteric artery; ‡Inferior mesenteric artery.

al angiography, selective angiography, CT, or MDCT angiography, allows the identification of such a variation before scheduled, or emergency surgery so that any complication is avoided in the operating room, or during any other clinical interventions and examination (4, 6). Wadhwa and Barua, 2008, also concluded that a pre-operative selective arteriogram, or other available techniques are important to determine any anomalies in the arterial supply of the pancreas prior to performing selective pancreatic resections (14). Such a procedure would be ultimately useful in the case of a patient like ours with this rare variation.

Conclusions

In a cadaveric specimen we observed an unusual case of an MMA, originating from the abdominal aorta, with two branches which substituted the posterior and anterior branches of the Inferior Pancreaticoduodenal Artery. Our report is most possibly the first to describe this branching. As this kind of vessel is rarely encountered, our case may have a practical impact on diagnosis, or even upon the method and range of surgical treatment.

What is already known on this topic

The presence of an MMA is considered rare. However, this vessel, arising directly from the aorta, has a broad spectrum of branching variations.

What this study adds

Our case reports an MMA which gives two branches to the head of the pancreas before its termination as an MCA. This peculiar branching testifies the variety of anatomic possibilities of an MMA.

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Historical Article

Case Report
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Multiple Abnormalities in the Skull of a Prostitute. An Autopsy Report (1900)

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Key words: Criminal Anthropology ▪ Abele De Blasio ▪ Morphological Anomaly ▪ Autoptic Examination.

Objective. The study presents and comments on the publication of an autopsy report. **Case Report.** In 1900 De Blasio published an article entitled "Multiple abnormalities in a prostitute's skull" in the "Journal of Psychiatry, Criminal Anthropology and related sciences". In this work De Blasio related anomalies at the cranial level to the presence of mental pathologies. The skull belonged to a 24-year-old prostitute who died of syphilitic hepatitis. In his article, De Blasio described the life of the woman, after which he gave a macroscopic description of the skull. De Blasio believed that the subject's amoral behavior was caused by the anomalous shape of the subject's skull. **Conclusion.** From the study, it is evident that the school of criminal anthropology influenced De Blasio's autopsy medical practice, and it is interesting to note the interpretation of anthropologists of the time who tried to describe the link between physical and behavioral anomalies.

Introduction

In 1900, Abele De Blasio (1858-1945) (1) a physician and anthropologist affiliated to the Lombrosian School of Criminal Anthropology, published an article entitled "Multiple Anomalies in the skull of a prostitute" in the "Journal of Forensic Psychiatry, Criminal Anthropology and Related Sciences" (2). This is another example of the positivist pseudo-science inspired by social Darwinism, which linked abnormal behavioural traits to irregular anatomy.

We discuss a particular autopsy report by the positivistic school of Italian criminal anthropology.

Case Report

In this paper, De Blasio describes the skull of Carmela, a 24-year-old prostitute who died of syphilitic hepatitis. During the autoptic examination, De Blasio recorded an abnormality in the shape of the skull (Figure 1) which he believed was the cause of a nervous system pathology (3) and correlated it to amoral behaviour.

The girl was at the age of eleven when she left home and during her life was found guilty of theft and became smeared with human blood as a consequence of scratching her companion. She was then accused of being involved in a criminal offense and for

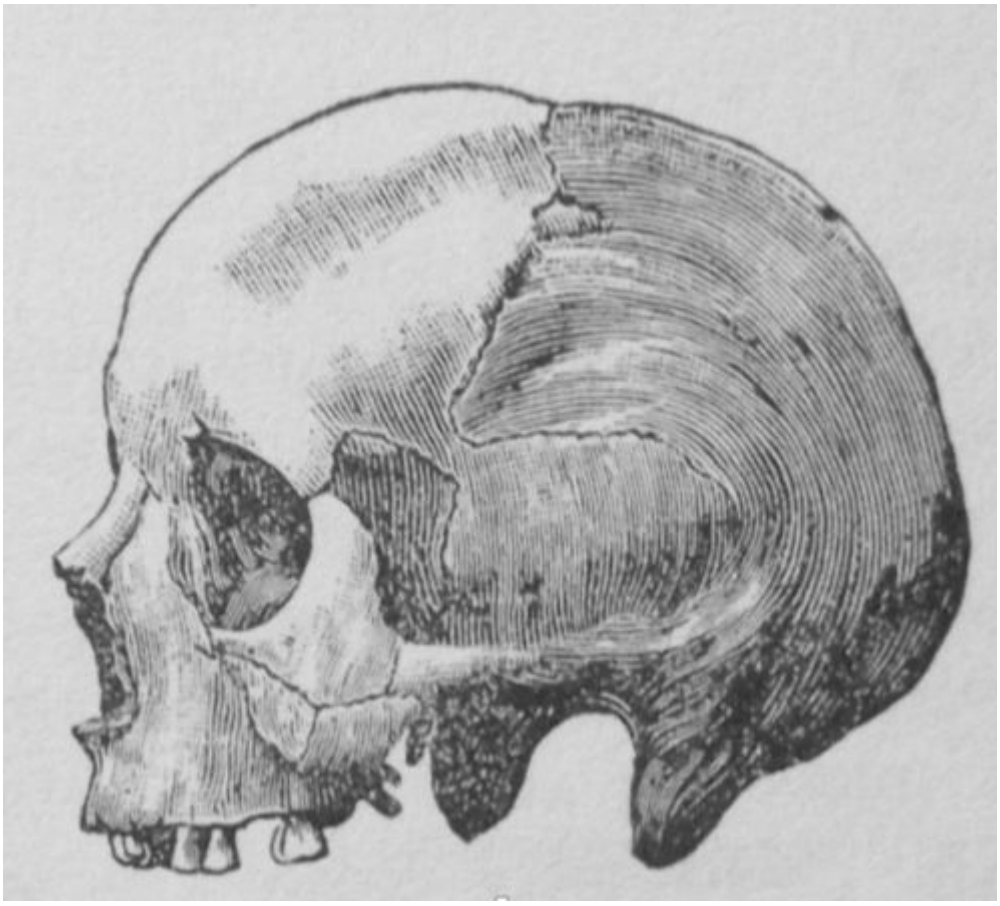

Figure 1. The drawing of the prostitute's skull shows the skeletal anomalies described by De Blasio in the article (2).

breaching regulations, and was placed under special police surveillance. The skull of the woman was described as follows: a narrow and high forehead, large orbital cavities, with thin upper edges, a high and narrow nose opening. The jawbones are divided in two and the upper edge of the upper jawbone resembles the shape of a horseshoe. An anomaly is noticeable in the skull when observed in a lateral plane. It is asymmetric with the obvious manifestation of latero-occipital plagiocephaly. In addition, the sagittal suture is wavy, while the other sutures are jagged. Another important observation made was evidence of a star shaped wormian along the right coronal suture, an extra isolated bone that can occur within a suture in the skull.

Moreover, the presence of accessory bones, in relation to the right and left regions of the parieto-occipital, increases the degree of deformity of the skull. In addition to these malformations, the limited cranial capacity of the subject (1225 c.c.) highlights Blasio's opinion that the brain, contained in such a small and malformed skull, did not allow the person to think correctly (4, 5).

Discussion

In light of this finding, De Blasio cites the opinion of Lombroso who, in his studies of criminal anthropology, considered that one of the characteristics of the delinquent was a skull capacity lower compared to normal

(6, 7). Especially for the criminal woman, Lombroso theorized prostitution as a congenital and anthropometrically measurable defect. In his work "The delinquent woman, the prostitute and the normal woman" (La donna delinquente, la prostituta e la donna normale), Lombroso reported prostitution as a regression of the normal woman, equating prostitutes and 'primitive' (non-white) women because the primitive woman was a prostitute (8, 9).

A particular morphological anomaly is represented by the division of the jaw bones, which is a rarity in Europe. Some scholars interpret this alteration as an atavistic feature because it has been found in some quadrumans and in invertebrates, including reptiles and fish (10-12).

Another peculiarity discovered by De Blasio during the anthropological study was the lack of a glenoid fossa of the temporal bone. To give a better interpretation of this absence, he cited his colleague, Giuffrida-Ruggieri, who argued that the absence of this cavity is a feature of non-human primates, especially anthropomorphic apes (13). Finally, De Blasio reports that he even saw the same morphological feature in two specimens of Gorilla savagei.

Interestingly, De Blasio returns to Giuffrida-Ruggieri's interpretation and features it in his contributions. In fact, Giuffrida proposed a comparison between the presence and absence of the glenoid cavity of the temporal bone between the skulls of alienates and those of delinquents. Responding to the lack of the glenoid cavity in the temporal bone in some skulls belonging to these two categories (13 out of 1000 in the first and 1 in 25 in the second), it is clear that the authors' intention was to interpret this feature as an element that could be evident in people who possess limited intellectual capacities. As for the presence of accessory bones, De Blasio, using the studies of Marimò and Bianchi, demonstrated that the existence of this characteristic increased to 1.67% in criminal subjects. One of the other skeletal anomalies found in the young woman was plagiocephaly, a deformation of the skull bones that occurs in infants, which gives the head a parallelogram shape. According to De Blasio, the possible causes of this malformation were: rickets, uterine contractions, adaptation of the head of the foetus in the spoiled basin, slow and continuous compression of the head by an intrapelvic tumour, or perhaps as a child she had always slept on the same side, which according to Virchow, caused the premature synostosis of the coronal suture (14). It is relevant to note at this point how, no matter what the cause, the author thinks this deformity is more pronounced in delinquents (15).

That being said, the author was convinced that the skull malformation was responsible for the woman's low intellect (16, 17). In conclusion, in order to reinforce his hypothesis, he reported the views of other scholars: Penta: "anthropological anomalies have immense value when they are many and are found in parts that have more direct relation to the nervous system" (18), Laurent: "the skull deformity reveals a defect or at least an intellectual irregularity" (19) and Venturi "in no way more than the skull, containing the organ that is the direct instrument of the psyche, can faithfully translate the nature of degeneration that has altered the psyche itself" (20).

According to these arguments, skull malformations can indicate a mental irregularity that may occur through complex disorders of the nervous system, with atypical behaviour. In this regard, it is also interesting to note that some scholars of that time tried to find corroboration in the Lombrosian theories of the Criminal Anthropology. In particular, Goring made a statistical study on 3000 English convicts, in which he proposed to establish whether there were physical or mental anomalies in the criminal classes

that distinguished them from ordinary people (21). The study, published in 1913, is one of the most comprehensive criminological works of its time. Goring sustained: "the physical and mental constitution of both criminals and law-abiding people of the same age, height, class and intelligence, are identical. There is no such thing as an anthropological criminal type" (21). Through his work, he became convinced that it was not only physical features that were related to criminal behaviour but also environmental factors (22).

It is now known that these theories have been discredited due to the absence of scientific foundation but it is clear that the evolution of both scientific and social theories of that time, together with the contribution of De Blasio which we are now learning about, contributed to the birth of forensic psychopathology (23).

Conclusion

We would like to conclude this article by pointing out other issues that should be taken into consideration in the studies concerning Criminal Anthropology, that is, the abuse in the past of the mortal remains of the poor in medical research, but also today's ethical issues concerning the study and the museum exposition of human remains (24, 25). The case of the denied request to rebury Villella's skull, studied by Lombroso, is an exemplary case (7).

What is already known on this topic

We know that in the age of Positivism, anthropology, particularly the Lombrosian kind, interpreted human behavior through naturalistic observation. The case presented here is a testimony to how the psychiatry of that time exploited the theories of Criminal Anthropology.

What this study adds

This study presents a case of a very unusual published autopsy report. The author of the report, Abele De Blasio, doctor and anthropologist, is little known by the scientific community but certainly represents one of the most interesting figures among the followers of Criminal Anthropology.

Authors' contributions: Conception and design: ML; Acquisition, analysis and interpretation of the data: ML; Drafting of the article: ML; Revising it critically for important intellectual content: MT, OL, SI, and CT; Approved final version of the manuscript: ML, OL, CT and SI.

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Looking Forward to the New Medical School in Croatia

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Dear Editor,

I was happy to read about the opening of a new medical school in Croatia, at the Catholic University of Croatia (CUC) (1). I applaud the concept of the school and wish to comment on it. Of all models of medical education that I have encountered so far, this one fulfils my expectations and wishes for an excellent, relevant and responsible clinical education. Of the four pillars of the CUC Medical School (1) multi-centred medical education that involves health institutions outside major medical centres, 2) the concept of transformative learning, 3) teaching and practicing evidence-based medicine, and 4) implementation of quality management principles supported by information technology), the one I appreciate most is the multi-centred medical education. Medical education at leading university departments has several setbacks: the busy professors lack time for students, and there is a case selection bias towards high-tech medicine, rare and heavy diseases, and this often results in lower student attendance and interest. I expect that the education of CUC students in small towns and hospitals will bring the students closer and more regularly to everyday cases of the kind they will encounter after graduation, and will open them to the social and economic aspects of patients' life. This will, in turn, facilitate the concept of patient-centred care and shared decision making. The quality of the supervision of this field work is very considerable, on the basis of planned comprehensive two weekly "virtual" reports to professors at CUC. This scheme allows spontaneous and concrete transformational learning (2). Separated from other students in small hospitals, the students will have more time and opportunities to concentrate on their patients, especially because they will be following them until they are discharged from hospital. I especially like the idea of students writing a comprehensible report for the patient on their release. At our School in Split, we have used that model, and patients appreciate it (3).

IT technology applied to quality management is also an original and potentially efficient strategy (4), and, again based on our experience from School of Medicine in Split, an online schedule makes the teachers' administration significantly easier and less-time consuming (5). I was pleased to learn from the report (1) that our colleagues from Split have assisted their colleagues

from CUC to build their educational philosophy, the curriculum and organizational scheme, insofar as the aspects built into the CUC Medical School have proved effective in Split. The key difference, to the advantage of the CUC, is the multi-centred medical education, involving health institutions outside major medical centres. To conclude, I see this concept as highly appropriate in terms of producing the main final products of Medical Schools, which are general practitioners trained to provide general medical care on the front line of the health care system.

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Why Hippocrates? A Clash Between Avarice and Morality in Ancient Greek Medical Ethics that Still Resounds

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Key words: Asclepius ▪ Hippocrates ▪ Physicians' Fee ▪ Avarice ▪ Medical Ethics.

Dear Editor,

While tracing the origins of Western Medicine, we reach the era of Asclepius (Greek: Ασκληπιός), the great ancient Greek patron of therapeutics in about the 13th century BC. This secondary Thessalian deity was born as a mythical commoner, who became a hero in the ancient city of Trikki and was finally nurtured at the top of Mount Olympus among the gods of Greek antiquity, acquiring a binary form of human and snake (the ancient chthonic symbol of resurrection-rebirth). As all Olympians, he himself had a fatal moral flaw of mortals. Asclepius, and therefore all of his followers-priests, as well as the lineage of physicians who embraced his religion (the Asclepiads), had a strong affection for gold - a mortal sin which was vividly described by the authors of the era. His whole religion was surprisingly based on rich gifts, ex-votos and venality, while his entire sect was fond of huge remuneration. If Asclepius was to perform his medical skills, as a god in any of his forms, human or snake, he had to be highly compensated as Pausanias stated. Thus, this binary divine and early protector of the medical arts depicted the first avaricious figure in the history of medicine (1). Usually, an ex-voto was not enough, as the priests demanded enormous amounts of gold, thousands of golden staters from the worshipers, in order for the god to appear and propose a cure, or to send a prescription in distant cases (Greek: Σεσημασμένη δέλτο), or even to resurrect the dead from Hades, provoking the wrath of Zeus. Once Asclepius was summoned to treat Theseus' (Greek: Θησέας) son, Ippolytos (Greek: Ιππόλυτος). To save him from a tragic demise to the Underworld, he requested "gold in hand". When Zeus find this out, "He raised his hand against both and instantaneously cut their breath throughout their chests, sealing with a flaming thunder their end" (2). In Asclepius' prime, in the 5th century BC, a new dogma appeared that changed every aspect of health care. Hippocrates and his followers-pupils introduced a whole new approach, proposing an oath for all medico-philosophers, limiting the

physicians' fees. A compensation was recommended, named "Iatra" (from the Greek word for physician, iatros, ιατρός), a fee which should be paid for any intervention (sometimes as farm animals or fruit, or simply a shelter). The charismatic new doctrine suggested a thrifty way of living for all (both physicians and citizens), while medical and philosophical education, experience and the personalized exercise of medicine, with a holistic approach including both the body and the soul, were introduced as a more humane relationship with sufferers. The clash between theurgic and scientific medicine lasted less than a century in classical Greece. The "Hippocratic Oath" established medical ethics in antiquity and its validity still determines physicians' behaviour globally (3). It was the exaggerated fee of gold of that time that motivated the change, the shift of the society towards a new mode of compensation. In our modern world, where the client's resources are limited and physicians' fees are once again being elevated to a more and more costly commodity, price transparency initiatives encourage patients to save money by choosing physicians with a relatively low price per office visit or intervention. Moreover, studies have proven that the patients of low-price physicians who have substantively lower overall spending compared to the patients of high-price physicians, enjoy equal services (4). Patients are kept in the dark about the going rates for health care services, while the need to "bend the cost curve" has become increasingly urgent over recent decades due to economic instability. Stripped to its core, modern medicine has become a service industry, with financial conflicts of interest which may cloud clinical judgment and practice, and further burden public health care systems and their users (5). To answer the question concerning the best physician on the basis of his fee, we may recall the stigma left by the Hippocratic School. An educated and experienced physician, regardless of his low cost reward, could treat any disease and be at the same time beneficial to society, equally as someone who demands pricey compensation. If we are called upon to decide between an "Asclepiad" and a "Hippocrates", between avarice and morality, between exaggeration and normality, the answer arises effortlessly. In Ancient Greece Zeus annihilated avarice, while in the modern era all physicians should kill their inner passion themselves in order to serve society better and provide a public service and intergenerational solidarity, by simply remembering the example of the temperate Ancient Greek medico-philosophers.

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by Nerma Tanović

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Cancer-Pain.org [homepage on the Internet]. New York: Association of Cancer Online Resources, Inc.; c2000-01 [updated 2002 May 16; cited 2002 Jul 9]. Available from: http://www.cancer-pain.org/.

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