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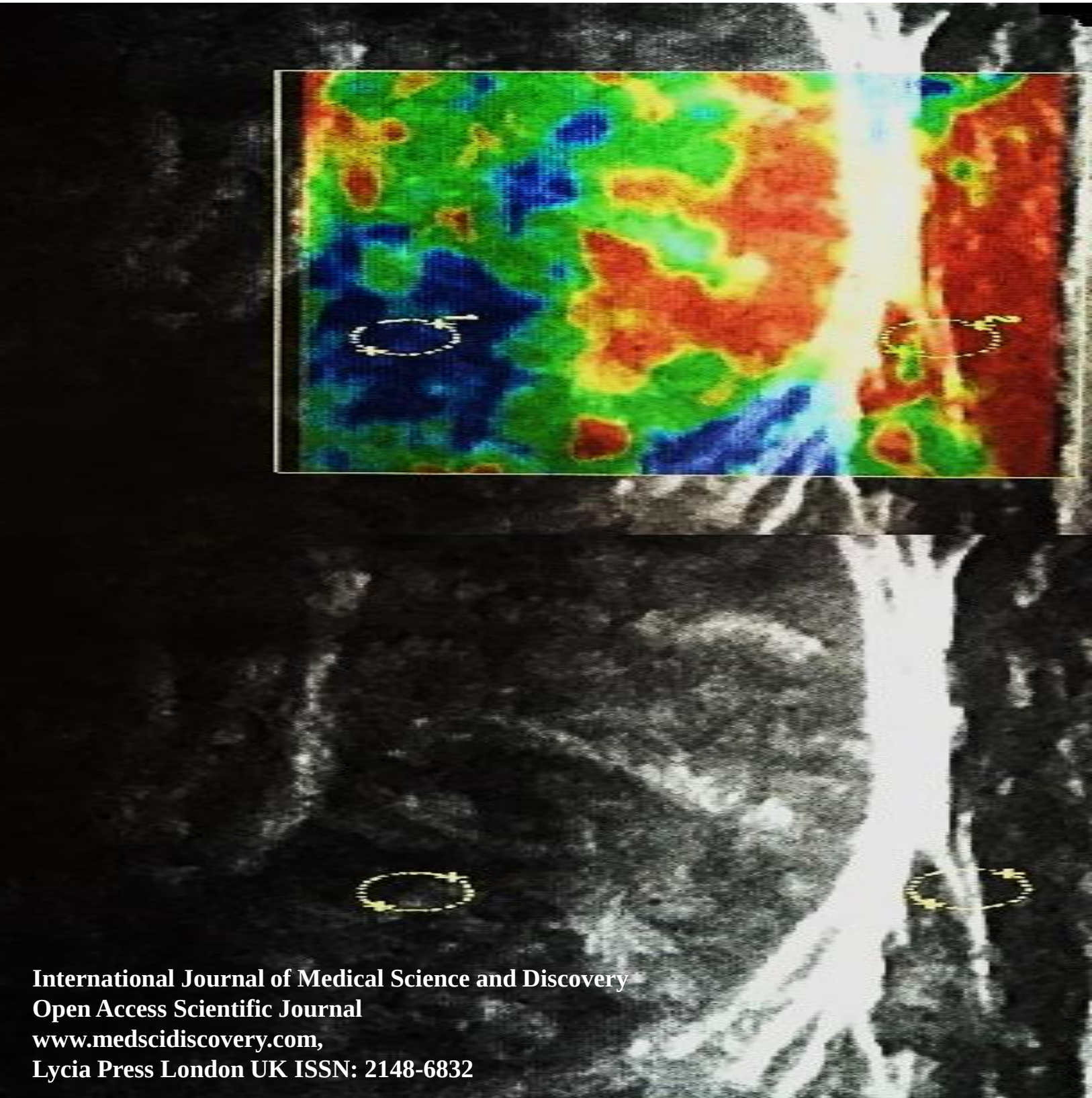

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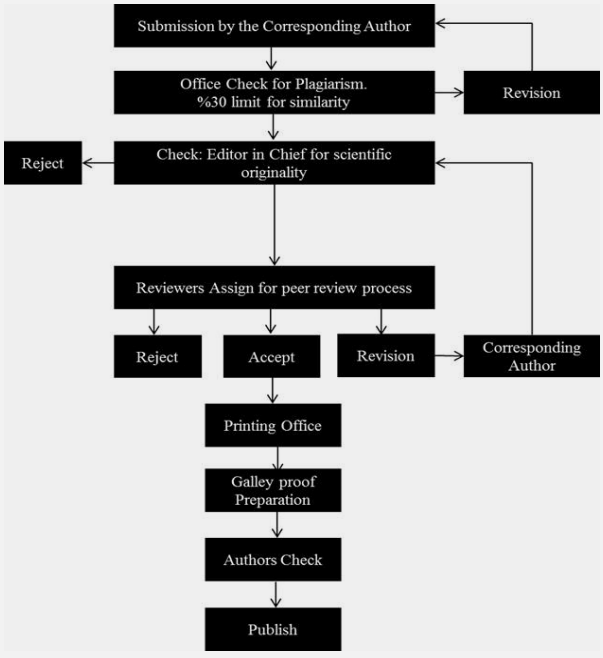

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Review Article Doi: 10.36472/msd.v6i11.322

Genetics of male infertility and related genes within Y chromosome

Tutku Melis Aygün[1]*

Abstract

Objective: The infertility is a reproductive health problem that affects nearly 7% of all couples in the human population. It has been estimated that nearly 50% of infertility cases are due to genetic defects. Male infertility may be contributory to 30 - 40 % of infertile couples. Male infertility focuses on genetic factors impairing spermatogenesis and structural abnormalities such as Y chromosome microdeletions. The Y chromosome microdeletions are the most frequent genetic cause of male infertility. In this review article, we will focus on the structural abnormality and related gene functions on infertility.

Key words: AZF regions, male infertility, spermatogenetic failure, Y chromosome microdeletions

Introduction

Infertility is defined as the inability to conceive an offspring after a year of regular unprotected intercourse [1]. Nearly 15% of couples are affected with infertility, in which male factor infertility accounts for approximately 50% with genetic abnormalities such as structural abnormalities [2]. Genetic factors contribute to male infertility by influencing hormonal balance, spermatogenesis, and sperm quality. Male infertility screening is carried out by using semen analysis according to the standard criteria of the World Health Organization (WHO) [3].

In structural abnormalities, microdeletions of the Y chromosome is considered to be a major cause of male infertility for azoospermic males [4]. Mostly the male infertility is a de novo event of genetic origin that originates during the normal process of spermatogenesis. Azoospermia is referred

to as the absence of spermatozoa in the ejaculate of a man. More than 4000 genes are mentioned to be involved in human spermatogenesis [5,6,7].

Recognition of Azoospermia Factor (AZF) region on the long arm of the Y chromosome (Yq) is the second most common genetic cause of spermatogenic failure [8]. Molecular screening of Y chromosome microdeletions explain some related region that determine azoospermia factors like AZFa, AZFb, AZFc region which are responsible for regulating the spermatogenesis [9,10].

In this review article, I present a brief overview of the AZFc subregion as microdeletions in this region that is a genetically risk factor for spermatogenic failure, also to understand the genetic problem of the AZFc subregion of the human Y chromosome [11,12].

Structure and organization of y chromosome

Y chromosome is the smallest chromosome that consists of 2-3% of the haploid genome and contains between 70 and 200 genes in their structure [13]. Cytogenetic observations are based on chromosome banding studies that are allowed different Y regions to be identified, the pseudoautosomal portion, PAR1 and PAR2, the euchromatic and heterochromatic regions.

Several phenotypes have been associated with the non-recombining portion of the Y chromosome [14]. For obvious reasons, most of these are male-specific and make the Y a specialised chromosome during human evolution. The most characterising features of this chromosome remain its implication in human sex determination and in male germ cell development and maintenance [15,16].

Some of the important genes, also regions (Azoospermia Factor – AZF) on the human Y-chromosome have been discovered and then characterized [17]. These genes have been covered in this review. Important features such as cytogenetic location, function, and mutational deficiencies associated with some of the male-related genes are shown below in Table 1.

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Table 1. Male-Related Functional Genes (Azoospermia / Infertility)

GENE	LOCATION	LONG NAME	FUNCTION	X HOMOLOGS
USP9Y	Yq: 5C	Ubiquitin-specific Protease	Azoospermia	+
DBY	Yq: 5C	DEAD box, Y	Infertility	+
UTY	Yq: 5C	Ubiquitous TRY motif, Y	Infertility	+
TB4Y	Yq: 5D	Thymosin 4, Y isoform	Infertility	+
EIF1AY	Yq: 5Q	Translation initiation factor 1A, Y	Infertility	+
CDY	Yq: 5L, 6F	Chromodomain, Y	Infertility	–
RBMY	Yp + q	RNA-binding motif, Y	Infertility	–
PRY	Y: 4A, 6E	Putative tyrosine phosphatase protein-related Y	Infertility	
DAZ	Yq: 6F	Deleted in azoospermia	Infertility	+

Table 2. AZF Regions and Their Functions within the Y Chromosome

LOCUS	FUNCTIONS
AZF - A	Deletion of AZFa associated with lack of germ cells and Sertoli Cell Only Syndrome.
AZF - B	Deletion of AZFb associated with spermatogenesis arrest.
AZF - C	Deletion of AZFc associated with the failure of the maturation process of germ cells**.**

Functional genes on three azf regions

The azoospermia factor (AZF) region on the Y chromosome consists of genes required for spermatogenesis. The AZFa harbours some single-copy genes which are involved in spermatogenesis that have X-homologs [18,19]. The overlapping AZFb and AZFc regions are jointly termed as AZF2. In the AZFb region, the eukaryotic translation initiation factor EIF1AY and RBMY genes have been mapped in man. EIF1A protein is involved in stabilizing the binding of the initiator methionine-bearing-tRNA to 40S ribosomal subunits.

The AZFc region harbours five genes: DAZ, BPY2, PRY. The candidate gene of AZFc is known as deleted in azoospermia gene, which is studied with interest because it is involved in germ cell development and most frequently deleted genes leading to azoospermia [20]. Also, AZF regions and their functions are shown in summarize, in Table 2.

Azf-a locus its genes and functions

The AZFa encodes only single-copy genes. It is constituted by single-copy, ubiquitously expressed genes with X homologs that escape inactivation. genes have been mapped to AZFa.

*USP9Y: USP9Y is a single copy gene that is located in the AZFa region. USP9Y enzyme belongs to the peptidase C19 family and has a role in sperm cell production and development in mammals.

Besides, its role in spermatogenesis, studies have discovered that a nine-residue peptide derived from USP9Y represents a minor histocompatibility antigen involved in graft rejection.

*DBY: AZFa microdeletion is a result of non-homologous end joining (NHEJ) between two nearly identical repeats. The general view is the deletion of one gene is, this. DBY plays a key role in the spermatogenic process which is essential for cell cycle progression from G1 to S phase.

*UTY: In human, the six mRNA transcripts of UTY gene translate into the enzyme histone demethylase UTY that contains tetra-trico-peptide repeats and are thought to be involved in protein-protein interactions. The UTY protein being a minor histocompatibility antigen could induce rejection of male stem cell grafts. Suppression of recombination between the homologous genes UTY and X-chromosomal UTX, results in a point mutation in mRNA transcripts of these genes, whereas the reading frames. UTY has essential for prostate differentiation and that disruption of this network predisposes males to prostate cancer.

*TB4Y: TB4Y is expressed in various tissues that encodes a novel human leukocyte antigen HLA-A*3303-restricted, minor histocompatibility antigen and is a key activator of natural killer cell cytotoxicity. The involvement of TBY4 in testicular functions is unknown.

Azf-b locus its genes and functions

AZFb microdeletions cause spermatogenesis arrest at the spermatocyte stage, loss of mature sperm and milder azoospermia. The AZFb region has a complex structure that prone to NHEJ. The AZFb microdeletions remove multiple copies of testis-specific CDY, RBMY and PRY genes [21].

*CDY: This gene aids in regulation of gene expression and encodes a histone acetyltransferase. Deletion of this gene associated with azoospermia and severe oligozoospermia.

*RBMY: It is one of the most important genes of the AZFb region within the Y chromosome. Deletion of this gene leads to a decrease in sperm count in semen. RBMY must have diverse functional roles during different stages of spermatogenesis. Indeed analysis of the human testicular RBMY bound transcriptome have led to identification of 20 target genes some of which are testis-specific and have diverse cellular functions and is proposed to regulate alternative splicing during the spermatogenesis.

*PRY: It is a testis-specific gene that encodes a protein similar to protein tyrosine phosphatase. When PRY levels are increased in sperm which can lead the abnormal semen parameters, suggesting a link between its expression and defective spermatogenesis.

Azf-c locus its genes and functions

AZFa and AZFb regions are essential in initiating spermatogenesis, the AZFc region is essential to complete the process of spermatogenesis [22,23]. The AZFc is the most commonly deleted region of the AZF locus in infertile men. There are no single-copy sequences in the AZFc. The AZFc region includes 12 genes and transcription units, each present in a variable number of copies making a total of 32 copies. Amongst the various transcriptional units, only active copies of four protein-coding gene families map to the AZFc interval. These include the PRY2, BPY2, DAZ and CDY1 [24,25].

*PRY2: The expression of PRY in germ cells is heterogeneous, with the protein being detected only in a few sperm and spermatids. Furthermore, PRY levels are increased in ejaculated sperm obtained from males with abnormal semen parameters, suggesting a link between its expression and defective spermatogenesis [26]. The PRY genes are thought to be involved in the regulation of apoptosis implicated in the removal of abnormal sperm. Deletions that include the PRY1 and PRY2 genes have also been reported to cause meiotic arrest.

*BPY2: It is expressed specifically in testis and its protein product is involved in male germ cell development. Three nearly identical copies of this gene exist on Y chromosome BPY2A, BPY2B and BPY2C. BPY2 is localized in the nuclei of spermatocytes, round spermatids and spermatogonia. The BPY2 gene encodes for a small positively charged protein which is thought to be involved in cytoskeletal regulation in spermatogenesis [27]. Due to its small size and high charge, it is thought that BPY proteins may functionally interact with DNA in a manner that resembles chromatin-associated proteins such as histones and high mobility group proteins which are known to play a role in the regulation of processes such as transcription, replication, recombination and DNA repair.

*DAZ: This is the first candidate gene to be isolated from the AZFc locus and was originally identified as a frequently deleted gene on the Y chromosome of infertile males. AZFc region contained palindromic duplications of DAZ as two clusters of four genes, DAZ1,2,3,4. The four DAZ copies are expressed in spermatogonia, encoding an RNA-binding protein important for spermatogenesis and these genes are expressed in all stages of germ cell development. Using human embryonic stem cells, it is shown that DAZ family genes function in germ cell formation. Therefore, all DAZ family genes are regarded as critical for germ cell development.

*CDY1: The human Y chromosome has two identical copies (CDY1A and CDY1B) of this gene within the AZFc region. This gene aids in regulation of gene expression, chromatin remodelling and encodes a histone acetyltransferase. This protein has been reported to concentrate in the round spermatid nucleus, where histone hyperacetylation occurs and causes the replacement of histones by the sperm-specific DNA packaging proteins.

A genetic disorder related to y chromosome abnormality

*Azoospermia

The reproductive disorder of male known as azoospermia is characterized by the absence of sperm in ejaculate affecting approximately 20% of male fertility situations, in general. A variety of causes responsible for azoospermia which is due to abnormal chromosomes or structural abnormality. Disease-like varicocele is associated with the AZFa region of the Y chromosome. EIF1A protein results in azoospermia when deleted. Some studies have been investigated that deletion of DAZ1/DAZ2 but not DAZ3/DAZ4 is associated with spermatogenic failure [28,29].

Male infertility and y chromosome microdeletion

Deletion of genetic material in the region of Y-chromosome (AZF) results in male infertility. Some studies have been reported that the natural transmission of deletions which involves the USP9Y gene suggests that the absence of the USP9Y gene product does not have sperm-fertilizing ability. Thus, it is not critical for spermiogenesis. Deletion in DAZ1/DAZ2 gene copies, which is difficult to detect due to multicopy and will result in spermatogenetic failure [30].

Missing genes within the Y chromosome result in microdeletions. Y chromosome microdeletions are recently diagnosed by isolated DNA from peripheral blood (leukocytes) and then, mixing it with some of about hundreds of known genetic markers for sequence-tagged sites (STS) on the Y chromosome, then using PCR amplification -also FISH techniques (if it's possible)- and gel electrophoresis to test whether the DNA sequence corresponding to the selected markers is present in the DNA.

Conclusion

The advantages of next-generation sequencing and some of the new perspectives have enabled researchers to identify a number of novel genes. The Y chromosomal genes have been explored to associated with several male fertility-specific traits in human.

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Investigation of EGFR Mutation and ALK Gene Rearrangement Rates in Lung Adenocarcinoma Patients in Mardin

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Abstract

Objective: Non-Small Cell Lung Cancer (NSCLC) is a heterogeneous group of tumors comprising different histologic subtypes and genetic mutations. Important mutations are EGFR (Epidermal Growth Factor Receptor), ALK (Anaplastic Lymphoma Kinase) rearrangement and ROS 1 rearrangement. This study aimed to determine the mutation rates of lung adenocarcinoma patients admitted to Mardin State Hospital Oncology clinic and to review the literature on the term mutually exclusivity.

Materials and Methods: The records of patients admitted to Mardin State Hospital Medical Oncology Clinic between 2014-2018 were retrospectively analyzed. The descriptive statistics for continuous variables mean/median; for categorical variables, frequency (n) and percentage (%) were shown.

Results: There were 39 lung adenocarcinoma patients (30.2%) among 130 lung cancer patients. The median age of female patients was 49.31 (27-74), while the median age of male patients was 58.87 (43-78). There were 6 EGFR mutant (15.4%) patients and 2 (5.1%) patients with ALK rearrangement. There were no ROS-1 positive patients.

Conclusion: This study indicates that EGFR mutation rates may be very low in Turkey compared to the literature and ALK rates may be close to the literature. To determine the actual mutation rates and factors affecting genetic alterations in Turkey, there are needed to further studies.

Keywords: EGFR, ALK, Mutually Exclusive, Mardin, Turkey

Introduction

Non-Small Cell Lung Cancer (NSCLC) is a heterogeneous group of tumors comprising different histologic subtypes and genetic mutations, accounting for almost 85-90% of lung cancers. (1, 2) Important mutations are EGFR (Epidermal Growth Factor Receptor), ALK (Anaplastic Lymphoma Kinase) rearrangement and ROS-1 rearrangement. Recent studies suggest that molecular tests should be performed in all NSCLC cases. It is even recommended to perform at selected squamous cell carcinomas (non-smoker or mild drinkers). (3) With the detection of ALK gene rearrangement in NSCLC patients in 2007, a new molecular subtype emerged in lung cancer. (4) Approximately 3-5% of ALK re-arrangement is detected in NSCLC patients. This feature has distinct clinical and pathological features such as adenocarcinoma histology, and the presence of young, non-smoker or low-smoking patients. (5-8) EGFR mutation rate has been reported between 17-50%. (9-12) This mutation is mostly detected in adenocarcinoma histology. ALK re-arrangement and other mutations (EGFR, KRAS) are mainly mutually exclusive with each other (only one is present and the other is not available) (6, 13) Only 3-5% of cases have overlapping (doublet or multiple mutations). (14, 15)

This study aimed to determine the mutation rates of lung adenocarcinoma patients admitted to Mardin State Hospital Oncology clinic and to review the literature on the term mutually exclusive.

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Materials and Methods

The records of patients admitted to Mardin State Hospital Medical Oncology Clinic between 2014-2018 were retrospectively analyzed. The local Ethics committee approved the study. Patients over 18 years of age were included in the study. Patients who have not pathological diagnosis were excluded from the study. In addition to age, sex and disease diagnosis, admission and diagnosis stages of the patients were recorded. Statistical analyses were performed over the whole group, followed by male and female patients. Statistical analyses were performed using Statistical Package for Social Sciences (SPSS) for Windows v20.0 (SPSS Inc, Chicago, Illinois, USA). The descriptive statistics for continuous variables mean/median; for categorical variables, frequency (n) and percentage (%) were shown. FISH method was used for ALK rearrangement, and real-time (RT) PCR was used for EGFR mutation evaluation.

Results

There were 39 lung adenocarcinoma patients (30.2%) among 130 lung cancer patients. While the median age of these patients was 57.82 (27-78), there were 11 female (28.2%) and 28 male (71.8%) patients. The median age of female patients was 49.31 (27-74), while the median age of male patients was 58.87 (43-78). When the disease stages were examined, There were 4 (10.3%) patients in stage 1; 2 (5.1%) patients in stage 2; 11 (28.2%) patients in stage 3 and 22 (56.4%) patients in stage 4. While 11 (28.2%) of these patients had never smoked, 11 (28.2%) were ex-smokers and 17 (43.6%) were those who continued to smoke at or after diagnosis. The number of patients who had mutation/rearrangement tests performed was 24 (61.5%). 15 (38.5%) of the patients who were not tested / unknown. There were 6 (15.4%) EGFR mutant patients and 2 (5.1%) ALK rearrangement positive patients. Of the 6 patients with EGFR mutation, 3 were female and 3 were male. The ALK-positive patients were equal (1 female and 1 male). While 3 of the EGFR positive patients had never smoked, 1 consisted of active smokers and the other 2 had quit smoking. One of the 2 ALK-positive patients had never smoked and the others had quit. There were no mutations or rearrangements in 16 patients (41%) (Table 1). There were no ROS-1 positive patients.

Discussion

In a study that includes 1683 NSCLC patients reported by Gainor et al.(9) EGFR mutation was found in 301 (17.8%) patients and ALK rearrangement in 75 (4.4%) patients. In this study, EGFR mutation and ALK re-arrangement were reported as mutually exclusive. In a study by Won et al. (10) a total of 1445 NSCLC patients were examined for EGFR mutations and ALK translocations, and the mutation rates were detected 42.4% (612/1445) and 6.3% (91/1445), respectively. Simultaneous EGFR and ALK changes were detected in 4 patients (4/91, 4.4% based on ALK-positive group) and 4/612, 0.7% based on EGFR mutant group. In a study by Yank et al.(11) 336 (32.7%) EGFR mutations and 70 (6.8%) ALK gene rearrangement positivity were detected in 977 Chinese NSCLC patients. The frequency of simultaneous EGFR mutation and ALK rearrangement was reported to be 1.3% (13/977 patients). In a meta-analysis conducted by Fengzhi Zhao et al. (16) 6950 patients from 27 retrospective studies were examined. The ALK fusion rate was 6.8% (472/6950). In addition, in terms of male and female gender, the ALK fusion gene was examined in 26 of 27 studies. There was no significant sex difference between the two groups. Mardin's study also showed no difference in terms of sex. However, the number of patients was low in our study. In a meta-analysis by Ying Wang et al. (17) a total of 4511 patients from 17 articles on NSCLC were examined. Considering the current 17 studies involving 4511 cases, the EML4-ALK fusion gene was highly correlated with none or mild smoking, female sex, and adenocarcinoma pathology and was commonly mutually exclusive with EGFR mutation. In a study by Lee et al. (12) 444 lung adenocarcinoma patients were examined for EGFR and ALK status. As a result, EGFR mutation was detected in 228 (51.4%) patients and ALK rearrangement in 34 (7.7%) patients. 4 (0.9%) patients had both EGFR mutation and ALK rearrangement. As can be seen, in some studies, very low rates of mutually exclusivity rules are broken. In a study by Cicek et al in Turkey (18), biopsy specimens of 114 patients (86 adenocarcinoma, 28 NOS) were examined. In this study, EGFR mutation rate was detected 11.4% (n: 13), ALK re-arrangement rate was detected 8% (n: 9) and ROS-1 rearrangement positivity rate was detected 1% (n: 1).

Table 1: Clinical and Demographic Characteristics of Patients

		Female (n:11, %28.2)	Male (n:28, % 71.8))	All Group (n:39)
Age (Median)		49.31 (27-74)	58.87 (43-78)	57.82 (27-78)
		n (%)	n (%)	n (%)
Stage	**Stage 1**	1(9.1)	3 (10.7)	4 (10.3)
	Stage 2	0	2 (7.1)	2 (5.1)
	Stage 3	3 (27.3)	8 (28.6)	11 (28.2)
	Stage 4	7 (63.6)	15 (53.6)	22 (56.4)
Smoking	**No-Smoker**	9 (81.8)	2 (7.1)	11 (28.2)
	Active Smoker	1 (9.1)	16 (57.1)	17 (43.6)
	Ex Smoker	1 (9.1)	10 (35.7)	11 (28.2)
EGFR Mutant		3 (27.3)	3 (10.7)	6 (15.5)
ALK positive		1 (9.1)	1 (3.6)	2 (5.1)
All (EGFRALK,ROS-1) Negative		3 (27.3)	13 (46.4)	16 (41)
Unknown/No-Tested		4 (36.4)	11 (39.3)	15 (38.5)

Conclusion

In the Current Study (Mardin's Study), EGFR positivity rate was 15% and ALK rearrangement rate was 5%. These results were close to the results of the study by Cicek et al and these two studies suggest indicates that EGFR mutation rates may be are very low in Turkey compared to the literature and ALK rates are may be close to the literature. To determine the actual mutation rates and factors affecting genetic alterations in Turkey, there are needed to further studies.

Conflict of Interest: The authors declare no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Author's Contributions: AA; Patient examination**,** research the literature, Collection of the Data. **AA;** Revision of the article.

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Relationship between learning styles of faculty members and orthodontic and dentofacial orthopedic residents: An analytical cross-sectional study in an accredited dental school in Latin America

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Abstract

Objective: Information regarding the correlation between the learning styles of faculty members and orthodontic and dentofacial orthopedic residents is scant. The objective of this study was to evaluate the relationship between the learning styles of faculty members and orthodontic and dentofacial orthopedic residents.

Material and Methods: In this analytical cross-sectional study, faculty members and orthodontic and dentofacial orthopedic residents of the School of Dentistry at the Universidad de Antioquia, Medellín, Colombia completed a structured questionnaire to identify their learning styles.

Results: A total of 24 residents (100%) and 36 (100%) faculty members responded to the questionnaire. Residents and faculty members presented preference for the theorist and reflector styles; however, the faculty members had a higher value in the theorist style. Statistical significant Pearson correlations were identified among men residents with theorist style (r=0,36; p=0.24), and among men faculty members with active (r=0,37; p=0.026) and pragmatist styles (r=0,5; p<0.0001). Consequently, an association was observed among men residents with the theorist style, which persisted after adjusting for age and semester enrolled (OR=1.5; p=0.03). On the other hand, associations were detected among men faculty members with the active (OR=1.3; p=0.02) and the pragmatist styles (OR=1.4; p=0.005), which also remained after adjusting for age in the multivariate models.

Conclusion: Residents and faculty members showed a preference for the theorist and reflector styles. Besides, this paper found associations between gender and some specific learning styles: men residents were associated with the theorist style, and men faculty members were associated with the active and pragmatist styles.

Keywords: dental faculty, dental students, education, learning, orthodontics

Introduction

A group of researchers envisioned the learning styles; they specified different standards and mechanisms complicating the designation of the most appropriate (1). Alonso et al. (2), incorporated a recognized one, from work stablished by Keefe (3), defining the learning styles as perceptive, emotional and functional idiosyncrasies that aid apprentices to differentiate, correlate and respond to their learning context. The learners are the creators of their educational development, replicating on a cyclic method from practice. The Learning Styles Questionnaire (LSQ) commended by Honey and Mumford (4) recognized a total of four learning styles: "activist, reflector, theorist and pragmatist" (Figure 1), settled on the inventory of learning styles of Kolb (5), which correspondingly specified four styles of learning (accommodating, assimilating, divergent, and convergent). The LSQ was proved for commercial objectives and was revised, proved, and transformed into Spanish scholastic framework (2). To interpret the four styles of learning, Alonso et al. (2) conferred a scale to organize the results in five tendencies: "very high, high, moderate, low and very low." The CHAEA survey was modified from this variation, and it was operated in health sciences curriculums (6-8). It was edited regarding difficulties discerned in the moment of its accomplishment, then the perceptive of the issues was improved conserving its essence (9). Thus, the CAMEA40 was created and proved with university pupils. To teach and to learn include a multifaceted dynamic in dental faculties, comprising the empathy between learners and mentors, the program, the theoretical-practical interface, the university environment,

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and the culture (10,11). The features of the subcultures are essentials in higher education because of these surroundings can disturb the learning (11).

Dentistry contains a mixture of education options, including seminars, lectures, expositions, problem-solving cases, and practical training; thus, a variety of approaches could be adopted to profit learning (12). Conventionally, orthodontic postgraduate programs have principally applied lectures and training to improve clinical abilities. It has been postulated that as residents advance into an orthodontics program, they will develop a robust inclination for realistic rather than conceptual information and select a structured location with substantial practical learning chances. While students are commonly educated beyond interest to their specific learning styles, a perception of the traditional style of learner approaches in orthodontic and dentofacial orthopedic residents would be satisfactory to the development of an exemplary residency learning program (13).

Instead, irrespective of the educational context, the comprehension of learning styles benefits educators to monitor scholar learning appropriately (14), and it is even commended that the instructors identify their manner of learning, since it may control the method of teaching (15). Besides, persons with similar learning styles correspond enhanced (16). A distinguishing of learning styles will benefit both residents and faculty members to augment understanding more competently. Furthermore, it is significant for the professor to be skilled in recognizing the potencies and boundaries of the residents' learning experience (17).

Unfortunately, there are little data regarding the connection that may exist in the learning styles of faculty members and orthodontic and dentofacial orthopedic residents. Thus, the objective of this research was to identify the relationship between the learning styles of faculty members and orthodontic and dentofacial orthopedic residents in a higher education program.

Material and Methods

The present research had a cross-sectional design that was authorized by the Institutional Bioethics Board (IRB03-03-19). The participants fulfilled the CAMEA40 (9) form and signed the informed consent freely, agreeing with their attendance in this investigation.

Orthodontic and dentofacial orthopedic residents enrolled in the academic period 2019-1, and their professors attended this research. The selection criteria contained: orthodontic and dentofacial orthopedic residents enrolled in the accredited programs of orthodontics and dentofacial orthopedics at the School of Dentistry of the Universidad de Antioquia; faculty members of the same programs were also included. Thus, sixty faculty members and residents confirmed the solicitation to participate. The forms were concluded in the classroom after the explanation of the research purposes.

CAMEA40 (9) developed to recognize the learning styles is constituted by two parts. Initially, the questionnaire explores topics allied to the socio-academic facts. The next segment encloses forty brief interrogations with five chances of feedback (always, almost always, many times, sometimes and never) assigning a rate of 5, 4, 3, 2, and 1, correspondingly. The product is the computation of all the responses (They are dispersed in four columns, equivalent to each learning style).

The form is unintentionally arranged; therefore, it is presented ten issues relate to each learning style ("activist, reflector, theorist and pragmatist"). To decode them, Alonso et al. (2), advised a grading to order the products in five dispositions: "very high, high, moderate, low and very low"; for example, high pragmatist, low activist. The conformation of the survey admits that each resident/faculty member selects more than one style of learning.

Statistical Analysis

Primarily, the descriptive statistic was managed. Then, it was used bivariate analyses (Chi-Square and Pearson correlation); also, the T-student test was executed to observe differences between groups. The Kolmogorov-Smirnov normality analysis was used to explore the data distribution. Besides, logistic regression was done, stated in ORs, complemented by confidence intervals of 95% (CI 95%) and statistical significance. P values <0.05 were contemplated statistically significant. A statistical software (SPSS version 24.0; SPSS, Chicago, IL) operated all the analyses.

Results

A total of 24 residents (100%) and 36 (100%) faculty members answered to the CAMEA40 form that classified their learning styles. Table 2 depicts the socio-academic features of the sixty contestants. The number of females was superior in the residents' group and reduced in the faculty members' group. Besides, 50% of the residents studied at a public high school, and 63% had a job. The predilection of learning styles between the groups was contrasted (Table 3). Residents and faculty members preferred for the theorist and reflector styles; nonetheless, it was superior to the rate of the faculty members that preferred the theorist style. Differently, the pragmatist style revealed a moderate scale in the residents, whereas the faculty members had a low rate in that style.

Statistical significant Pearson correlations were identified among men residents with theorist style (r=0,36; p=0.24), and among men faculty members with active (r=0,37; p=0.026) and pragmatist styles (r=0,5; p<0.0001).

Bearing in mind these correlations, logistic regressions were run. Tables 4, 5, and 6 display the crude and multivariate analyses. The association among men residents with theorist style remained in the simple model (OR= 1.4; p=0.03); this association persisted after adjusting for age and semester enrolled (OR=1.5; p=0.03) (Table 4). Additionally, the associations among men faculty members with active (OR=1.2; p=0.03) (Table 5) and pragmatist styles (OR=1.4; p=0.006) (Table 6) also persisted in the crude model; these associations remained after adjustment for confounders (Tables 5 and 6).

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Table 1. Socio-academic characteristics in 60 residents and faculty members

Parameter	Residents (n=24)	Faculty members (n=36)	*P*-value
Age (years)	29±2.9[a]	45±9[a]	<0001[c]
Gender			
Female	17 (71%)[b]	16 (44%)[b]	NS[d]
Male	7 (29%)[b]	20 (56%)[b]	0.04
GPA[e]	4.23±0.2[b]	----------	---------
Public high school	12 (50%)[b]	----------	---------
Job (yes)	15 (63%)[b]	35 (97%)[b]	0.001[c]

[a)]Values are presented as a mean±standard deviation, [b)]Values are presented as number and percentage, [c)]Statistically significant differences between faculty members and residents. [d)]NS=not statistically significant, [e)]GPA=grade point average

Table 2. Mean values and rating scale of the learning styles in residents and faculty members

Learning Style	Residents (n=24)	Rating scale	Faculty members (n=36)	Rating scale	P value
Activist	23±4.5	l	23±4	l	NS
Reflector	31.6±4	m	32.6±4	m	NS
Theorist	33±4.3	m	35±4.8	h	NS
Pragmatist	27.6±4.6	m	26±5.2	l	NS

Values are presented as a mean±standard deviation, Rating scale: very high (vh), high (h), moderate (m), low (l) y very low (vl). NS= not statistically significant

Table 3. Multivariable regression analysis for men residents and the theorist learning style

Variable	Crude OR (95% CI)	*P* Value	Adjusted* (95% CI)	*P* Value
Theorist learning style	1.4 (1.2-1.8)	0.03	1.5 (1.2-2.3)	0.03
Age (years)			0.8(0.4-1.2)	NS
Semester			0.7 (0.3-1.4)	NS

*Adjusted for age and semester enrolled. NS= Not significant association

Table 4. Multivariable regression analysis for men faculty members and the active and pragmatist learning styles

Learning style	Crude OR (95% CI)	*P* Value	Adjusted* (95% CI)	*P* Value
Active learning style	1.2 (1.1-1.5)	0.03	1.3 (1.1-1.6)	0.02
Age (years)			1.0 (0.9-1.1)	NS
Pragmatist learning style	1.4 (1.2-1.7)	0.006	1.4 (1.2-1.7)	0.005
Age (years)			1.1 (0.9-1.1)	NS

*Adjusted for age. NS: Not significant association

Figure 1. Features of learning styles (4)

Discussion

Whereas residents are habitually educated without interest in their learning styles, comprehension of their traditional structure in a specific group such as orthodontic and dentofacial orthopedic residents could be advantageous to the formation of a representative residency education process (13). The career selected by the resident could be a relevant point that can impact the learning styles, affecting enormously the changeability in learning (16). The habituation of residents and faculty members with their learning styles can spread understanding of their fortes in learning and consider the necessity to intensify their less usual styles (3). Likewise, when faculty members know the learners` inclinations, it is more reasonable to find approaches that permit residents to learn more competently (6).

The CAMEA40 was effected in university students (9, 17, 18), and it was adjusted into the Italian language (19).

To our knowledge, no research has contrasted learning style predilections between faculty members and residents in a dentistry residency program. This research depicts that residents and faculty members preferred the theorist and reflector styles; nevertheless, the faculty members had a higher value in the theorist style, but without significant differences. An investigation in a residence program of internal medicine revealed that faculty members and students chose the reflector style (20). Moreover, the theorist and reflector styles were selected among neurosurgeons, neurosurgery residents, and neurology residents (21). When the similar learning style is mutual, a pedagogical relation is expected, and educational success could rise (20). Scholars have denoted that precise contextual needs, such as educational specialization, demand faculties for professional obligations, and malleable aptitudes, influence the learning styles of residents and faculty members (21).

The theorist and reflector styles were also chosen for literature (9), pharmacy (6), and medicine pupils (7). Consequently, personnel with a tendency in the theorist style (Figure 1) desire to estimate troubles from several outlooks; they prefer to observe, questioning the material with less predisposition to automatic learning. Reflectors (Figure 1) are likewise eyewitnesses, serene, critical, also demonstrate an exceptional personality concerning the learning process (7).

Richard et al. (22) reported that the majority of residents and faculty in an orthopedic residency program preferred the pragmatist style. Also, Engels and de Gara (23) found that the predominant learning styles of the general surgery residents and general surgery faculty were a pragmatist and active styles. In this study, the pragmatist style was observed in residents on a moderate scale, while faculty members had a low value in that style. It was explained that pragmatist was more successful in problem-based learning curriculums in medical scholars (24).

This research found that the activist style was observed in residents and faculty members in a low scale; these findings confirm those reported in students of dental campuses from other cultural backgrounds (25, 26). Nevertheless, researchers founded diversified products of leading learning styles among faculty and students of different health programs (27). Various cultures around the world showed that the context and their customs influence learning styles (11). Furthermore, it was found that Hispanic-Latino presented a distinctive learning style predilections because their learning styles and environmental contexts comprise peculiarities (28). No specific learning style is consistently concomitant with improved learning consequences. This circumstance is possibly due to the adaptable capacities of university scholars (13).

Interestingly, this paper found associations between gender and some specific learning styles. The theorist style was related to men residents; this association continued after adjusting for age and semester enrolled. Moreover, associations among men faculty members with active and pragmatist styles also continued in the multivariate analysis, after adjusting for age. Hughes et al. (13) described that age and gender did not stamp a peculiarity in the learning styles prevalent in the orthodontic community in the United States and Canada. Nonetheless, two recent types of research informed that male and females depict distinctive inclinations for learning styles in medical pupils in Asian universities (29, 30).

Besides, it was documented that women more feasible than men learn progressively (31). This information is crucial, considering that female orthodontic resident is increasing (32). Additionally, it has been reported that cultural multiplicities may create a distinction in the predilections of learning styles, considering reasoning and intercommunication varieties (11, 27). The facts mentioned above could justify the findings observed in this research.

The augmentation of further cognitive aptitudes associated with specific postures to learning has the potentiality to transform a more prosperous autonomous student. Considering the knowledge of the specific fortitudes and boundaries as learners, faculty members will convert more attracted to learn and subsequently turn into persistent learners (1), which is crucial for orthodontic and dentofacial orthopedic curricula.

The boundaries of this study included the cross-sectional design that eludes temporal causality. Besides, the participants studied are not a representative sample of the nation; nevertheless, the Universidad de Antioquia compile a relative volume of the applicants from diverse areas of the country. Additionally, all the faculty members and residents respond to the questionnaire.

These conclusions also noticeably provide to the scarcity of researches in dental curricula correlated preferences in learning styles of faculty and residents and their concurrent qualities. More reports investigating learning styles in orthodontic and dentofacial orthopedic curricula are essential to juxtapose these findings with diverse cultural backgrounds.

Conclusion

In the present research, residents and faculty members showed a preference for the theorist and reflector styles. Besides, this paper found associations between gender and some specific learning styles: Men residents were associated with the theorist style, and men faculty members were associated with the active and pragmatist styles. These specific regional and cultural findings could warrant to create policies in the learning-teaching method and institute significant antecedents to formulate guidelines and educational schemes in orthodontic and dentofacial orthopedic programs. Imminent investigations to validate these outcomes will be esteemed.

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Author's Contributions: The correspondent author conceived the idea, carried out the design, and supervised the findings of this work. The correspondent author and co-authors verified the analytical methods and wrote the manuscript. All authors discussed the results and contributed to the final manuscript.

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The comparison of antioxidant enzyme activities in Quince Fruit (Cydonia Oblonga) grown in Van, Ankara and İzmir

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Abstract

Objective: In this study, it was aimed to determine the activity of some antioxidant enzymes in the quince fruit (Cydonia Oblonga) which grown in different regions of Turkey.

Materials and Methods: For this study, firstly, quince fruit grown in different provinces such as Van, Ankara and İzmir was obtained for this study. Then, extracts of quince fruit were prepared and antioxidant enzyme activities were determined by spectrophotometric method. The findings were analyzed using statistical methods and the results were interpreted.

Results: The difference between the means in terms of Superoxide Dismutase, Catalase and Glutathione Reductase (SOD, CAT and GR) enzyme levels was found to be statistically significant for quince fruit grown in Van, Ankara and İzmir ($p < 0.05$). Accordingly, CAT, SOD and GR levels in quince fruit grown in İzmir were significantly higher than other regions.

Conclusion: As a result, the antioxidant property of quince fruit seems to be very important. The consumption of quince fruit especially in winter can be protective against some diseases, especially winter diseases. Further research on quince fruit should be done.

Key words: Quince, catalase, superoxide dismutase.

Introduction

Quince (Cydonia oblonga Miller) tree drops leaves in winter. Quince is a sturdy fruit. It has been reported to be hard and acidic when the chemical and physical properties are examined. In the studies conducted in Eastern and Far East countries, quince fruit has been recommended to be consumed against diseases such as colds and coughs. Flavonoids are abundant in fruits and vegetables. They are also phenolic (1). In different studies, colorful fruits and vegetables have been determined to be rich in phenolic substances (2).

Free radicals are substances that contain uncombined electron pairs. When free radicals are over-synthesized, they can cause some damage to living organisms. Antioxidant enzymes serve as a shield against these damages (3, 4).

The studies conducted have focused on dust and extract in quince seeds. The above-mentioned substances have begun to be used in the cosmetic industry, espacially for beauty and skin care purposes (5). In literature studies, some antioxidant parameters of quince fruit seeds have been investigated (6).

This study aims to determine the antioxidant enyzme activities in quince fruit grown in different regions of Turkey.

Material and Method

Determination of superoxide dismutase (SOD) activity

SOD activity was determined using the method recommended by Sun et al. (7).

Preparation of Reagent Solution:

1. 0.3 mM Xanthine: 4.56 mg of xanthine (Sigma X7375) was first dissolved in a few drops of 1N NaOH and dissolved in 100 ml of bi-distilled water.

2. 0.6 mM EDTA: 4.46 mg EDTA was dissolved in 20 ml bi-distilled water.

3. 150 mg / L NBT: 12.3 mg NBT (Sigma N6876) was dissolved in 100 ml bi-distilled water.

4. 400 mM Na_2CO_3: 2.544 gr Na 2 CO 3 was dissolved in 60 ml bi-distilled water.

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5. Bovine serum albumin (1 g/L): 12 mg BSA (Sigma A2153) was dissolved in 12 ml bi-distilled water.

Preparation of the reagent solution

40 ml of xanthine solution, 20 ml of EDTA solution, 20 ml of NBT solution, 12 ml of Na_2CO_3 solution and 6 ml of BSA were mixed.

-16 µl of xanthine oxidase (167/l/L) (Sigma X1875) was taken and dissolved in 1 ml 2 M $(NH_4)2SO_4$.

-2M $(NH_4)2SO_4$: 2.643 g $(NH_4)2SO_4$ was completed to 10 ml with distilled water (stored at +4 °C).

-0.8 mM $CuCl_2$ $2H_2O$ 13.6 mg of $CuCl_2$ $2H_2O$ was prepared and completed to 100 ml with distilled water.

Table 1.1. Method of determination of SOD activity.

Blind	Sample	
Reaktif	1.425 µl	1.425 µl
Sample	-	50 µl
Bi-distilled	100 µl	-
Xanthine oxidase	25 µl	25 µl
It was kept for 20 minutes at room temperature of 25˚C		
$CuCI_2$	50 µl	50 µl

After pipetting as indicated in Table 1.1, the absorbances in blind and sample tubes were determined versus bidistilled water at 560 nm.

Activity Account:

% inhibition: [(Blind OD - Sample OD) / Blind OD]x100

1 Unit SOD: The enzyme activity that inhibits NBT reduction by 50%.

Activity= (% inhibition)/(50x0.1)

Activity; Calculated in U/ml.

Determination of catalase (CAT) activity

In this study in which hydrogen peroxide was used as substrate, the catalase activity was determined through Aeibi method. The activity was carried out as follows: 1.4 ml of 30 mM H_2O_2 was added to the blinded tube and 0.1 ml of phosphate buffer was added. 1.4 ml of 30 mM H2O2 was added to the sample tube. 0.1 ml of enzyme was added and mixed with vortex. Absorbances at 240 nm were determined twice at 30 second intervals, and thus activity was prescribed (8).

Solutions used:

1. Preparation of 30 mM H_2O_2: 34 ml of 30% H_2O_2 was added into 10 ml of bidistillated water (25.8 ml of 35% H_2O_2).

2. Preparation of 50 mM Phosphate Buffer: 6.81 gr of KH_2PO_4 and 7.1 gr of Na_2HPO_4 were dissolved in bidistillated water, the pH of the buffer was adjusted to 7.4 with 1N NaOH and the volume was completed to 1 litre.

Activity Account:

E.Ü. = (2,3 / Δx) x [(log A1 / log A2)] Activity; Calculated in U / L.

Δx = 30 seconds

2,3 = the optical density given by 1 olmol H_2O_2 in 1 cm of light path.

Determination of glutathione reductase (GR) activity:

Solutions used:

1. 100 mM Na_2HPO_4 buffer with a pH of 8 was prepared. 7.1 gr of Na_2HPO_4 was dissolved in 400 ml of bidistilled water, a few drops of 1N NaOH were added, the pH was adjusted to 8 and the total volume was completed to 500 ml with the remaining 100 ml of bidistilled water.

2. Daily buffer: Prepared by dissolving 0.12 mM NADPH (Sigma N7505) and 1 mM GSSG (Sigma G4626) in buffer. Buffer solutions were stirred magnetically and the indicated amount of NADPH and GSSG was melted.

50 tests (must be prepared daily in buffer): 0.0050 gr of NADPH was dissolved in 50 ml of buffer, 0.0328 g of GSSG was dissolved in the same buffer.

Experimental Procedure:

1-) 100 µl of purified water and 900 µl of daily buffer were put in the blind tube.

2-) 900 ul daily buffer and 100 seruml serum were added to the sample tube and the tubes were vortexed.

3-) Tubes were incubated at 37 C for 10 minutes.

4-) Absorbances were determined at 340 nm in 0th and 5th minutes versus blind tube

Activity Calculation

(U/ml): (ΔOD/6.22) x (Vt/V0)

ΔOD = absorbance change over time.

Vt=Total volume.

V0=Sample volume.

6.22 = OD value given by 1 nmol NADPH in 1 cm of light path (9).

Statistical analysis

Mean, standard deviation, standard error, minimum and maximum values were used in descriptive statistics of the data. Univariate analysis of variance was used in cases where normal distribution condition was provided, and Kruskal Wallis test statistic was used in cases where normal distribution condition was not provided. The statistical significance level was taken as $p<0.05$ and the SPSS statistical software version 19.0 (SPSS Inc, Chicago, III, USA) pack has used for analyses.

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Results

Table 1. Descriptive statistics and comparison results of parameters CAT, SOD and GR

		n	Mean±Std. Dev.	Std. Error	Minimum	Maximum	p
CAT (U/L)	Van	20	2,555±0,22118	0,04946	2,20	2,90	0.001
	Ankara	20	1,225±0,11180	0,02500	1,10	1,40	
	İzmir	20	3,7±0,14510	0,03244	3,50	3,90	
SOD (U/L)	Van	20	4,54±0,25005	0,05591	4,20	4,90	0.001
	Ankara	20	2,53±0,17800	0,03980	2,30	2,80	
	İzmir	20	5,06±0,19029	0,04255	4,80	5,30	
GR (U/L)	Van	20	7,1655±0,07571	0,01693	7,05	7,32	0.001
	Ankara	20	6,109±0,04745	0,01061	6,04	6,19	
	İzmir	20	8,119±0,08855	0,01980	7,96	8,25	

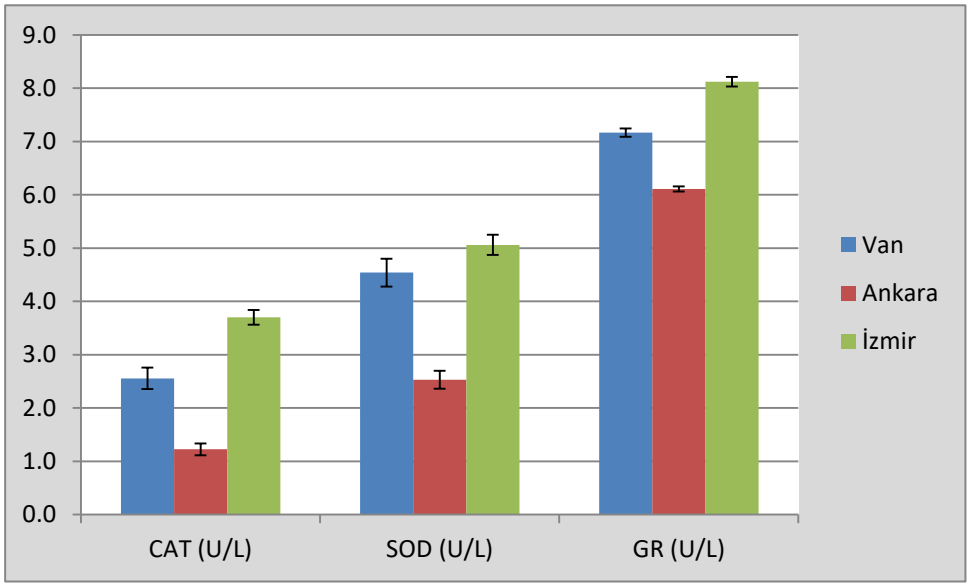

Figure 1. CAT, SOD and GR levels of quince fruit by provinces

Descriptive statistics and comparison results for CAT, SOD and GR are given in Table 1. When Table 1 was examined, the difference between the means in terms of CAT, SOD and GR levels was found to be statistically significant for quince fruit grown in Van, Ankara and İzmir ($p < 0.05$). CAT levels were found to be 2,555 in the quince fruit grown in Van, 1,225 in the quince fruit grown in Ankara, and 3.7 in the quince fruit grown in İzmir. SOD levels were found to be 4.54 in quince fruits grown in Van, 2.53 in quince fruits grown in Ankara, and 5.06 in quince fruits grown in Izmir. GR level was found to be 7,1655 for quince fruits grown in Van, 6,109 for quince fruits grown in Ankara, and 8,119 for quince fruits grown in İzmir. CAT, SOD and GR levels in quince fruit grown in İzmir province were significantly higher than other regions (Figure 1).

Discussion

Free oxygen radicals are known to cause many diseases such as diabetic, cancer, arterosclerosis, cardiovascular diseases, malaria, neurodegenerative diseases, kidney disorders, immune system disorder, cataract, DNA damage and many age-associated diseases (10).

Consumption of fruit and vegetables has been reported to be an important protector against many diseases, because many fruits and vegetables contain great amounts of phenolic substances. In the studies, it can be said that the amount of antioxidant also increases if the amount of phenolic substance is high. The fruits are rich in Vitamin E, vitamin C and carotenoids. It has been reported that consuming fruit reduces oxidative stress and cellular damage (11).

Quince fruit is a rich vitamin store. In studies, quince fruit has been observed to have great amounts of trace elements, macro and micro mineral substances and sugar (12).

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In literature, it has been stated that quince fruit has antioxidant, antimicrobial and antiulcerative properties (11, 13).

Descriptive statistics and comparison results for CAT, SOD and GR are given in Table 1. When Table 1 was examined, the difference between the means in terms of CAT, SOD and GR levels was found to be statistically significant for quince fruit grown in Van, Ankara and İzmir ($p < 0.05$). CAT levels were found to be 2,555 in the quince fruit grown in Van, 1,225 in the quince fruit grown in Ankara, and 3.7 in the quince fruit grown in İzmir. SOD levels were found to be 4.54 in quince fruits grown in Van, 2.53 in quince fruits grown in Ankara, and 5.06 in quince fruits grown in Izmir. GR level was found to be 7,1655 for quince fruits grown in Van, 6,109 for quince fruits grown in Ankara, and 8,119 for quince fruits grown in İzmir. CAT, SOD and GR levels in quince fruit grown in İzmir province were significantly higher than other regions (Figure 1).

As a result, the antioxidant property of quince fruit seems to be very important and shows differentiation among the different regions. Further research on quince fruit should be done.

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Author's Contributions: The correspondent author conceived the idea, carried out the design, and supervised the findings of this work. The correspondent author and co-authors verified the analytical methods and wrote the manuscript. All authors discussed the results and contributed to the final manuscript.

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The influence of bacterial vaginozis and cervical length on preterm delivery in pregnant women in the second trimester

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Abstract

Objective: Preterm birth is one of the major cause of perinatal morbidity and mortality. Clinical studies have pointed out the association between preterm birth and bacterial vaginosis (BV) infection. Our aim is to discover the incidence of BV and search for the mean cervical length and parameters for the prediction of preterm delivery.

Materials and Methods: 130 pregnant woman between the 16th and 24th gestational week were included in our study. A detailed medical history was obtained from all of the women, and patients with a history of preterm delivery and the Vaginal Ph values and cervical length measurement were evaluated. Vaginal samples were analyzed, gram staining was performed, and a bacterial vaginosis diagnosis was made with Nugent's criteria.

Results: Of 130 woman that we included in our study, only 19 had bacterial vaginosis (14.6 %), and the mean cervical length was measured as 41.79 mm. Preterm birth occurred in nine of the pregnant women (6.9%), and no statistically significant difference was found between BV and shortened cervical length or preterm labor. When we excluded the known preterm birth risk factors from our study, we could not find a significant difference between preterm labor and BV.

Conclusion: We concluded that BV by itself is not a preterm risk factor. The frequency of BV in the pregnant women in our study group according to the preterm delivery rate and the mean cervical length were similar to those in international studies in which the relationship between cervical length and preterm delivery has been established. We did not come to a significant conclusion in our research; nevertheless, we can relate this result to the preterm delivery rate that is found to be lower than expected.

Key words: Second Trimester Pregnancy, Bacterial Vaginozis, Cervical Length, Preterm Delivery

Introduction

Preterm delivery (termination of pregnancy before 37th week of gestational) is among the important causes of perinatal mortality and morbidity (1,2). There is no previous history of preterm delivery in 70% of preterm deliveries (1,3).

While etiology of preterm delivery is multi-factorial including major risk factors like smoking, ethnicity, the relationship with bacterial vaginozis (BV) was emphasized in many clinical studies (4,5). Bacterial vaginozis is characterized by impairment of vaginal microbiota through the decrease in Lactobacillus species and the increase in anaerobic microorganisms and Mycoplasma species. Diagnosis of BV is made by Amsel criteria (6) or Nugent scoring system based on the decrease in Lactobacillus species and the increase in Gram-stained anaerobic bacteriae (7).

Prevalence of BV was found to be 7,1% in a study conducted with 14.193 pregnant women and used Nugent criteria for diagnosis although it varies among countries (8). Patho-physiologic mechanism of BV could not be fully explained, data are available reporting that BV significantly increases the risk for preterm delivery during the first two trimesters of pregnancy besides the literature data proposing the opposite (9).

Measurement of cervical length between 20-24th week of gestation showed high accuracy for prediction of preterm delivery and different cut-off values were given (10,11,12).

The aim of the present study is to detect the incidence of bacterial vaginozis (BV) and mean cervical length, and also the value of these parameters for prediction of preterm delivery in pregnant women in our population.

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Material and Method

Pregnant women in the second trimester (between 16-24th weeks of gestation) who were admitted to obstetrics outpatient clinic for routine control and who had the complaint of vaginal discharge were included in the study. All participants were informed about the procedures and 136 pregnant women who agreed for participation were included.

A detailed anamnesis was obtained from all participants and data about gestational age, number of pregnancies and parities, complaint of vaginal odor and medical history were recorded.

Exclusion criteria included the following;

*Ages younger than 18 years or older than 40 years,

* History of smoking and medication use,

* Multiple pregnancies,

* History of preterm labor or premature rupture of the membranes,

* Uterine malformations,

* History or diagnosis of cervical insufficiency,

* Presence of medical problems like maternal hypertension, type 1 or type 2 diabetes or thyroid dysfunction,

* Unexplained vaginal bleeding,

* Pregnant women who did not know the date of the last menstruation or whose gestational week cannot be estimated due to the absence of a previous ultrasonography,

* History of in-utero still fetus or congenital anomalies.

The participants were taken to the lithotomy position after a detailed second trimester ultrasonography examination including detection of gestational week, presence of congenital malformations or uterine anomalies had been performed, smear was obtained from the lateral wall of the vagina with a sterile swab by using disposable plastic Graves type speculum and by paying care for not touching cervical mucus plug. Fixation was done in open air after the specimen was spread on the lam. At the second step, vaginal pH was measured with a universal pH stick.

Afterwards, the speculum was removed, the same ultrasonography device was prepared with a lubricant condom, trans-cervical length was measured with vaginal probe at 5 MHz. Care was paid for the urinary bladder's being empty, each measurement was performed in 3 min due to the potential cervical spasms.Vaginal smear was evaluated for Nugent criteria with Gram staining.

Telephone numbers and addresses were obtained from all participants for obtaining delivery data and the required ones were called for control again.

The study was conducted in accordance with the principles of human experiments and informed consent was obtained from the participants prior to the study. Ethics committee approval was obtained from the local ethics committee (date: 9.09.2004/ number:54).

Statistical Analysis

Data were analyzed by using SPSS (Statistical Package for the Social Sciences) ver. 20.0. Number, percent, mean, standard deviation, minimum, maximum values were used. Chi-square test was used for analysis of categorical variables. Significance test of the difference between two averages was used as parametric test according to the results of normality distribution. A p level of <0,05 was accepted as statistically significant.

Results

Of 136 pregnant women, 2 were excluded due to severe preeclampsia beginning at the advanced stage of pregnancy, one was excluded due to intra-uterine still birth and 3 were excluded as they were lost to follow up.

Mean time of admission was 21 weeks and 3 days. Cervical length varied between 28 mm and 52 mm (mean 41.79 mm). Time of delivery varied between 31 weeks and 3 days, and 41 weeks and 6 days (mean 38 weeks and 6 days). Birth weight varied between 1290 gr and 4500 gr (mean 3249 gr) (Table 1).

Of the participants, 79 (60.8%) were multiparous and 51 (39.2%) were nulliparous. Seventy three out of all women (56.2%) also had the complaint of vaginal odor. While bacterial vaginozis was detected in 19 out of 130 women (14.6%), preterm delivery occurred in 9 (6.9%) (Table 2).

No difference was found between the pregnant women who had or who did not have preterm labor (p>0.05). As expected, birth week and birth weight of the cases with preterm labor were found to be significantly lower (p<0.001) (Table 3).

No significant difference was found in the pregnant women who had preterm labor with regard to nulliparity and presence of BV (p>0.05) (Table 4).

No significant difference was found between the pregnant women with and without BV with regard to mean cervical length, birth week and birth weight (p>0.05) (Table 5).

Table 1. Distribution of pregnant women and findings

	Minimum	Maximum	Mean	SD
Week of admission	16	24	21,63	2,1
Cervical length(mm)	28	52	41,79	5,25
Vaginal pH	4,0	6,0	4,28	0,43
Gestational week	31,43	41,86	38,9	1,55
Weight (gram)	1290	4500	3249,23	496,77

(mm:milimeter) SD: standard deviation

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Table 2. Results of patient statistics

		n	%
Nulliparity	No	79	60,8
	Yes	51	39,2
Odor	No	57	43,8
	Yes	73	56,2
Bacterial vaginozis	No	111	85,4
	Yes	19	14,6
Preterm labor	No	121	93,1
	Yes	9	6,9

Table 3. Comparison of the women who had preterm delivery or normal vaginal delivery

Preterm Labor	No		Yes		
	Mean	**SD**	**Mean**	**SD**	**p**
Week of admission	21,6	2,10	22,00	2,18	,523
Cervical length	41,95	5,14	39,67	6,44	,323
Vaginal pH	4,28	0,43	4,31	0,451	,778
Weight	3324,88	401,45	2232,22	558,30	< **0,001**
Gestational week	39,1783	1,0740	35,3016	2,4583	< **0,001**

SD;Standard deviation,p: Significance test of the difference between two averages

Table 4. Characteristics of the pregnant women who had preterm labor

Preterm labor		No		Yes		p
		n	**%**	**n**	**%**	
Nulliparity	No	75	94,9	4	5,1	0,313
	Yes	46	90,2	5	9,8	
Odor	No	52	91,2	5	8,8	0,504
	Yes	69	94,5	4	5,5	
Bv	No	104	93,7	7	6,3	0,619
	Yes	17	89,5	2	10,5	

Table 5. Comparison of pregnant women who had or who did not have bacterial vaginozis

Bacterial Vaginozis	No		Yes		
	Mean	**SD**	**Mean**	**SD**	**p**
Week of admission	21,70	2,07	21,21	2,27	,347
Cervical length	41,70	5,31	42,32	4,97	,640
Vaginal pH	4,141	,239	5,111	,356	< **0,001**
Weight	3263,92	490,13	3163,42	539,84	,417
Gestational week	38,94	1,44	38,69	2,14	,525

SD;Standard deviation,p: Significance test of the difference between two averages

Discussion

The significance of prediction of preterm delivery and informing the risky pregnant women about the potential symptoms would be understood better considering the burden of intensive care of premature babies, loss of labor of the health staff and the potential sequels.

Preterm delivery is usually multi-factorial and many parameters that could be a risk factor for preterm delivery were accepted through an ample of studies.

However no consensus is available about the mechanism of these risk factors, effectiveness of these risk factors alone or in combination.

An ample amount of international studies are available investigating the relationship between BV and cervical length measurement and preterm delivery.

In the study of Surbek et al., bacterial vaginozis was detected in 36 out of 112 preterm deliveries (32%) and cervical length of these cases were found to be significantly shorter than that of the women with normal vaginal flora (13) (p=0.001). A statistically significant difference was not detected in cervical length of 235 primigravid pregnant women who were diagnosed with vaginitis/cervicitis compared to the women who did not have vaginitis/cervicitis. Incidence of BV was found to be 15.7% in pregnancy (14).

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Diagnosis of BV was made based on Nugent criteria in the study of Joesoef M. et al. investigating the incidence of BV in pregnancy and the relationship with preterm labor in 490 pregnant women with gestational age of 16-20.weeks. We also used Nugent criteria. Incidence of BV was found to be 17%, while ratio of preterm delivery was 20.2% in these cases, this ratio was found to be 11.8% in BV negative pregnant women (Odds ratio:1,8). It was concluded that there was a significant relationship between BV and preterm delivery. Differently from our study, the pregnant women with the history of preterm delivery were not excluded from the study (15).

In the study of Michael G. et al. which did not include the subjects with the history of preterm delivery, as in our study, while prevalence of BV was found to be 19% in 534 pregnant women, this ratio was significantly higher in women with the history of preterm delivery (16) ($p<0.01$). In multi-center, double-blinded, randomized PREMEVA study, a significant difference could not be found between groups with regard to late abortion and spontaneous preterm delivery in the Clindamycin or placebo arms in 2869 pregnant women who were diagnosed with BV at 12nd week of gestation (17).

When two meta-analyses were evaluated, while one showed that Clindamycin use reduced preterm delivery risk 40% in pregnant women who had abnormal vaginal flora before 22nd week of gestation (18), another did not report a significant difference (19).

Studies made on asymptomatic pregnancies have gained importance when pregnant women have symptomatic infection and medical treatment in many studies in literature. . Krauss-silva reported that the frequency of asymptomatic BV in pregnancy was high in the early gestational weeks and 40% spontaneously became negative within 8 weeks(20). Cervical length measurement according to Mancusto study was found to be significantly short in BV positive asymptomatic pregnant women with at least 1 spontaneous abortion history but when the covariate adjustment was considered, the result was null(21).

Cervical length measured at 20-24th weeks of gestation was shown to be an important factor for prediction of preterm labor in another data investigating the relationship between cervical length and preterm delivery which is another arm of our study (10,11,12). Different cut-off values were investigated for cervical length, 30 mm length was detected to increase the risk 3.79 fold and shorter than 26 mm length was detected to increase the risk 6.19 fold in the study of D.Iams et al. conducted with 2915 pregnant women (22).

Conclusion

In conclusion, the data of prevalence of BV in pregnant women, ratio of preterm delivery and mean cervical length were similar with those of found in international studies. We could not find a significant difference between cervical length and preterm labor, and concluded that it was not a risk factor for preterm delivery alone. We may explain not finding a significant difference between cervical length and preterm delivery with the small number of preterm deliveries.

Conflict of Interest: The authors declare no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Author's Contributions: The correspondent author conceived the idea, carried out the design, and supervised the findings of this work. The correspondent author and co-authors verified the analytical methods and wrote the manuscript. All authors discussed the results and contributed to the final manuscript.

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A case of Sheehan Syndrome with chronic diffuse muscle pain and weakness

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Abstract

Objective: Sheehan's syndrome is pituitary deficiency induced by intrapartum and postpartum hemorrhage and hypovolemia. It is still frequent in underdeveloped and developing countries. Sheehan's syndrome is one of the reason of empty sella. The symptoms of the syndrome can be seen months to years later depend on the degree of pituitary damage. History of postpartum hemorrhage, failure to lactate and cessation of menses are important clues to the diagnosis. Early diagnosis and appropriate treatment are very important to reduce morbidity and mortality of the patients.

Case: In this study sheehan's syndrome which led to auto pan-hypopituitarism and developed gradually in a patient with sheehan's syndrome which in this case, delivered a baby at home 27 years ago and had severe postpartum hemorrhage will be presented. And this 63-year-old female patient was diagnosed as Sjogren's syndrome and sheehan syndrome by clinical and laboratory findings for the purpose of further investigation and treatment because of symptoms of fever and anemia

Keywords: Sheehan's syndrome, pituitary deficiency, postpartum hemorarhage

Introduction

Sheehan syndrome is a pituitary and adrenal insufficiency due to postpartum hemorrhage and hypovolemia. It is rarely seen without massive bleeding or after normal birth. The main mechanism is the development of necrosis in the anterior pituitary as a result of decreased blood volume.

The frequency of this syndrome decreases worldwide. Although it is a rare cause of hypopituitarism in developed countries due to developments in obstetric treatments, it is one of the common causes of hypopituitarism in developing countries and underdeveloped countries (1).

Patients may apply to health care facilities with various signs and symptoms ranging from coma to nonspecific symptoms. The diagnosis may be missed due to the slow development of Sheehan syndrome.

Sheehan syndrome is one of the causes of secondary Empty Sella Syndrome. Empty Sella Syndrome is a variable level of pituitary insufficiency resulting from subarachnoid herniation into the Sella Tursica associated with stretching the pituitary stem and flattening the pituitary gland towards the sellar base (2).

The etiology of Empty Sella Syndrome may be primary or secondary. Secondary Empty Sella Syndrome may occur due to pituitary adenomas, infection, autoimmunity, trauma, radiotherapy, drugs and surgery (3, 4).

In this case, Sheehan's syndrome, which developed slowly after years of postpartum hemorrhage and diagnosed after years, and Shögren's Syndrome with nonspecific symptoms such as anemia, dry skin, dry mouth, dry eye, fatigue, fatigue will be presented.

Case

A 63-year-old female patient; She presented to our outpatient clinic with fatigue, diffuse muscle pain, dry mouth, nausea and vomiting. In her medical history, it was learned that she had no known chronic disease except Alzheimer's disease and that she did not use any regular medication. It was also learned that the patient's last birth was 27 years ago, she had bleeding during childbirth and was unable to breastfeed her child. On physical examination: skin was pale and dry, other system examinations were normal.

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Table 1: Laboratory findings of the patient

Parameters	Patient	Normal Range
Hemoglobin(mg/dl)	8.9	12-14
Na(mg/dl)	123	135-145
Igf-1(ng/dL)	23	71-290
FSH (mlU / ml)	2.77	2.8-11.3
LH(mlU / ml)	0.84	1.1-11.6
Prolactin(ng / mL)	3.5	3.4-24.1
FT4(ng/dL)	0.73	0.91-1.71
TSH(mIU/L)	3.72	0.5-5.5

FT4: Free thyroxine; TSH: Thyroid-stimulating hormone; FSH: Follicle stimulating hormone; LH: Luteinizing hormone

Figure 1.The appearance of the patient

Brain MR: Empty Sella was observed to be compatible with the appearance of the pituitary gland height was reported as 2 mm in sagittal. Oral dryness, dry eye, dryness of the skin, scleroderma was the typical finding of scleroderma. Anti-Ro:> 100 (+), Anti-La: <3.3 (-), Antisintrometer: <3 (-) and Anti Scl-70: <3 (-) were detected. The Schirmer test was bilateral: 2mm and was considered positive. Treatment for dry eyes was organized. The patient was evaluated as Sjogren's Syndrome by clinoco-laboratory correlations.

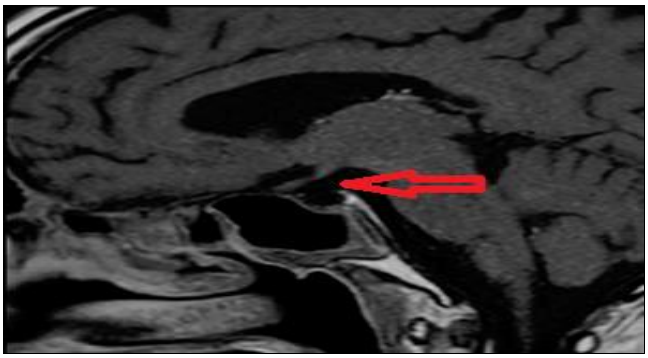

Figure 2. Pituitary gland height decreased Empty Sella compatible with pituitary MR Image.

She was diagnosed with Sheehan Syndrome and Sjogren's, although Empty Sella was observed as a result of cranial MRI and there was no TSH response to low st4, low IgG1 for age and low FSH and LH despite postmenopausal period.

The patient was started on methylprednisolone 5mg tb 2x1 + hydroxychloroquine tb 2x1 for Sjogren Syndrome and then levothyroxine sodium 25 mcg tb 1x1 was added to the treatment. Control biochemistry: Na: 141, and nausea, vomiting, fatigue and fatigue had been decreased during follow-up.

Discussion

TSH levels may be normal or high in Sheehan syndrome. The pulsality of TSH secretion is impaired and begins to be secreted in a tonic manner. Its biological activity decreases. Decreased TSH response to TRH stimulation had been taken (5,6). Lactation insufficiency or difficulty may be the first common symptom. Many women may describe postpartum amenorrhea. Hyponatremia may occur. Hypothyroidism can cause hyponatremia by reducing free water clearance, reducing free water clearance independent of glucocorticoid insufficiency vasopressin, and hypopituitarism itself stimulating vasopressin secretion and inducing inappropriate antidiuretic hormone (ADH) secretion (7).

In Sheehan Syndrome, normostatic normochromic anemia and sometimes pancytopenia and hematological abnormalities are common (8, 9). Anemia is believed to be caused by a lack of anterior pituitary hormones or the absence of unspecified factors normally secreted from the pituitary. Pancytopenia is associated with hypocellular bone marrow. Glucocorticoid replacement was more important than thyroxine replacement to restore pancytopenia in these patients who had complete recovery with treatment.

The aim of treatment in Sheehan syndrome is to replace the insufficient hormones. Treatment includes first hydrocortisone followed by thyroid hormone replacement and estrogen-progestron or estrogen replacement depending on the presence or absence of uterus. Since thyroxine treatment can exacerbate glucocorticoid insufficiency and induce adrenal crisis, hydrocortisone replacement is primarily performed.

Conclusion

In our case, Sheehan syndrome had a slow development, was subclinical, triggered by intervening Sjogren syndrome, had anemia, initially had severe hyponatremia, diffuse muscle pain and weakness and did not respond to sodium replacement and responded to hormone replacement (hydrocortisone).

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Author's Contributions: EÖ, ŞA, KO; Patient examination, research the literature, Collection of the Data. **EÖ;** Revision of the article.

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