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Oasis of knowledge

The hand drawn illustration on the cover of JSTMU encapsulates philosophy of the University and its Journal. It depicts a traveler in the desert stopping by an oasis to take a note to themselves, symbolizing the point after which their journey requires steadfastness and dedication. The note is an excerpt from the Qur'an where God beseeches human beings to reflect. This is the essence of scientific research which prescribes itself in the University logo and is represented through red and blue color in the form of the water and the red sand, and taking further inspiration in the form of the notebook and the quill.

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The *Journal of Shifa Tameer-e-Millat University (JSTMU)* is an open access bi-annually peer reviewed medical journal of the Shifa Tameer-e-Millat University (STMU), Islamabad, Pakistan. The journal encompasses papers from biomedical research, clinical specialties and interdisciplinary medical fields; thereby entertaining the scientific, research and clinical work of a wide variety of health care professionals such as medical practitioners, surgeons, nurses, pharmacists, medical technicians, paramedics, laboratory scientists, physiotherapists, dietitians and bioengineers. The journal is premised on creating influence on the academic as well as corporate thinkers. It is dedicated to presenting advances in medical sciences supporting the recognition and publication of medical scientific research and its effects on human health and well-being. A key question we apply to submission is, "Is this paper going to help readers better understand and conceptualize the research topic while adding something new and innovative to the current pool of knowledge?"

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EDITORIAL

Oral/Dental health services for intellectually/physically challenged individuals in Pakistan

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Keywords: *Dental health services, Intellectually Challenged, Physically Challenged, Dental profession.*

The societal moral compass hinges on two critical benchmarks: first, how the society looks after its elderly population and second, the care afforded to individuals with special healthcare needs. In Pakistan, a nation enriched with cultural and religious values, a commendable tradition of honouring and caring for older people exists. However, a significant gap persists, particularly within the healthcare sector, in addressing the needs of those individuals who are intellectually and physically challenged.[1, 2]

Pakistan has one of the highest reported rates of childhood intellectual and physical disabilities in the world.[3, 4] While efforts have been made to cater these challenged individuals' general health requirements, a glaring oversight remains in attending to their dental health needs.[5] It is imperative for the dental profession to acknowledge this responsibility and take proactive steps to deliver essential dental services to this segment of society. This editorial aims to redirect the profession's attention towards this critical but often neglected professional obligation, hoping to spark meaningful efforts to address it. The dental health of individuals with disabilities, encompassing those with physical or mental special healthcare needs, demands heightened consideration for several reasons. [5]

These individuals often contend with additional general health issues alongside their primary conditions, potentially exacerbating their overall health. Moreover, compromised oral health and aesthetics may further hinder positive societal interaction and contribute to negative perceptions of these individuals. Consequently, the dental profession must act swiftly in some areas. Foremost among these is a concerted effort to enhance professional skills and competency in providing oral and dental health care to these individuals with special healthcare needs. Dental management of such individuals should be an integral part of dental education at the undergraduate and postgraduate levels. The lack of sufficient training in dental curricula has hindered providing adequate dental services to these individuals. Therefore, dental educators must promptly address this deficiency, incorporating the management of individuals with special healthcare needs into dental school curricula and professional training programs.

Traditionally and historically, pediatric dentists have taken responsibility for the oral health care of these intellectually/physically challenged individuals. Unfortunately, some quarters are continuously resisting mainstreaming of this subject at the undergraduate level. Additionally, organizations overseeing continuing dental education should facilitate the dissemination of professional information/training in oral/dental care for our country's intellectually/physically challenged population.

Equally crucial is raising awareness among relevant authorities and advocating for allocating substantial financial and organizational resources to provide dental health services to these individuals. Dentists, whether in the public or private sector, should actively engage authorities responsible for the welfare of intellectually/physically challenged individuals at all levels. They should underscore the importance of good dental

health for optimal general health and dispel the misconception that oral/dental treatment for these individuals is less important than that of the general public.

To overcome communication challenges with intellectually/physically challenged individuals, dentists must equip themselves with various behavioural modalities and familiarize themselves with the characteristics of significant disabilities and their related psychosocial problems. Preventable dental conditions such as dental caries and periodontitis necessitate dentists' commitment to community-wide disease prevention, especially within the intellectually/physically challenged population. Collaboration with schools and institutions and, educating caretakers/guardians of these individuals becomes pivotal in this preventive effort.

While these efforts may not yield significant financial returns for the dental profession, they undoubtedly improve oral health and, consequently, the overall quality of life in these individuals. Providing dental care to this demographic may pose challenges but promises spiritually gratifying experiences. As previously stated, Pakistan has high reported rates of childhood intellectual and physical disabilities.[6] Recognizing its past avoidance, the dental profession must now embark on coordinated, multi-level efforts, acknowledging its responsibilities and working collectively to address the oral/dental health needs of our population's intellectually/physically challenged segments.

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ORIGINAL ARTICLE

Cytopenia in dengue fever and their associations: A Cohort Study

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[2, 3] Synopsis writing, referencing of manuscript, analysis

[4] Synopsis review, data collection, manuscript review

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A B S T R A C T

Introduction: Dengue fever is endemic in countries like Pakistan and has multiple complications. Leukopenia and thrombocytopenia are common cytopenia that sometimes lead to complex outcomes. So, we considered it essential to find the associations of dengue-related cytopenia and planned this study.

Methodology: An observational, retrospective cohort study was conducted at Shifa International Hospital Islamabad. 125 patients from the inpatient department diagnosed with dengue fever based on clinical presentation and positive dengue non-structural protein 1 (NS1) were enrolled. Their vitamin B12 levels, minimum values of TLC (total leukocyte count), and platelet counts during admission were found in their records. All information was entered and analyzed using the SPSS 23 version. After descriptive statistics, Patients' age, gender, residence, and B12 levels were cross tabulated against the TLC and platelet count values using the chi-square test. The descriptive results were expressed in percentages, while chi-square was described as a $p < 0.05$, considered statistically significant.

Results: 125 patients with dengue fever were included in the study; 73 (58.4%) were male, and 52 (41.6%) were female. The mean age was 42.8, the mean B12 level was 94.3 pmol/L, the mean platelet count was 57,000/ µL, and the mean TLC was 5084.8/ µL. Age, gender, residence, and B12 levels did not affect leukopenia and thrombocytopenia in dengue patients ($p > 0.05$).

Conclusion: Dengue-related cytopenia is not correlated with the differences in age, gender, residence and B12 levels and mandates further research work.

Keywords: *Dengue fever, Cytopenia in dengue, Thrombocytopenia in dengue, Leukopenia in dengue, B12 deficiency in dengue.*

Introduction

Dengue is an acute viral illness caused by the RNA virus of the Flaviviridae and spread by Aedes mosquitoes.[1] It is predominantly distributed in tropical and subtropical regions that are the natural home for its vector. Humans and mosquitoes are the only two known hosts.

Clinical presentation of dengue fever Infection with any of the 4 dengue virus serotypes results in a diverse range of symptoms, from mild undifferentiated fever to life-threatening hemorrhagic fever and shock.[2] Cytopenia, particularly thrombocytopenia, is the well-known presentation of dengue fever. It concerns the severity of severe thrombocytopenia in 11.5% of the cases.[3] Dengue fever is classified, in order of increasing severity, as dengue fever (DF), dengue hemorrhagic fever (DHF) or dengue shock syndrome (DSS). More recently, the WHO proposed a revised classification of clinical Infection: dengue, dengue with warning signs, and severe dengue. It is a self-limiting infection but can often progress to a life-

threatening shock syndrome.[4] The detection of NS1 is quite helpful for early detection of dengue fever.[5]

Different studies have described various predisposing factors responsible for dengue-related thrombocytopenia. Castilho BM and colleagues concluded that older age, male gender, and higher MCH are risk factors.[4] Ravichandran S et al. have identified ABO blood groups for dengue-related complications.[6] Take S et al., in their study, concluded that low B12 levels can cause dengue-related severe thrombocytopenia.[7] Since B12 deficiency is quite prevalent in our country and thrombocytopenia and even leukopenia are well-recognized hematological effects of B12 deficiency, it is logical to think about the possible connection between B12 deficiency and dengue-related cytopenia. So, we planned this study to see the effect of age, gender, urban or rural residence (considering nutritional differences among them) and B12 levels on dengue-related cytopenia to find solutions related to anticipating and managing dengue complications.

Methodology

After obtaining due permission and protocol approval from the IRB & Ethics Committee of Shifa International Hospital Islamabad (IRB No.=035-855-2020), all dengue patients meeting inclusion criteria were included those who presented to Shifa Hospital in dengue season 2020 and 2021. Patients with diagnostic discrepancies, known cytopenia, chronic liver disease, chronic kidney disease, on cytotoxic drugs, taking steroids, taking antiplatelet medicines or anti-coagulants, were excluded due to the expected disease-modifying effect. Patients who did not have their B12 levels done were also excluded from the study. The details of patients' demographic features like age, gender, and residence (urban or rural) were noted down. Patients' daily TLC (total leukocyte count) and platelet count values were followed from their records, and minimum values were reported.

B12 levels were also noted down from their record. TLC count<4000/μL was considered low (leukopenia). While platelet count<150000/μL was considered insufficient (thrombocytopenia). B12 levels <25 pmol/L were deemed inadequate. All information was entered, and IBM-SPSS version 23 was used for statistical analysis. The descriptive stats were calculated for both qualitative and quantitative data. For qualitative data like gender and residence, % ages, tables, and figures were presented. Range and means were calculated for quantitative data like age and laboratory values. To see the effect of age, gender, residence and B12 levels on minimum noted TLC and platelet count, a chi-square test was applied and expressed as a $p<0.05$ with a 95% confidence interval considered statistically significant.

Results

The 125 patients with dengue fever were included in the study, of which 73(58.4%) were male and 52(41.6%) were females. The mean age was 42.8 (15 to 84 years), the mean B12 level was 94.3 (12 to 265 pmol/L), the mean platelet count was 57,000 (5000 to 265000/μL) and the mean total leucocyte count was found to be 5084.8 (660 to 17300/ μL). Among the category of severity of dengue fever, 107(85.6%) had dengue fever, 17(13.6%) had dengue hemorrhagic fever, and only one (0.8%) patient presented with dengue shock syndrome. Baseline characteristics of patients (Table 1).

We observed the effect of different variables on the category of cytopenia (monocytopenia or bicytopenia). Demographic features, age, gender, and residence did not affect the type of cytopenia (p-values 0.592, 0.249, and 0.588, respectively). B12 levels also did not affect the development of either monocytopenia or bicytopenia ($p = 0.559$). However, 80% of patients above 70 developed only Monocytopenia (Table 2). We then computed results to see the effect of different variables on values of TLC count (minimum TLC count during admission). The demographic features, age, gender, and residence did not affect the TLC count (p-value 0.368, 0.176, 0.589, respectively). B12 levels also did not affect the value of TLC ($p = 0.632$). However, it was noted that 80% of the patients with ages above 70 years did not develop leukopenia (TLC <4000/μL) (Table 3).

We calculated the effect of variables on the platelet count value (minimum platelet count during admission). The demographic features, age, gender and residence did not affect the platelet count (p-value 0.657, 0.911, 0.525, respectively). B12 levels also did not affect the value of TLC ($p = 0.194$). However, it was noted that 90% of patients with age above 70 years did not develop thrombocytopenia (platelet count < 150,000/ μL) (Table 4).

Table 1: Baseline characteristics of the study population (n = 125)

Baseline characteristics		Frequency	Percentage
Gender	Male	73	58.4
	Female	52	41.6
Age (Years)	15-30	39	31.2
	31-50	42	33.6
	51-70	34	27.2
	>70	10	8.0
Residence	Urban	103	82.4
	Rural	22	17.6
TLC (per µL)	<4000	56	44.8
	>4000	69	55.2
Platelets (per µL)	<150	33	26.4
	>150	92	73.6
Category of Cytopenias	Monocytopenia	69	55.2
	Bicytopenia	52	41.6
	None	4	3.2
B12 levels (pmol/L)	<25	18	14.4
	>25	107	85.6

Table 2: Effect of variables on the category of Cytopenia (n = 125)

Variable		Category of Cytopenia			Total	p value
		Monocytopenia	Bicytopenia	None		
Age category (years)	15-30	20 (51.3%)	18 (46%)	1 (2.7%)	39	0.592
	31-50	20 (47.6%)	20 (47.6%)	2 (4.8%)	42	
	51-70	21 (61.7%)	12 (35.3%)	1 (3%)	34	
	>70	8 (80%)	2 (20%)	0 (0%)	10	
Gender	Male	44 (60.3%)	26 (35.6%)	3 (4.1%)	73	0.249
	Female	25 (48%)	26 (50%)	1 (2%)	52	
Residence	Urban	59 (57.1%)	41 (40%)	3 (2.9%)	103	0.588
	Rural	10 (46%)	11 (50%)	1 (4%)	22	
Category of B12 levels (pmol/L)	<25	8 (44.4%)	9 (50%)	1 (5.6%)	18	0.559
	>25	61 (57%)	43 (40.2%)	3 (2.8%)	107	

Table 3: Effect of variables on TLC count (n = 125)

Variable		TLC count (per µL)		Total	p value
		<4000	>4000		
Age category (years)	15-30	20 (51.3%)	19 (48.7%)	39	0.368
	31-50	19 (59.3%)	13 (40.7%)	32	
	51-70	15 (44.1%)	19 (58.89%)	34	
	>70	2 (20%)	8 (80%)	10	
Gender	Male	29 (39.7%)	44 (60.27%)	73	0.176
	Female	27 (52%)	25 (48%)	52	
Residence	Urban	45 (43.7%)	58 (56.3%)	103	0.589
	Rural	11 (50%)	11 (50%)	22	
Category of B12 levels (pmol/L)	<25	9 (50%)	9 (50%)	18	0.632
	>25	47 (44%)	60 (56%)	107	

Table 4: Effect of variables on platelet count. (n = 125)

Variable		Platelet count (per µL)		Total	P value
		<150,000	>150,000		
Age category (years)	15-30	11 (28.2%)	28 (71.8%)	39	0.657
	31-50	11 (26.2%)	31 (73.8%)	42	
	51-70	10 (29.4%)	24 (70.6%)	34	
	>70	1 (10%)	9 (90%)	10	
Gender	Male	19 (26%)	54 (74%)	73	0.911
	Female	14 (27%)	38 (73%)	52	
Residence	Urban	26 (25.2%)	77 (74.8%)	103	0.525
	Rural	7 (31.8%)	15 (68.2%)	22	
Category of B12 levels (pmol/L)	<25	7 (39%)	11 (61%)	18	0.194
	>25	26 (24.3%)	81 (75.7%)	107	

Discussion

We started this study to find out some factors affecting the total leukocyte count and platelet count in patients with dengue fever to grab those factors in the future while treating dengue fever. Most of our patients belonged to the age group below 50 years, with male predominance. These findings support the published literature, as Khan DM also concluded in their study that dengue is more prevalent in younger age groups.[8] Our study concluded that gender and age do not correlate with dengue-related cytopenia. Though not statistically significant, we observed that the elderly population above

70 years were less likely to develop bicytopenia, leukopenia and thrombocytopenia. This is against the observations that have already been published. Castilho BM and colleagues described male gender and elder age as risk factors for dengue-related thrombocytopenia.[4] There might be racial differences or differences in the general health of the elderly population of these two nations that resulted in this research discrepancy.

We intended to see the effect of residence on the dengue-related cytopenia. The reason was the understanding of nutritional differences, which we generally consider among urban and rural citizens.[9,10] This is based on the concept that the rural population eats a purer and natural diet and is considered healthier than the urban. However, our study results showed no difference in dengue-related cytopenia based on residence. This indicates either this myth is wrong or dengue-related cytopenia is unrelated to diets and nutrition.[11]

We also checked the effect of B12 levels on dengue-related cytopenia. Our study results did not find any connection between the two. Most researchers have connected dengue fever-related thrombocytopenia and bleeding manifestations with vitamin B12 deficiency.[12] Sagar V et al. and Kansara Y K et al. concluded similarly in their study when they found a significant positive correlation between the severity of thrombocytopenia and vitamin B12 deficiency.[14] They also treated patients with vitamin B12 supplementation and found improved hematological and biochemical parameters.[15]

However, our study results remained non-significant in this regard. Though we could not find any study supporting our impact, we could find some research on micronutrients in dengue fever. A survey of micronutrients from the perspective of B12 concluded that dengue and non-dengue were not different according to B12 levels.[16] Ahmad S and colleagues found out in their review article that the role of micronutrients in dengue is inadequately studied and needs further work to make clear recommendations. In a recent review article,[17] Langerman SD and colleagues have concluded the same way.[18] So, the role of micronutrients in developing dengue and its related complications still needs to be explored in randomized controlled trials.

This is a small sample study, which limited its impacts. However, our results are collected honestly and accurately. We suggest and aim to do more extensive studies to observe the effects of multiple nutritional and non-nutritional factors to determine the fundamental elements affecting dengue-related cytopenia to make guidelines for effective management.

Conclusion

Dengue cytopenia is not correlated with differences in age, gender, residence and B12 levels. Confirmation of these findings and the search for other correlations between dengue and related complications demand further research work.

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ORIGINAL ARTICLE

Case-based learning with a twist: Testing the effectiveness of integrated case-based learning in an undergraduate dental curriculum

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A B S T R A C T

Introduction: Integrated Case-based learning (i-CBL) is a variation of traditional case-based learning in which integrated cases are developed to emulate real-life scenarios that healthcare practitioners encounter in everyday practice. This study explores the effectiveness and relative success of i-CBL pedagogy in an undergraduate dental curriculum.

Objective: To assess the impact of the i-CBL as a pedagogical strategy in an undergraduate dental curriculum..

Methodology: i-CBL was introduced in three years of a Bachelor of Dental Surgery (BDS) program. Cases based on integrated modules in the curriculum were developed and vetted by trained faculty. Students were also introduced to the i-CBL concept, and their detailed online feedback was taken on completing each i-CBL session in their academic year. Descriptive and analytic statistics were used for the Likert response data, and thematic analysis was conducted for the free text items.

Results: Eighty-three feedback questionnaires were collected from students throughout the year (18.2% first year, 47.5% second Year and 34.3% third Year). There was a significant difference in the students' perceptions regarding the conduct of the i-CBL over the three BDS years (p=0.00). However, there was no significant difference in their delivery by the concerned tutors (p=0.468) and the scenario construct (p=0.55). Thematic analysis of free text comments also highlighted overall student satisfaction with the i-CBL pedagogy.

Conclusion: This study highlights the value of introducing i-CBL. More focus on faculty training and the development of appropriate cases will be helpful for effective student learning.

Keywords: *Case-based learning, Dental Education, Integrated learning, Integration*

Introduction

Across the world, undergraduate (UG) medical and dental curriculum planners now accept the value and benefits of integrating curricular content to facilitate student learning, enhancing the motivation of the students and using critical thinking as a key to improving learning qualities typically overlooked in the formal traditional curriculum of students.[1] Integration enables students to become active learners and critical thinkers by developing their ability to apply knowledge in realistic, life-like scenarios or cases. They need to find, evaluate and utilize relevant information.[2] To inculcate these traits in individual learners, an environment of active learning and critical thinking needs to be promoted among the students

at the level of UG education by promoting student-centred pedagogical techniques.[3]

The health education curriculum has developed and implemented Multiple small-group teaching strategies according to available resources and student needs. These strategies aim to provide a learner-centred environment to the students. Case-based learning (CBL), team-based learning (TBL), and problem-based learning (PBL) are among the popular small-group teaching methods. PBL uses a guided learning format where learning takes place through problem-solving and self-study. The facilitator usually is only present at the second meeting. CBL is an inquiry-based learning format where a structured and critical approach is encouraged to solve clinical problems. Compared to PBL, CBL is less time-consuming and draws the students' focus to crucial points of the clinical case.[4]

Similarly, PBL is more complex and demanding because the students have to solve without the help from the instructor directly. At the same time, CBL is facilitated by an instructor who is a subject specialist and helps the students throughout the session. However, the success of each approach depends on how it is implemented and must be adapted to suit the student, instructor and available resources.[5, 6]

Case-based learning (CBL) is a student-centred learning approach designed around a clinical problem through which students identify their learning requirements, enquire, and correlate theory and practice.[6] Active participation of the students in case-based learning sessions enhances their ability to clinically apply their knowledge and become better prepared for patient treatment in workplace settings.[7, 8] CBL has emerged as a powerful tool in reforming traditional teaching methods with its group discussion-styled teaching approach. However, although CBL is a commonly used teaching modality in many institutions across the globe, cases developed by faculty are usually discipline-specific and may not adequately represent real-life scenarios.[9, 10]

The full benefits of integration can only be achieved when various teaching and learning activities within a curriculum are also developed and implemented consciously, keeping in perspective the integrated approach which may have been used to align the curricular content.[11] In line with this view, Integrated case-based learning (i-CBL), an innovation of CBL, seems to be a more suitable pedagogy for student learning. In i-CBL, cases are developed, emulating real-life scenarios where health professionals may face many problems in a single case.[12-14] Although much information exists on traditional discipline-focused case-based learning, we could not find much literature supporting the use of integrated case-based learning in UG Health Professions Education. The few studies that reported its use documented that i-CBLs provide students with a learning environment like actual practice with reality-based situations. Thus improving their professional encounters with their patients.[12, 13]

This study aims to evaluate the overall effectiveness of i-CBL as a pedagogy in undergraduate dental education and compares the success of i-CBL across basic, preclinical and clinical years in a UG dental program in Pakistan.

Methodology

Ethical approval for this study was taken from the Institutional Review Board (IRB) of the Shifa Tameer-e-Millat University (STMU) with approval number IRB # 093-22. All study participants provided their informed consent before participating in the study.

Study design:

A cross-sectional descriptive study was carried out using a self-administered questionnaire. The duration of the study was 8 months after the approval of the Institutional Review Board, Shifa International Hospital.

Study Setting:

The college where our study was conducted was established in 2020. The Bachelor of Dental Surgery (BDS) program at the college is a four-year undergraduate program with curriculum content integrated horizontally and vertically across the years. The curriculum content is integrated based on body systems and diseases, with separate integrated modules covering each component. In line with this vision and keeping in view the design of the curriculum, it was decided to introduce integrated case-based learning (i-CBL)

throughout the four curricular years to ensure the development of students' problem-solving and critical thinking abilities. To ensure that i-CBL was effectively implemented, faculty members were initially trained to develop i-CBL scenarios and conduct and evaluate an i-CBL session. After training, i-CBL scenarios were created by the faculty and reviewed by the Department of Medical Education. Introductory sessions about the i-CBL methodology and its implementation were held with students each academic year.

The i-CBL sessions were then conducted in various integrated modules in the three running years of the BDS program throughout the Academic Year 2022. Each integrated module had two separately dedicated i-CBL sessions placed near the completion of the module. i-CBL session 1 introduced the students to the case under discussion, provided them with the learning objectives and resources, and encouraged them to utilize their self-study skills. i-CBL session 2 focused on students discussing their proposed solutions to the case and addressing their queries. After the i-CBL session II, the students evaluated the entire i-CBL process by filling in an online feedback questionnaire focused on the three aspects covered in the faculty training session.

Participants

Dental students in the first three years of the BDS program who attended the i-CBL sessions at the end of each teaching module for the Academic Year 2022 were invited to provide feedback via an online questionnaire. Convenient sampling was used for the study. The inclusion criteria included:

1. Students willing to participate in the study.

2. All students who attend both i-CBL sessions during a particular module.

The exclusion criteria were as follows:

1. Students not willing to participate

2. Students who were not present in both i-CBL sessions.

Sample size: The sample size was not calculated as all participants meeting the inclusion criteria and providing informed consent were requested to participate.

Data collection:

The post i-CBL questionnaire consisted of 9 items divided into three sections related to the i-CBL scenario, i-CBL conduction and i-CBL tutor preparedness. Participants were also asked to fill in free text fields at the end of each section with suggestions for improvements in the scenario and conduct of the i-CBL, along with their feedback on the tutor.

A five-point Likert scale from strongly agree to disagree strongly was developed and divided into three sections, each with three more items. Each section also had a free text question at the end. The three educationists reviewed the questionnaire for face validity before administration to the participants. Pilot testing of the questionnaire was done on a sample of students from different academic years to ensure reliability.

After conducting the second i-CBL session, these questionnaires were shared with the students through Google Forms and data was collected online. All participants were requested to provide informed consent before completing the questionnaire.

No selection bias was identified. All students who agreed to participate and satisfied the eligibility criteria were included.

Data analysis:

The Likert scale responses for each variable were analyzed individually using descriptive statistics through SPSS (ver. 23.0; SPSS inc, Chicago, IL, USA). The sum of the responses for each of the three categories was also analyzed similarly. Pearson's chi-square test was performed to determine any statistical significance in the student responses for the three categories related to the construct of the i-CBL scenario, their conduction, and their delivery by the i-CBL tutors across the BDS years. Two authors (TS and LSA) analyzed the free text comments using open coding to generate initial codes. The codes were reviewed to identify and develop themes through further discussion between the same authors (TS and LSA).

Results

Quantitative Results:

Across the academic year 2022, 14 i-CBLs were conducted. A total of 183 participants filled in the feedback questionnaires, of which 18.2% were in the first year, 47.5% were in 2nd year, and 34.3% were in third Year BDS. The responses were anonymous, and descriptive data of the participants was not collected. The feedback survey was sent to all students who attended the i-CBL sessions. Students were repetitively invited to provide feedback after each i-CBL session they attended so that each i-CBL could be evaluated independently. The number of responses for each i-CBL session across the years can be seen in Figure 1.

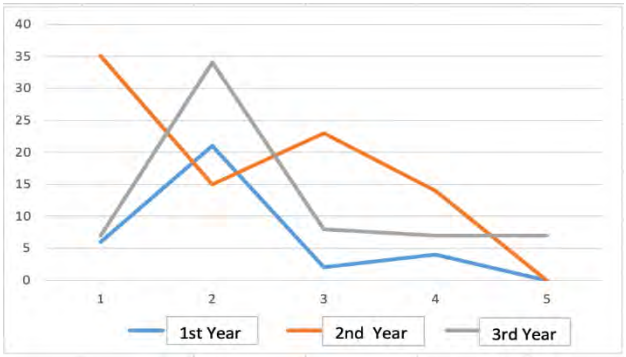

Figure 1: Number of responses received for each i-CBL session across 3 years of the BDS program.

Our results showed that in all three years of the BDS program, students were overall satisfied with the i-CBL pedagogy. Table 1.1 presents the mean and standard deviation values for student responses related to the construct of the i-CBL scenarios. Students from the 1st Year (M= 4.24 ± .867) were slightly less satisfied with the elaborateness of the i-CBL scenario as compared to the 2nd (M= 4.51±.834) and 3rd years (M=4.59±.557). This is also reflected in the response of the 1st year students regarding ease of discussion for the scenario (M=4.30+- .585).

Table 1.2 presents mean and standard deviation values for student responses related to the conduction of the i-CBL sessions. 1st-year students again felt that they were provided less time for preparation of i-CBL sessions (M= 3.76 ±1.347) compared to other years, while 2nd and 3rd years seemed satisfied not only with the preparation time for the i-CBL sessions but also the time provided for discussion during the i-CBL session itself.

Table 1.3 represents the mean and standard deviation values for the students' responses related to facilitation skills by the tutor. Responses showed high means regarding the encouragement of student participation (4.60±.703), maintaining the direction of the session (4.6±.680) and providing timely feedback (4.55±.754) from all three years.

Table 1.1: Mean and Std. Deviation values for the construct of the i-CBL scenario

Academic Year	1st Year	2nd Year	3rd year	Overall Score
	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD
The scenario was elaborate and had all the relevant information	4.24 ± 0.86	4.51 ± 0.83	4.59 ± 0.55	4.49 ± 0.76
The scenario was concise and clear	4.48 ± 0.56	4.49 ± 0.77	4.68 ± 0.53	4.56 ± 0.66
The scenario was easy to discuss	4.30 ± 0.58	4.54 ± 0.80	4.59 ± 0.58	4.51 ± 0.70

Table 2.2: Mean and Std. Deviation values for the conduct of the i-CBL session

Academic Year	1st Year	2nd Year	3rd year	Overall Score
	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD
Enough time was given for the preparation of i-CBL	3.76 ± 1.34	4.41 ± 0.99	4.62 ± 0.55	4.37 ± 0.99
Adequate time was available for discussion of i-CBL	4.00 ± 1.25	4.63 ± 0.74	4.51 ± 0.71	4.48 ± 0.87
The discussions facilitated learning and integration of concept	4.12 ± 0.89	4.55 ± 0.74	4.65 ± 0.51	4.51 ± 0.72

Overall responses show that the participants were satisfied with the facilitator and their preparedness. Students felt that the tutors not only encouraged equal participation of all students but also maintained the direction of the session and provided timely feedback. However, the participants reported that the i-CBL scenarios were not elaborate and needed improvement. Pearson's chi-square test was applied to determine any

statistical significance in the student responses for the three categories related to the construct of the i-CBL scenario, their conduction, and their delivery by the i-CBL tutors across the BDS years.

Table 3.3: Mean and Std. Deviation values for Facilitation by the i-CBL tutor

Academic Year	1st Year	2nd Year	3rd year	Overall Score
	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD
Encouraged equal participation of all students in discussion	4.55 ± 0.83	4.60 ± 0.75	4.63 ± 0.54	4.60 ± 0.70
Maintained the direction of the session	4.45 ± 0.79	4.63 ± 0.73	4.62 ± 0.52	4.60 ± 0.68
Provided timely feedback during the discussion	4.33 ± 0.99	4.62 ± 0.73	4.56 ± 0.61	4.55 ± 0.75

Our results show that there was a significant difference in the perceptions of the students regarding their conduct over the three BDS years. However, there was no significant difference in their delivery by the concerned tutors and the scenario construct, as shown in Table 2.

Table 4: Percentage agreement values and statistical relationship in each of the three categories across the three years of the BDS program

Academic Year	1st Year	2nd Year	3rd year	Chi-square Value	df	Asymptomatic significance
Construct of the i-CBL Scenario	86.6	90.2	92.2	3.045 (LR= 4.327)	4	0.55 (0.364)
Conduct of i-CBL session	79	90.6	91.8	27.622 (LR= 23.65)	4	0.00 (0.000)
Facilitation by the i-CBL tutor	88.8	92.2	92	3.563 (LR= 4.719)	4	0.468 (0.395)

Qualitative Results:

Two researchers (TS and LSA) analyzed the qualitative data manually. Codes were selected as words/statements., which gave concepts of the participant's perceptions. Similar codes were combined to develop themes. The main themes the participants highlighted were "Increase the number of i-CBL sessions" and "Facilitation by the i-CBL tutor". A few participant quotes are mentioned below in Table 3.

Discussion

Integrated case-based learning as a pedagogy has been well received by students studying in an undergraduate dental curriculum. Like any other pedagogy, the factors that aided in implementing i-CBLs successfully in our context were planned faculty trainings.[15, 16.] However, all the faculty were trained at the same level. Students in our program's first year experienced some difficulty understanding and discussing the integrated cases compared to students in preclinical and clinical years. This is understandable, as students in their first year usually adapt to a new, professionally-oriented curriculum and take time to grasp more contemporary pedagogies.[17, 18] Interestingly However, first-year students had difficulties regarding the i-CBL cases and conduct. They were delighted with their tutors. Therefore, in the coming years, we proposed to review the i-CBL cases and adapt them to cater to the level of our learners.

Our thematic analysis of student comments showed that most participants were satisfied with the i-CBL sessions. The participants were more eager to have i-CBL sessions than traditional teaching methodologies. Participants also indicated their satisfaction with the tutors involved in the i-CBLs, as they motivated them to have discussions and ask questions. The teacher's preparedness was reflected in the participant's responses, and their tutors answered most of their queries and difficulties during the discussions.

A recent systematic review on the effectiveness of case-based learning in Chinese dental education lists 21 studies that utilized case-based learning in various dental courses or specialities. [19] Almost all these studies

elucidate the benefits of case-based learning in independent or separate specialities but do not provide evidence of developing integrated cases. It must be noted that the aim of any undergraduate health professions education degree is usually to produce a general practitioner, and general practitioners are exposed to patients with an array of complaints which fall in the domain of multiple specialities. Thus, an undergraduate program requires students to be exposed to various integrated real-life scenarios or cases that can better prepare them for practice. Our results are similar to the few studies on i-CBL,[12, 20] that we could find in the literature. We feel that this study will be helpful for educators planning to introduce i-CBL in undergraduate Health Professions education curricula. One of the aims of modern-day professional education is to ensure that future professionals develop self-directed and lifelong learning skills, and the i-CBL pedagogy can also be a valuable aid in achieving this aim in all phases of undergraduate education.

Table 5: Qualitative quotes by the participants

Domain	Participant quotes
Increase the number of i-CBL sessions.	"There should be more CBLs in one module."
	"We want more CBLs in the module…."
	"Consider more CBLs for better presentations."
Facilitation by the i-CBL tutor	"Provides all information concisely and clearly."
	"Asked thought-provoking questions and provided enlightening information."
	"Allowing all students to speak comfortably while also asking relevant questions."
	"Cooperative, helpful understanding and has full knowledge of the topic."
	"Maintained discipline and encouraged participation."
	"She had good communication, motivation, enthusiastic, friendly and encouraged independence."

We advocate that further implementation and research on the i-CBL pedagogy in undergraduate health professions curricula will benefit students and better prepare them to become active and self-directed learners.

Conclusion

This study provides evidence of the effectiveness of the i-CBL pedagogy in the undergraduate dental curriculum. Curriculum planners and faculty involved must also ensure that i-CBL cases are planned and developed keeping in view the curriculum structure and context, along with the level for learners for which they are intended. The authors acknowledge that the main limitation of our study is that it is a single-centre study. However, our integrated dental curriculum based on our i-CBL strategy is unique yet implemented only in our institution.

We also acknowledge that since our students were asked to provide feedback on the same questionnaire throughout the year, they may have been affected by repetition bias regarding the conduct of the i-CBL sessions. This study shall be helpful for the medical teachers in planning and implementing i-CBLs, keeping in mind the aspects reported by the students to have halted their learning and preparedness for the sessions. The teachers can be given training mainly focusing on constructions of i-CBL scenarios for smooth implementation and effective student learning.

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ORIGINAL ARTICLE

Qualities of good medical teacher as perceived by medical (MBBS) students of a private medical college in Lahore, Pakistan.

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A B S T R A C T

Introduction: In human societies, teaching and teachers play a fundamental role, and a teacher is more than just an educator. Qualities determining a teacher to be a role model are intricate and broad. The present research aims to analyze the perceptions of medical (MBBS) students towards the personality traits and qualities of an excellent medical teacher so that we can adequately set standards for our teaching philosophy.

Methodology: This observational cross-sectional study was conducted at Azra Naheed Medical College, Superior University Lahore. After informed consent, 200 medical (MBBS) students of both genders participated in the study. Each student filled out a questionnaire compromising the qualities of an excellent medical teacher. All the data was entered and analyzed through SPSS, version 23.

Result: According to the student responses, the most commonly agreed factor for an excellent medical teacher was 'Medical Teacher uses simple language' reported by 113 (56.5%) students, followed by 'Medical Teacher uses technology' in 107 (53.5%), 'Medical Teacher has command on the subject' in 106 (53.0%), 'Medical Teacher is enthusiastic about the subject' 105 (52.5%), 'Medical Teacher summarizes topic at the end of the lecture' 105 (52.5%), 'Medical Teacher announces topic one week before lecture' 96 (48.0%), Textbooks are allowed by Medical Teacher during lectures' (94 (47.0%), 'Medical Teacher begins class by asking questions related to the topic' 86 (43%), students reported 'Handouts are given to students by medical teacher' 83 (41.5%) and 61 (30.5%) students said 'There are breaks for discussions and group activities for students during class'.

Conclusion: According to medical (MBBS) students, an excellent medical teacher uses simple language technology, has command of the subject, is enthusiastic and summarizes the topic at the end of the lecture.

Keywords: *Medical Teacher, Medical Students, MBBS, Lecture, Medical College.*

Introduction

As a diverse and continuously evolving race, human beings are adaptive and responsive to environmental changes and alterations. The capability to transfer knowledge is a primary reason for this continual progression in human lives. Therefore, in human societies, teaching and teachers play a fundamental role. However, a teacher is more than just an educator. Qualities determining a teacher to be a role model are intricate and broad.[1] The approach to teacher education varies from institution to institution, but the educational aim remains the

same: to develop effective and competent graduates. For this purpose, a teacher must be more than an educator.[2] The teacher's foremost duty is to support students' intellectual/creative development and ethical dimensions, including motivation, character, and self-esteem.[3] Teaching is not an easy responsibility in the present era.

A teacher should be flexible and versatile, have much enthusiasm for the subject, have a caring attitude towards students, have a thorough understanding of their subject and have much involvement with parents.[4] According to Strong et al., a good teacher's responsibility is to create an environment that motivates and intrigues students based on trust, respect, and fairness, wherein a positive learning climate is maintained and cultivated.[5]

According to Walker et al., five characteristics of a good teacher, as described by students, were: he is punctual, the most creative teacher, funny, gives respect to all students, and kind and empathic.[6] Arnon et al. mentioned another quality that plays a tremendous part in a teacher's personality: being considerate, understanding, caring and patient.[7] Bakx et al., in the project 'View of characteristics of good primary school teacher' in the Netherlands, indicated that a good teacher's qualities included a teacher's personality, professional role, pedagogic skills, and authority figure while supporting and encouraging the students.[8] The present research aims to analyze students' perceptions towards the personality traits of an ideal medical teacher so that we can set standards for our teaching philosophy.

Methodology

This observational cross-sectional study was carried out at Azra Naheed Medical College, Superior University Lahore, to determine medical (MBBS) students' views about the qualities of an excellent medical teacher by taking their feedback on a pre-designed questionnaire. Medical students from MBBS classes of both genders were included in the study. Students of paramedical and non-medical fields were excluded from the study. After informed consent, 200 medical (MBBS) students participated in the study. Each student filled out a questionnaire compromising demographic information and the qualities of an excellent medical teacher. The qualities asked included the medical teacher announcing the topic one week before class, the medical teacher being enthusiastic about the subject, the medical teacher beginning class by asking questions related to the topic, the medical teacher using technology, their breaks for discussions and group activities for students during class, the medical teacher uses simple language, handouts are given to students by medical teacher, textbooks are allowed by the medical teacher during lectures, medical teacher summarizes the topic at end of class, and medical teacher has command on subject.

All the data was entered and analyzed through SPSS, version 23. Mean and standard deviations were calculated for quantitative variables, while frequency and percentages were generated for qualitative variables. A chi-square test was applied, taking $p<0.05$ as significant.

Results

200 students participated in the study after informed consent, of which 122 (61.0%) were males and 78 (39.0%) were females. The mean age of the participants was 21.3+3.8 years. Sixty-eight (34.0%) students belonged to rural regions compared to 132 (66.0%) from urban areas. Based on their MBBS year, 55 (27.5%) students were from the second year, followed by 51 (25.5%) from the fourth year, 36 (18.0%) first year, 33 (16.5%) third year and 25 (12.5%) students were from final year. The distribution of gender and background regions in each class (Table 1).

Table 1: Background region and Gender distribution of the students according to their MBBS year

Demographic Variable	1st Year	2nd Year	3rd Year	4th Year	Final Year
Background region					
Rural	18 (9.0%)	16 (8.0%)	14 (7.0%)	13 (6.5%)	08 (4.0%)
Urban	18 (9.0%)	40 (20.0%)	19 (9.5%)	37 (18.5%)	17 (8.5%)
Gender distribution					
Male	22 (11.0%)	32 (16.0%)	20 (10.0%)	32 (16.0%)	16 (8.0%)
Female	14 (7.0%)	24 (12.0%)	13 (6.5%)	18 (9.0%)	09 (4.5%)

According to the student responses, the most commonly agreed factor for an excellent medical teacher was 'Medical Teacher uses simple language' reported by 113 (56.5%) students, followed by 'Medical Teacher uses technology' by 107 (53.5%), 'Medical Teacher has command on the subject' in 106 (53.0%), 'Medical Teacher is enthusiastic about the subject' 105 (52.5%), 'Medical Teacher summarizes topic at the end of the lecture' 105 (52.5%), 'Medical Teacher announces topic one week before lecture' 96 (48.0%), Textbooks are allowed by Medical Teacher during lectures' (94 (47.0%), 'Medical Teacher begins class by asking questions related to topic' 86 (43%), students reported 'Handouts are given to students by medical teacher' 83 (41.5%) and 61 (30.5%) students said 'There are breaks for discussions and group activities for students during class (Table 2).

Table 2: Analysis of student's response to the questionnaire

Questions	Students Response	Frequency	%age
Medical teacher announces topic one week before class:	Agree	96	48.0
	Strongly Agree	22	11.0
	Neither Agree Nor Disagree	31	15.5
	Disagree	30	15.0
	Strongly Disagree	21	10.5
Medical teacher is enthusiastic about subject:	Agree	105	52.5
	Strongly Agree	38	19.0
	Neither Agree Nor Disagree	29	14.5
	Disagree	19	9.5
	Strongly Disagree	09	4.5
Medical teacher begins class by asking questions related to the topic:	Agree	86	43.0
	Strongly Agree	36	18.0
	Neither Agree Nor Disagree	36	18.0
	Disagree	29	14.5
	Strongly Disagree	13	6.5
Medical teacher uses technology:	Agree	107	53.5
	Strongly Agree	35	17.5
	Neither Agree Nor Disagree	24	12.0
	Disagree	20	10.0
	Strongly Disagree	14	7.0
There are breaks for discussions and group activities for students during class:	Agree	61	30.5
	Strongly Agree	34	17.0
	Neither Agree Nor Disagree	20	10.0
	Disagree	51	25.5
	Strongly Disagree	34	17.0
Medical teacher uses simple language:	Agree	113	56.5
	Strongly Agree	42	21.0
	Neither Agree Nor Disagree	24	12.0
	Disagree	14	7.0
	Strongly Disagree	07	3.5
Handouts are given to students by Medical Teacher:	Agree	83	41.5
	Strongly Agree	29	14.5
	Neither Agree Nor Disagree	30	15.0
	Disagree	42	21.0
	Strongly Disagree	16	8.0
Textbooks are allowed by Medical Teachers during lectures:	Agree	94	47.0
	Strongly Agree	36	18.0
	Neither Agree Nor Disagree	41	20.5
	Disagree	17	8.5
	Strongly Disagree	12	6.0
Medical teacher summarizes the topic at the end of the lecture:	Agree	105	52.5
	Strongly Agree	46	23.0
	Neither Agree Nor Disagree	18	9.0
	Disagree	19	9.5
	Strongly Disagree	12	6.0
Medical teacher has command of the subject:	Agree	106	53.0
	Strongly Agree	68	34.0
	Neither Agree nor Disagree	17	8.5
	Disagree	06	3.0
	Strongly Disagree	03	1.5

Stratification of the 5 most common factors of a good medical teacher concerning the students' background, region, and gender (Table 3).

Discussion

According to Harding et al., a good teacher has acquired the attributes and competencies to excel as an educator, can communicate efficiently with students, loves the process of learning and genuinely enjoys sharing the passion of teaching by engaging in various pedagogical practices to engage learners.[9] They know how to negotiate, mediate and invite students to participate actively in their learning. Prompt identification of academic weaknesses and subsequent interventions improves retention, academic performance and course commitment.[10]

A credible student feedback process may be employed to modify and enhance teaching practices according to available resources and learning objectives.[10, 11] Lectures, a large-group teaching method, are a mainstay in medical teaching. Lectures are an easy and convenient method of imparting knowledge to many students, especially in settings with limited resources. Therefore, an excellent

medical teacher should equip the students with various tools to engage them and enhance their learning.

Table 3: Stratification of the 5 most common factors of a good medical teacher with regards to the background region and gender of the students.

Background & Gender	Agree	Strongly Agree	Neither Agree nor Disagree	Disagree	Strongly Disagree	p-value
Medical teacher uses simple language:						
Rural	35 (17.5%)	15 (7.5%)	09 (4.5%)	05 (2.5%)	04 (2.0%)	0.028
Urban	78 (39.0%)	27 (13.5%)	15 (7.5%)	09 (4.5%)	03 (1.5%)	
Male	76 (38.0%)	23 (11.5%)	11 (5.5%)	07 (3.5%)	05 (2.5%)	0.036
Female	37 (18.5%)	19 (9.5%)	13 (6.5%)	07 (3.5%)	02 (1.0%)	
Medical teacher uses technology:						
Rural	32 (16.0%)	18 (9.0%)	08 (4.0%)	06 (3.0%)	04 (2.0%)	0.005
Urban	75 (37.5%)	17 (8.5%)	16 (8.0%)	14 (7.0%)	10 (5.0%)	
Male	69 (34.5%)	22 (11.0%)	19 (9.5%)	08 (4.0%)	04 (2.0%)	0.041
Female	38 (19.0%)	13 (6.5%)	05 (2.5%)	12 (6.0%)	10 (5.0%)	
Medical teacher has command of the subject:						
Rural	33 (16.5%)	27 (13.5%)	05 (2.5%)	03 (1.5%)	01 (0.5%)	0.691
Urban	72 (36.0%)	41 (20.5%)	13 (6.5%)	03 (1.5%)	02 (1.0%)	
Male	66 (33.0%)	41 (20.5%)	08 (4.0%)	05 (2.5%)	02 (1.0%)	0.608
Female	39 (19.5%)	27 (13.5%)	10 (5.0%)	01 (0.5%)	01 (0.5%)	
Medical teacher is enthusiastic about the subject:						
Rural	42 (21.0%)	11 (5.5%)	09 (4.5%)	05 (2.5%)	02 (1.0%)	0.450
Urban	63 (31.5%)	26 (13.0%)	21 (10.5%)	14 (7.0%)	07 (3.5%)	
Male	64 (32.0%)	22 (11.0%)	17 (8.5%)	10 (5.0%)	09 (4.5%)	0.881
Female	41 (20.5%)	15 (7.5%)	13 (6.5%)	09 (4.5%)	00 (0.0%)	
Medical teacher summarizes the topic at the end of the lecture:						
Rural	39 (19.5%)	16 (8.0%)	05 (2.5%)	07 (3.5%)	02 (1.0%)	0.883
Urban	66 (33.0%)	30 (15.0%)	13 (6.5%)	12 (6.0%)	10 (5.0%)	
Male	69 (34.5%)	22 (11.0%)	10 (5.0%)	12 (6.0%)	09 (4.5%)	0.430
Female	36 (18.0%)	24 (12.0%)	08 (4.0%)	07 (3.5%)	03 (1.5%)	

In the present study, most students (55, 27.5%) were from second year MBBS, followed by 51 (25.5%) from fourth year MBBS. The most agreed factor for an excellent medical teacher in the present study was 'Medical Teacher uses simple language,' which 113 (56.5%) students reported. Other essential factors reported by medical (MBBS) students in the present study were 'Medical Teacher uses technology' by 107 (53.5%) students, 'Medical Teacher has command on the subject' in 106 (53.0%), 'Medical Teacher is enthusiastic about the subject' 105 (52.5%) and 'Medical Teacher summarizes topic at the end of the lecture' 105 (52.5%).

According to students' views, an excellent medical teacher should introduce the relevance of the topic, which can help students develop into engaged, motivated and self-regulated learners. Relevance is the perception that something is exciting and worth knowing. An excellent medical teacher should be able to communicate ideas effectively and straightforwardly.[12.]

A good teacher should be kind, have a big heart, and always be ready to listen.[13, 14] Good lectures trigger enthusiasm, and teachers are often passionate about the subject they teach, even if it is not that exciting.[15] As an aid to learning, laughter should be applied during lectures as it helps relieve students' pressure by lightening the tone and providing a minor break from what may seem like a lengthy, monotonous session. Furthermore, laughter and humor also help as memory triggers.[11]

Recommendation

A few recommendations to be considered are:

1. Teach skills, not just facts.
2. Make room for new content.
3. Focus more on student's learning.
4. Use simple language to make things easier.
5. Use audiovisual aids and more discussion regarding clinical and recent advances.
6. More animations/videos can be introduced for specific topics.
7. Facilitation of interactivity or self-directed learning (SDL) among students should be included.

Conclusion

According to medical (MBBS) students, an excellent medical teacher uses simple language technology, has command of the subject, is enthusiastic and summarizes the topic at the end of the lecture. It is important to consider students' views so that appropriate changes may be made in teaching styles to improve student learning.

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ORIGINAL ARTICLE

Prevalence and awareness of polycystic ovarian syndrome among medical students of Karachi, Pakistan.

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Author's Contribution

[1] Data analysis, result

[2] Literature review

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A B S T R A C T

Introduction: PCOS is the most common condition experienced by females of reproductive age across all ethnicities and cultures worldwide. The term "polycystic" refers to several cysts or many cysts, each harboring an immature egg.

Objective: The objective of this study is to determine the prevalence and awareness among female medical students regarding polycystic ovarian symptoms in Karachi.

Methodology: A cross-sectional study was conducted with a sample of 377 medical students, and data was collected using a questionnaire-based survey.

Results: The results revealed that 77.2% of participants showed awareness of PCOS. 10.9% were diagnosed with PCOS, and all of them were taking medication for this syndrome. However, 63.9% had regular menstrual cycles.

Conclusion: Most of the sample population was aware of PCOS. 10.9% were diagnosed with PCOS.

Keywords: *Awareness, Female medical students, Polycystic Ovary Syndrome.*

Introduction

Polycystic Ovarian Syndrome (PCOS) is known to be the most common condition experienced by females of reproductive age across all ethnicities and cultures worldwide.[1] Several cysts are present in the ovary containing immature eggs. As the eggs are immature, ovulation does not occur. This leads to alteration in levels of estrogen, progesterone, FSH, and LH. On the other hand, androgen will be higher than usual, but estrogen and progesterone will be lower.[2, 3] The leading cause of PCOS is uncertain; however, many researchers have recognized that changing lifestyles like dietary changes, lack of exercise, insulin resistance and genetic predisposition may also lead to PCOs.[4] Although previously believed to be an endocrine condition, PCOS is a broad-spectrum, multi-organ syndrome whose symptoms extend beyond the reproductive system and lead to significant metabolic disorders as well as psychological consequences.[5] There is a vast diversity in the symptoms of PCOS; these may include sleep apnea,[5] hirsutism,[6] amenorrhea,[7] oligomenorrhea,[8] acne,[9] anxiety, depression,[10] obesity[11] and type II diabetes.[12]

The widely used criteria for diagnosis of PCOS are Rotterdam Criteria.[13] Three features out of these two need to be present to confirm the diagnosis. These features are Oligomenorrhea or Amenorrhea and Hyperandrogenism, whether based on clinical findings or biological signs. Lastly, the presence of poly cysts on ultrasound scans. Most physicians use the Rotterdam Criteria for diagnosis.[16] Many of the patients suffering from PCOS have psychosocial impairments as well, but these are not well acknowledged. Many young physicians are likely to prescribe lifestyle modification along with medication for improvement in the condition.[16, 17] There are comorbidities related to the cardio-metabolic system

which are found to be associated with PCOS. Along with this, anxiety and depression were also associated with PCOS.[18] Quality of life is significantly affected by different symptoms.[19] A misperception regarding the condition is present among the population.[20] Studies show that females are well aware of the term [21] but a lack of awareness is found regarding complications associated with PCOS.[22] Also, females suffering from the condition tend to neglect to visit a gynecologist until and unless the condition becomes life-threatening.[23] An increase in BMI may tend to be a risk factor.[24] It is also reported that early detection and diagnosis of PCOS may help improve the individual's quality of life.[25]

The condition is very common however, according to Tahir H et al., among MBBS & BDS students, the prevalence of PCOS is 11.2%, and most of them seek treatment. Family history, diabetes, hypertension and other endocrine disorders have positive associations with the condition.[26] Zulfiqar S et al. showed that around 50% of females have suffered from one or other features of PCOS like obesity, facial hair growth, irregular periods/ menstrual flow, acne, etc.[27] Zafar et al. showed that its prevalence is 55.41% in the general population with the most common complaint to be irregularity in menstruation, hirsutism, acne obesity and infertility. Most of the patients suffering from PCOS are either overweight or obese. In recent years, its incidence has increased. Lifestyle changes have also rapidly changed in recent years. The dietary patterns and habits have altered a lot. All these changes also have effects on hormonal disturbances. These may directly or indirectly lead to the development of PCOS.[28]

PCOS has many symptoms that directly or indirectly affect the individuals' performance and quality of life.[19] Although people are aware of the term and suffer from various symptoms related to it.[28] PCOS is a misdiagnosed problem of reproductive-age females.[29] This study was planned to check the prevalence and awareness of PCOs among the medical students of Karachi, Pakistan, comprising MBBS, BDS and DPT.

Methodology

It was a quantitative cross-sectional study conducted through convenience purposive sampling techniques from different medical universities in Karachi. The study duration was six months. The sample size was 377, which Rao Soft online sample size calculator determined. Undergraduate female medical students from the first to the final year were included. The questionnaire was adopted from Tahir H et al. 2020. [28] It was distributed among the recruited participants who fulfilled the inclusion criteria: female undergraduate medical students from their first to final year. Informed consent was signed. The data was analyzed using SPSS version 20, which calculated the descriptive statistics.

The study's permission was obtained by coding from the Institutional Ethical Review Committee, Isra Institute of Rehabilitation Sciences, Isra University Karachi Campus.

Results

The 377 female medical students were included in the study. Among them, 25.5% were from the first year, 24.7% from the second year, 28.9% from the third year, 9.8% from the fourth year and 11.1% from the fifth year. 77.2% of participants were aware of the term PCOS. 10.9% of the respondents were diagnosed with PCOS, and all of them were taking treatment for it (Figure 1 to 4).

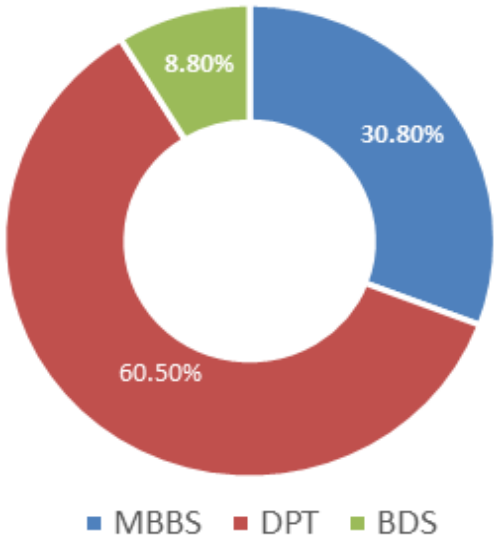

Figure 1: Distribution of respondents based on program of study

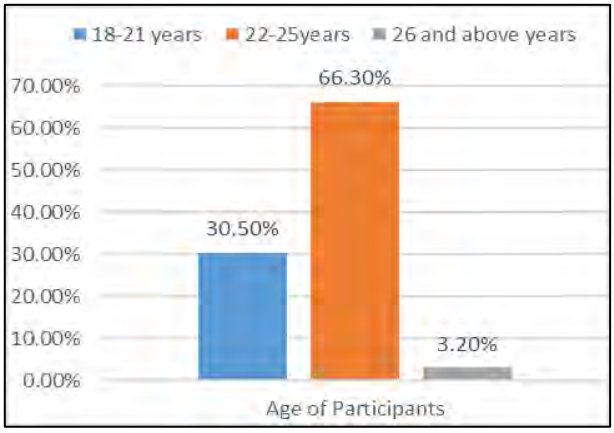

Figure 2: Age of Participants

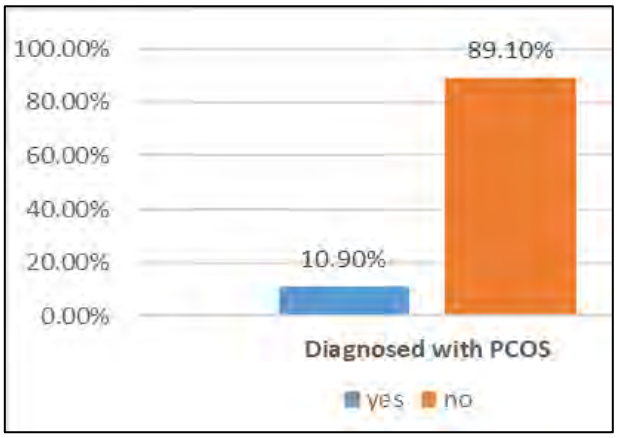

Figure 3: Diagnosed with Polycystic Ovary Disease

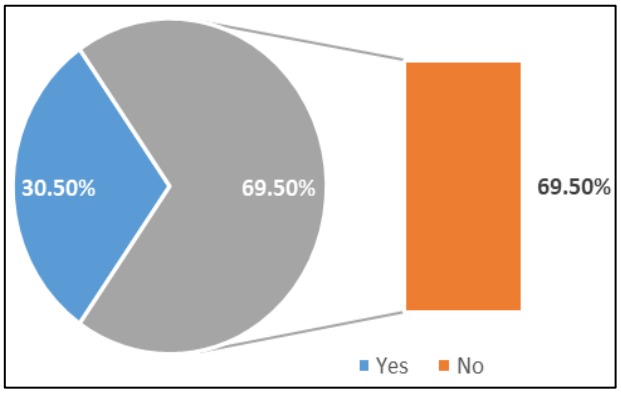

Figure 4: Responses regarding the question whether the participant's mother or at least one of your sisters also had similar symptoms

Discussion

According to one study, there is an effort to make better knowledge in students so that early cure and management of PCOS could be possible, while this study suggests that 77.2% of participants were aware of the term PCOS.[32] In another study, 74.5% of the individuals knew about the disease.[28] In this study, 28.10% of students heard about PCOS from University, 7.7% from hospitals, 14.6% from other people, 28.6% from the Internet or social media, 0.8% from television and 20% students were not aware at all, and Hamyel Tahir et al. found that 42.2% individuals aware from social media or Internet and the diagnosed cases was 11.2% while according to this study 10.9% of the participants was diagnosed with PCOS.[28]

Madhumati Chatterjee and Soma Aditya Bandyopadhyay suggested in a study that about 28% of participants were at high risk of PCOS. 85% of cases suffered from irregular and inconsistent menstrual blood flow, 19% had excessive facial hairs, 41% faced acne problems, 63% were affected with emotional issues, and 22% of participants had a family history. While the results of this study, we found that 36.15 participants suffered from irregular menstrual cycles, 30% had acne, 58.1% experienced excessive facial or body hair, 41.4% faced hair loss, 37.7% suffered from excessive weight, 70% affected from mood swing, 58.9% disturbed from loneliness or lack of interest and got aggressive,12.5% had change in voice quality, 44.8% involved with frequent headache,39.8% affected from chronic low back pain, 56.5% get tired quickly and 53.1% had family history of diabetes, hypertension or other endocrine disorder.[33]

According to one study, females having menorrhagia are affected by polycystic ovaries more than females having regular menstrual cycles.[33] In another research, generally worldwide, the quality of life of females is meaningfully affected due to PCOS.[32] During teenage years, many psychological and bodily changes occur that coincide with the symptoms of PCOS. That might be a significant challenge in finding out during this age, but for an adult woman, there are diagnostic criteria.[35]

One study shows that there is insufficient information and awareness about PCOS among medical and dental students. According to the results, 61.9% of the female students did not know enough about how this disease could be caused.[31] As in this study, 89.10% of students were not diagnosed with PCOS. According to one research, 71.7% of students thought that the most typical

indication of PCOS is an irregular menstrual cycle. Another study suggested that 42.2% of female students got awareness about PCOS from social media and the Internet, and in this study, 28.60% of students were informed by social media and the Internet. [28]

Sharifa M. Gaferi et al. suggested in their study that 66.3% of the females having PCOS were unaware of the hazards and symptoms of PCOS because of deficient discussions or awareness programs or social gatherings in the facilitation of female reproductive health in society at the school level and family.[33] While in this study, 20.20% of the female students had not heard at all about PCOS. Women are the core building blocks of society, family, and community. At childbearing age, there are many distresses faced by women physically and mentally, which can affect women's reproductive health related to PCOS and could cause the quality of life; hence awareness, enough knowledge about PCOS and a healthy lifestyle would help maintain reproductive health of females, and according to the study young females have not enough knowledge about PCOS and its early identification and prevention.[31] In the literature, there is a lack of awareness about PCOS, which is an indication that unsuitable deeds affecting lifestyle might lead females to PCOS, while this research also indicates less knowledge and understanding among students about PCOS. [35]

Table 1: Responses to questions related to symptoms

Items related to symptoms of PCOS	Yes (%)	No (%)
Do you suffer from irregular menstrual cycles or no menstrual cycles?	36.1	63.9
Do you suffer from acne or oily skin?	30.5	69.5
Do you experience excessive facial or body hair?	58.1	41.9
Do you suffer from hair loss or hair loss in a particular area of the hair?	41.4	58.6
Do you suffer from weight gain?	37.7	62.3
Do you suffer from mood swings?	70	30
Do you feel lonely, lose interest, or very aggressive frequently?	58.9	41.1
Do you experience frequent headaches or dizziness?	44.8	55.2
Do you suffer from chronic, frequent lower back pain?	39.8	60.2
Do you observe any change in voice?	12.5	87.5
Do you get tired quickly/or feel weak?	56.5	43.5
Do you have a family history of diabetes, hypertension or other endocrine disorders?	53.1	46.9

Conclusion

The results show that the level of awareness regarding PCOS among medical students is deficient. Furthermore, significant sources of understanding are universities and social media. Most participants had various associated symptoms, but only a few were diagnosed with PCOS. It is recommended that future studies include the male population to determine their level of awareness and knowledge regarding this female related issue and that awareness sessions should be conducted to overcome the dire need.

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ORIGINAL ARTICLE

Frequency and pattern of female genital tract malignancies in patients presenting with gynecological problems

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[1] Conception, design, drafting the article, data collection and analysis

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A B S T R A C T

Introduction: Significant morbidity and mortality is caused by cancers in women all over the world. Cancers of the female reproductive organs are called genital tract cancers. They include cervical cancer, ovarian cancer, endometrial cancer, vaginal carcinoma, cancer of the fallopian tubes and gestational trophoblastic tumor. After breast carcinomas, they account for the second most common carcinomas in females. This study will collect data from the local population and will enhance existing knowledge.

Objective: This study aimed to find the frequency of female genital tract malignancies in patients presenting with gynecological problems.

Methodology: This cross-sectional study was conducted from 1 June 2018 to 31 May 2022. After taking written informed consent, 256 patients presenting to Gynae A Unit, Ayub Teaching Hospital, Abbottabad, were included in the study. Patients with a history of menstrual irregularities, vaginal bleeding, abdominopelvic pain or mass were included, while those presenting with other gynecological problems were excluded. The confirmed diagnosis was made based on histopathology reports by the consultant pathologist of the laboratory in the hospital after the patient's surgery.

Results: Out of the 256 patients, 30 (11.71%) had female genital tract malignancies. The mean age was 48.79 years, and the standard deviation was 12.93 years. 17 patients (56.66%) had ovarian cancer, 5 (16.66%) had cervical cancer, 7 (23.33%) had endometrial cancer, and 1 (3.33%) had vaginal cancer. Ovarian cancer was the most common (56.66%), followed by endometrial cancer. Serous adenocarcinoma of the ovary was the most frequent type (26.66%). There was no significant difference in the proportion of malignancies between different age groups and between differences in parity.

Conclusion: The percentage of female genital tract malignancies in patients with gynecological problems is relatively high (11.71%), with serous adenocarcinoma of the ovary being the most common malignancy. Developing and implementing an effective health policy regarding early cancer detection and treatment is necessary.

Keywords: *Female genital tract malignancies, Ovarian carcinoma, Endometrial carcinoma, Cervical carcinoma, Vaginal carcinoma.*

Introduction

Significant morbidity and mortality are caused by cancers in women all over the world.[1] Cancers of the female reproductive organs are called genital tract cancers. They include cervical cancer, ovarian cancer, endometrial cancer, vaginal carcinoma, cancer of the fallopian tubes and gestational trophoblastic tumour.[2] After

breast carcinoma, these account for the second most common carcinomas in the female population.[3] The burden of carcinomas differs in various places due to ethnic background, environmental and cultural factors, and socioeconomic status. In developed countries, the cancer burden is higher as compared to developing countries, but more people die from it in developing countries.[4]

Out of all female genital tract malignancies encountered, cervical carcinoma is most typical in underdeveloped countries [5] in Pakistan, ovarian cancer is found to be the most frequently found.[6] In developing countries like Pakistan, most of the patients with female genital tract malignancies are encountered with advanced stage of disease. The reason is the absence of attainability of effective screening tools, treatment and facilities to diagnose cancer.[7]

Early detection of cancers is closely associated with better survival and cure rates. In developed countries, the most common gynecological cancer is ovarian cancer, which has non-specific symptoms and late detection of the tumor. Most of the patients are diagnosed in stage 3 or 4. In the absence of screening, its diagnosis in the advanced stages leads to fatality.[8] Options for prevention, detection, treatment, and palliative care for female genital tract malignancies are available. However, mortality from these cancers will exist unless means are adopted to control them in low-resource populations.[9]

Female genital tract malignancies vary with age. In the age group of 21 to 30 years, ovarian carcinoma is the most frequent, while in postmenopausal women, cervical carcinoma has the highest frequency.[9] Endometrial malignancies are most frequently present in older age groups.[10] The distribution of female genital tract cancers was studied by Jeph V et al. 67.2% of the cases were cervical cancers, 21.8% were ovarian cancers, 4.3% were endometrial, and no vaginal cancer was present among the patients studied.[11] This study aims to determine the frequency of female genital tract malignancies in the local population and will enhance existing knowledge. This may also help generate valuable data to build Pakistan's national cancer registry.

Methodology

This cross-sectional study was conducted from 1 June 2018 to 31 May 2022 after getting approval from the hospital's ethical and research committee. Patients meeting the inclusion criteria and seeking admission to Gynae A Unit, Ayub Teaching Hospital, Abbottabad, were included in the study after taking written informed consent. Patients of 18 to 70 years with a history of menstrual irregularities, vaginal bleeding, abdominopelvic pain or mass were included in the study, while those presenting with other gynecological problems were excluded. The confirmed diagnosis of female genital tract malignancy was made based on histopathology reports by a consultant pathologist of the laboratory in Ayub Medical College, Abbottabad, after surgery on female genital tract patients. The sample size was 256, calculated using the World Health Organization software "Sample size determination in health studies", assuming a confidence level of 95%, absolute precision of 4% and anticipated frequency of female genital tract malignancies to be 12.09%. [11] The sampling technique was non-probability consecutive sampling.

Data was analyzed by using SPSS version 21.0. Mean and standard deviation were calculated for numerical variables like age and parity. Frequencies and percentages were used for categorical variables like site of malignancy, type of malignancy and grade of malignancy. All results were presented in the form of diagrams and tables. The outcome variable was stratified by age and parity. The post-stratification chi-square test was used at a 5% level of significance.

Results

The sample size of our study was 256. Thirty patients (11.71%) were found to have female genital tract malignancies. Table 1 shows that 64 patients (25%) were aged 20 to 40. 62 (24.22%) had ages in the range of 41 to 50 years. 67 patients (26.17%) were in the age range of 51 to 60 years. 63 patients (24.61%) were aged between 61 and 70 years. The mean age was 48.79 years, and the standard deviation was 12.93 years. Table 2 shows that 17 out of 30 patients (56.66%) had ovarian cancer, 5 patients (16.66%) had cervical cancer, 7 patients (23.33%) had endometrial cancer and 1 patient (3.33%) had vaginal

cancer. Hence, ovarian cancer was the most common, followed by endometrial cancer.

Table 3 shows that 56 patients (21.88%) were nulliparous. 60 (23.44%) were primiparous, 66 (25.78%) were multiparous, and 74 (28.91%) were grand multiparous. Table 4 shows that 6 patients out of 30 were between 20 and 40, 7 were between 41 and 50, 10 were between 51 and 60, and 7 were 61 to 70 years old. Table 5 shows that 3 patients out of 30 were nulliparous, 5 were primiparous, 10 were multiparous, and 12 were grand multiparous. Table 6 shows that 19 out of 30 (63.33%) had low-grade malignancy, while 11 (36.66%) had high-grade malignancy. Table 7 shows the type of malignancy in patients. Serous adenocarcinoma of the ovary was the most frequently encountered type in our setup. 8 out of 30 patients (26.66%) had severe adenocarcinoma of the ovary. 5 out of 30 patients (16.66%) had mucinous adenocarcinoma of the ovary. 5 patients (16.66%) had squamous cell carcinoma of the cervix, 2 patients (6.66%) had mature cystic teratoma of the ovary, and 7 (23.33%) had endometrial adenocarcinoma. 1 patient (3.33%) had a mixed germ cell-sex cord-stromal tumor of the ovary, choriocarcinoma of the ovary and high-grade papillary serous carcinoma of the vagina each. No cases of vulval cancer or fallopian tube cancer were found.

Stratification of female genital tract malignancies concerning age and parity was performed. There was no statistically significant difference in the proportion of female genital tract malignancies between different age groups. Similarly, parity was also not associated with any statistically significant difference in the prevalence of female genital tract malignancies.

Table 1: Age Distribution (n=256)

Age (Years)	Frequency	Percentage
20- 40	64	25.00
41-50	62	24.22
51-60	67	26.17
61-70	63	24.61
Total	256	100

Table 2: Site distribution among 30 cancer patients

Site	Frequency	Percentage
Ovary	17	56.66
Cervix	5	16.66
Endometrium	7	23.33
Vagina	1	3.33
Total	30	100

Table 3: Parity of patients (n=256)

Parity	Frequency	Percentage
Nil	56	21.88
Primiparous	60	23.44
Multiparous (2-4)	66	25.78
Grand-multiparous (5 or more)	74	28.91
Total	256	100

Table 4: Stratification of malignancies concerning age

	Malignancy		
Years	Yes	No	Total
20-40	6	58	64
41-50	7	55	62
51-60	10	57	67
61-70	7	56	63
Total	30	226 $\pm$ 0.5	256 $\pm$ 0.5

Table 5: Stratification of malignancies parity

	Malignancy		
Years	Yes	No	Total
Nil	3	53	56
Primi	5	55	60
Multi	10	56	66
Grand-Multi	12	62	74
Total	30	226 $\pm$ 0.5	256 $\pm$ 0.5

Table 6: Grade of patients with malignancy

Grade	Frequency	Percentage
Low grade	19	63.33
High grade	11	36.66
Total	30	100

Table 7: Type of malignancy

Type	Frequency	Percentage
Mixed germ cell sex cord-stromal tumor ovary	1	3.33
Mature cystic teratoma of the ovary	2	6.66
High-grade papillary serous carcinoma of the vagina	1	3.33
Squamous cell carcinoma of the cervix	5	16.66
Adenocarcinoma endometrium	7	23.33
Mucinous adenocarcinoma of the ovary	5	16.66
Choriocarcinoma ovary	1	3.33
Serous adenocarcinoma of ovary	8	26.66
Total	30	100

Discussion

Female genital tract malignancies cause significant morbidity and mortality among women all over the world. Ovarian, endometrial, cervical and vaginal cancers are major female genital tract pathologies. Ovarian cancer is the seventh most frequently diagnosed genital cancer among women worldwide.[12] Approximately 239,000 cases and 152,000 mortalities worldwide are caused per year.[13] The cervical cancer incidence is from 8 to 30 newly encountered cases per 100,000 women per year, varying with differences in the countries and regions [14]. These tumors contribute to approximately half of all malignancies of the female genital tract.[15]

In our study, 30 (11.71%) patients were found to have female genital tract malignancies. The mean age of these patients was 48.79 ± 12.93 years. In our study, 24/ 30 (80%) were in their 5th decade or older, while 22/30 (73.3%) were either multi or grand multigravida. In a study in Haryana, India, most patients were from 51 to 60 years of age or older, and most were multiparous.[3] In Nigeria, the occurrence of all female genital tract cancers peaked between 46 and 60 years, which accounted for 32.3% of all cases.[16] Most patients (48.7%) had five or more previous pregnancies. A significant number of cases were found in patients with high parity. The red-flag symptoms of ovarian cancer are abdominal and pelvic pain, bloating and a feeling of fullness.[17] The most frequently found symptoms of endometrial cancer are vaginal discharge and abnormal uterine bleeding. Patients with advanced endometrial cancer may have symptoms the same as those with advanced ovarian pathology, such as abdominal or pelvic pain, distended abdomen, early satiation after food intake, or changes in bowel or urinary bladder functioning.[18]

Ovarian cancer was the most common in our study, followed by endometrial cancer. Among our patients, 17 (56.66%) had ovarian cancer, while 7 (23.33%) had endometrial, and 5 (16.66%) had cervical cancer. Similar to our study, the ovary was found to have the most number of patients in a study done in Jamshoro, Pakistan,[1] while in India, cervical cancer was found to be the most frequent.[3] Jamal et al. in Pakistan found ovarian cancer in 42.4% of their cancer patients, making it the most common cause of all female genital tract carcinomas in their study, followed by cervical cancer.[19] Cancer of the cervix was found in 66.3% of the cases, followed by ovarian cancer in 21.1% in a study conducted in Nigeria.[7] Another study from Nigeria reported that the most common gynecological cancer was cervical cancer (52.7%), with ovarian cancer being the second most common (28.1%). They found endometrial cancers in 10.2% of cancer patients.[16] A study conducted in Tehran showed that out of 450 cases, the highest percentage was ovarian cancer (55.5%). The uterine malignancies were second most common (24.9%), followed by cervical carcinomas (19.6%).[20] The incidence of cervical carcinomas is less in Pakistan than in developed nations. Despite this, the death rate is higher due to late diagnosis of cervical carcinoma,[21] the reason for which is the absence of a structured program for cervical cancer screening in Pakistan.[22]

Serous adenocarcinoma of the ovary was the most frequently encountered type in our setup (26.66%). Among ovarian tumors, serous cystadenocarcinoma was the most common cancer found in Delhi, India, [23] whereas Ahmed et al. found mucinous cystadenocarcinoma to be the most frequent in their study. [4] Our results show that 19 out of 30 (63.33%) patients had low-grade malignancy while 11 (36.66%) had high-grade malignancy. On the contrary, a Nigerian study found that 60.5% of cases presented in advanced stages of the disease.[16] There was no statistically significant difference in the proportion of female genital tract malignancies between different age groups. Similarly, parity was also not associated with any statistically significant difference in the prevalence of female genital tract malignancies.

Conclusion

Our study concludes that the percentage of female genital tract malignancies in patients with gynecological problems is relatively high (11.71%), with serous adenocarcinoma of the ovary being the most common malignancy. The majority of the cases presenting at an advanced stage suggest a need for the development and implementation of an effective health policy regarding early cancer detection and treatment.

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ORIGINAL ARTICLE

Frequency of Vitamin D deficiency in women with polycystic ovarian syndrome

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Author's Contribution

[1, 3] Study design, Data collection, Critical review, Final approval.
[2,4,5] Manuscript writing, Critical review, and Final approval.

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A B S T R A C T

Introduction: Approximately 20% of women who are of reproductive age suffer from the common endocrine illness known as polycystic ovarian syndrome, or PCOS. Vitamin D insufficiency is common among PCOS-affected women. The symptoms of PCOS seem to be regulated by the vitamin D pathway. According to studies, women with PCOS had high frequencies of vitamin D insufficiency, ranging from 65.0% to 70.3%. Thus, we aimed to discover how common vitamin D deficiency was in women diagnosed with PCOS.

Methodology: This cross-sectional study was conducted at the Department of Obstetrics & Gynecology, CMH- Rawalpindi, from January to July 2022. A total of 90 women with polycystic ovarian syndrome diagnosed on Rotterdam criteria, 18 to 40 years of age, were included through a non-probability consecutive sampling technique. Pregnant female patients with chronic illnesses were excluded. After informed consent, data was collected from patients on a self-developed questionnaire. In all patients, a 3 ml blood sample was taken and sent to the institutional pathology laboratory to measure vitamin D levels.

Results: The patients' average age was 28.91 ± 4.85 years—ages 18 to 30 comprised most of the 48 patients (53.33%). The average time a person had PCOS was 3.64 ± 1.58 years. The average body mass index was 29.02 ± 2.43 kg/m^2. Forty-one (45.56%) of the PCOS patients had vitamin D insufficiency.

Conclusion: As the frequency of vitamin D deficiency in women with PCOS is relatively high, we recommend that early identification through screening of the affected patients should be done.

Keywords: *Polycystic ovarian syndrome, Vitamin D deficiency, Insulin resistance, Metabolic syndrome.*

Introduction

Polycystic ovary syndrome (PCOS) is a prevalent endocrine system pathology that affects up to 20% of females in their reproductive age.[1] The exact prevalence is uncertain due to the lack of precise definition, but it is estimated to be 5-10% among women of reproductive age. The new Rotterdam criteria suggest that the prevalence in the general female population will increase to 10%.[2] Globally, PCOS affects approximately 2.2 to 26% of women, with roughly 1 in 15 women being affected. In India, the prevalence is exceptionally high, with 36% of women suffering from PCOS.[3] PCOS is a leading cause of female infertility and is characterized by symptoms such as anovulation-oligomenorrhea, amenorrhea, polycystic ovaries on ultrasound, excess androgenic hormones (leading to hirsutism, acne, alopecia, and seborrhea), and insulin resistance.[4]

Women with PCOS are also more prone to mental disorders such as anxiety, depression, binge eating disorder and even bipolar disorder.[5] PCOS is associated with excessive androgen secretion, which leads to increased estrogen production and disrupts folliculogenesis.[6] Hyperandrogenism and insulin resistance contribute to chronic anovulation and infertility in PCOS patients.[7] The body's resistance to insulin plays a critical role in the pathogenesis of PCOS, even in lean women. It is a key feature and predisposes patients to type II diabetes in the long run. While many PCOS patients are overweight or obese, some may have an average or lower body mass index (BMI). Identifying and screening PCOS patients for pre-diabetes and diabetes is crucial for counseling and implementing lifestyle modifications to delay or reduce the severity of diabetes mellitus.[8] Deficiency of vitamin D is prevalent in women with PCOS and is related to co-morbidities related to the syndrome. Hormonal abnormalities triggered by irregularities in steroidogenesis contribute to the clinical presentation of PCOS.[9] The vitamin D pathway is proposed to have a regulatory role in the endocrine symptoms of PCOS symptoms, leading to infertility and metabolic imbalance.[6]

According to studies, women with PCOS have a significantly high occurrence of vitamin D insufficiency, ranging from 65.0% to 70.3%.[8] To effectively diagnose and treat PCOS, one must comprehend its pathogenesis, including insulin resistance and vitamin D deficiency.2, 9 More studies are required to create tailored therapies for PCOS patients and investigate the processes behind these relationships. Our study aims to assess the prevalence of vitamin D deficiency in women diagnosed with PCOS. Despite existing research, there is a lack of local data, which limits the development of effective treatment strategies and modifications. The results will establish the local magnitude of the problem and enable clinicians to make practical recommendations for early diagnosis and management of PCOS, thereby improving fertility outcomes for affected women.

Methodology

We conducted this cross-sectional study at the Obstetrics & Gynecology Department of Combined Military Hospital- Rawalpindi. The study spanned from January 25, 2022, to July 24, 2022. Using the WHO calculator for single population proportion, the following assumptions were taken to calculate the sample size, confidence level (95%), margin of error (10%) and frequency of vitamin D deficiency in women with PCOS (65.0%). A sample size of 88 was calculated.[8] A non-probability consecutive sampling technique was employed to recruit a sample of 90 women who were diagnosed with PCOS and were between the age range of 18 to 40 years.

Inclusion criteria: The study included PCOS patients who met the Rotterdam criteria for PCOS diagnosis. According to the Rotterdam criteria, two of the following three symptoms must be present for PCOS to be diagnosed: Polycystic ovaries on ultrasonography, ovulation failure, and hyperandrogenism or hyperandrogenemia.[10]

Exclusion criteria: Pregnant women and individuals with chronic renal or liver disease, acid peptic disease, or a medical history of diabetes mellitus or hypertension.

Approval was obtained from the ethical committee of CMH Rawalpindi (ERC: 465- 12/09/2021), and informed consent was acquired from each participant. Data collection involved recording various demographic variables, including age, BMI, and duration of PCOS. In all patients, a 3 ml blood sample was taken and sent to the institutional pathology laboratory to measure vitamin D levels. Additional information was gathered regarding participants' place of residence (rural/urban), occupation (fieldwork/office work/domestic), sun exposure (frequency and duration), and the presence or absence of vitamin D deficiency. Vitamin D deficiency was determined based on the serum levels of vitamin D, with values below 20 ng/ml indicating a lack. The categorization of sun exposure levels is as follows: low exposure refers to sunlight exposure less than 3 times a week for less than 15 minutes per day over the past 3 months, medium exposure corresponds to sunlight exposure 3-4 times a week for 15-30 minutes at a time, and high exposure indicates sunlight exposure exceeding 5 times a week for more than 30 minutes at a time within the past 3 months. A pre-designed Performa was utilized to ensure accurate and consistent data collection.

SPSS V 25.0 was employed to conduct the statistical analysis. Mean and standard deviation (SD) were computed for age and BMI. Frequencies and percentages

were used to represent the length of PCOS, place of residence, occupation, and sun exposure. To investigate the possible impact of several factors on vitamin D deficiency, stratified controls were used to effect modifiers such as age, BMI, length of PCOS, place of residence, occupation, and sun exposure. The relationship between these variables and the existence of vitamin D insufficiency was examined using the post-stratification chi-square test. If the p-value was less than 0.05, it was deemed statistically significant.

Results

Table 1 and 2 shows the features of our patients, both clinical and sociodemographic. The mean ± SD of age and BMI of the patients in our study were 28.9 ± 4.85 years and 29.02 ± 2.43 kg/m^2, respectively. Most patients were in the age group of 18-30 years 48 (53.3%), lived in urban areas 50 (55.6%), did not have vitamin D deficiency 49 (54.4%), and had PCOS for more than 3 years 68 (75.6%), had low sun exposure 41 (45.6%) and were involved in domestic chores 45 (50.0%).

Table 3 summarizes the Mean and SD of age and BMI in patients with PCOS, stratified by vitamin D deficiency. No statistically significant difference was found in the mean age (P = 0.333) or mean BMI (P = 0.550) between patients with and without vitamin D deficiency.

Table 4 shows the cross-tabulation between vitamin D deficiency statuses with the categorical variables with Chi-square test p values applied to see any significant difference in the categories of the variables concerning vitamin D status. No statistically significant difference was found between the duration of PCOS (P = 0.616), BMI (P = 0.180), residence (P = 0.170), sun exposure (P = 0.185), or occupation (P = 0.154) in the vitamin D deficient and non-deficient PCOS patients.

Table 1: Age and BMI

Parameters	Mean ± SD	Range
Age in years	28.91 ± 4.85	22-37
BMI in g/m^2	29.02 ± 2.43	24-35

Table 2: Clinical and Sociodemographic Features of the Patients

Parameters	No. of Patients (n=90)	Percentage
Age (years)		
18-30	48	53.33
31-40	42	46.67
Residence		
Rural	40	44.44
Urban	50	55.66
Vitamin D deficiency		
Present	41	45.55
Absent	49	54.55
Duration of PCOS		
≤ 3 Years	22	24.55
>3 Years	68	75.55
Sun Exposure		
Low	27	30.00
Medium	41	45.55
High	22	24.55
Occupation		
Office work	19	21.11
Fieldwork	26	28.99
Domestic work	45	50.00

Table 3: Segregation of Vitamin D status of patients with age and BMI of patients

Parameters	Vitamin D deficiency		T-test (p-value)
	Present Mean ± SD. (n=41)	Absent Mean ± SD. (n=49)	
Age (Years)	28.37 ±4.78	29.37 ± 4.92	P = 0. 333
BMI (kg/m^2)	28.85 ± 2.24	29.16 ± 2.59s	P = 0. 550

Table 4: Segregation of Vitamin D status of patients with categorical variables

Parameters	Vitamin D deficiency		Chi-Square Test p-value
	Present (n=41)	Absent (n=49)	
Duration (years)			
≤ 3	9 (21.95%)	13 (26.53%)	0.616
> 3	32 (78.05%)	36 (73.67%)	

BMI (kg/m2) ≤ 25 > 25	 06 (14.63%) 35 (85.37%)	 03 (06.12%) 46 (93.88%)	0.180
Residence Rural Urban	 15 (37.59%) 26 (63.41%)	 25 (51.02%) 24 (48.98%)	0.170
Sun Exposure Low Medium High	 16 (39.02%) 15 (36.58%) 10 (24.40%)	 11 (22.45%) 26 (53.41%) 12 (24.49%)	0.185
Occupation Office work Fieldwork Domestic work	 10 (24.40%) 15 (36.58%) 16 (39.02%)	 09 (18.37%) 11 (22.45%) 29 (59.18%)	0.154

Discussion

Among women who are undergoing anovulation, PCOS is a common cause of ovarian dysfunction. Numerous genetic and environmental factors interact to impact a spectrum of gonadotropic and metabolic abnormalities, which are closely linked to the phenotypic expression of this condition.[1] Between 67 and 85% of women with PCOS had blood concentrations of 25 (OH) D less than 20 ng/ml, which indicates vitamin D insufficiency.[3] Insufficient levels of 25-hydroxyvitamin D [25(OH)D] have been found to potentially amplify the manifestations of PCOS, encompassing insulin resistance, disturbances in ovulation and menstruation, infertility, excessive androgen production, obesity, and increased susceptibility to cardiovascular ailments.[3, 9]

The age range of the studied patients was 22 to 37 years, with a mean age of 28.91 ± 4.85 years. Patients between 18 to 30 years of age were in the majority 48 (53.33%). A higher proportion of patients had vitamin D deficiency 41 (45.56%), a known risk factor for PCOS. Most patients had low sun exposure, which is another known risk factor for vitamin D deficiency and indirectly as well as directly for the development of PCOS. Most patients worked in office jobs, which may be a contributing factor to their low sun exposure. Our results align with the literature indicating the association of PCOS with lower vitamin D levels and altered hormonal profiles.

In Peshawar, a study assessing the vitamin D status of patients with PCOS found that only 19 (17.76%) patients with PCOS had vitamin D levels above 30 ng/ml, whereas 70 (65.42%) patients had vitamin D deficiency and 18 (16.82%) patients had vitamin D insufficiency.[11] According to an Indian study, women with PCOS had significantly lower serum 25 (OH) D concentrations than the control group (11.91 ± 10.57 vs 21.09 ± 18.07 ng/mL, P = 0.001). Additionally, compared to the control group, PCOS patients had a considerably greater frequency of vitamin D deficiency (61.84 vs. 38.16%, P < 0.0001).[12] A study from Iraq concluded that patients with PCOS exhibited a significantly lower vitamin D level than the healthy subjects' group (14.16 vs. 17.83 ng/ml; P = 0.010).[13]

After controlling for confounding variables, a relationship between increased vitamin D levels and PCOS was established in an investigation. The study did not, however, find any clear advantages of these increased vitamin D levels on metabolic disruption. This implies that while a correlation between elevated vitamin D levels and PCOS was noted, there was insufficient evidence in the study to substantiate a direct amelioration of metabolic dysfunction.[14] To determine if vitamin D deficiency and PCOS development are related, Kim et al. found that vitamin D deficiency was as common in patients as in controls.[15] Consequently, there is inconsistent research in the literature about the similarity of vitamin D levels between women with PCOS and those without the condition. The mean BMI of our patients was 29.02 ± 2.43 kg/m^2, which is within the range of overweight and obese. The range of BMIs in the study population was 24 to 35 kg/m^2, which suggests that the disease can affect women of all body sizes, but the majority of them are obese or overweight. There was no significant difference in mean age and BMI between our patients with and without vitamin D deficiency. This suggests that vitamin D deficiency is not affected by either age or BMI of the patients with PCOS.

Numerous scholars have comprehensively examined the correlation between adiposity, as measured by BMI, and vitamin D levels in women afflicted with PCOS. The BMI, while possessing certain limitations in terms of accuracy, remains widely employed as a means of assessing adiposity status across various populations. Numerous scholars have documented a negative correlation between BMI and levels of vitamin D. A study from Egypt reported that although Vitamin D level was significantly reduced in women with PCOS compared to healthy women, no remarkable changes in Vitamin D levels

were related to age group and BMI.[16]Kensara's study, after accounting for age and BMI as confounding variables, revealed a notable decrease in vitamin D levels among slender women afflicted with untreated PCOS compared to the control group.[17] Henceforth, in light of our investigations and the comprehensive examination of evidence, it can be posited that the diminishment of vitamin D in PCOS is not subject to direct influence by BMI. Nevertheless, it is plausible that BMI may influence the array of metabolic disruptions intricately linked to this malady.

Because 1 alpha-hydroxylase and vitamin D receptors (VDRs) are found in various tissues, previous research has linked vitamin D deficiency to infertility. The ovaries, uterus, and placenta are among the female reproductive organs where VDRs have been specifically found. Moreover, studies have shown that females with null vitamin D receptors may have poor folliculogenesis and infertility.[18] This data adds credence to the notion that vitamin D is essential for reproductive health and raises the possibility of a connection between problems with conception and vitamin D insufficiency.

Numerous scholarly investigations have delved into the correlation existing between the status of vitamin D and the hormonal or metabolic characteristics observed in patients afflicted with PCOS. In the context of individuals diagnosed with PCOS, it is postulated that a diminished concentration of vitamin D may be intricately linked to a plethora of metabolic risk factors. These include insulin resistance, elevated total cholesterol levels, hypertension, glucose deregulation, heightened C-reactive protein levels, augmented triglyceride levels, and diminished high-density lipoprotein (HDL) cholesterol concentration.[2, 3, 19] Meta-analyses of the randomized controlled trials have demonstrated that vitamin D administration can enhance specific metabolic parameters in PCOS patients.[3, 20] First, it was discovered that using vitamin D supplements significantly raised total testosterone levels in PCOS patients, indicating a favorable effect on hormonal balance (weighted mean difference [WMD] = -0.10, 95% CI [-0.18, -0.02]).[3] The homeostasis model assessment (HOMA-IR) score, which measures insulin resistance, also showed benefits with vitamin D administration, suggesting improved insulin sensitivity (WMD = -0.44, 95% CI [-0.86, -0.03]).[3] Additionally, vitamin D supplementation improved β-cell activity as determined by the HOMA-β index, indicating a beneficial effect on pancreatic β-cell function (WMD = -16.65, 95% CI [-19.49, -13.80]).[3]

A placebo-controlled, double-blind research that gave 50,000 IU of vitamin D every two weeks to the intervention group for eight weeks documented the positive effects of vitamin D supplementation on the lipid profile and insulin metabolism of PCOS-affected infertile women.[2] The findings above prove that vitamin D administration may be beneficial in treating metabolic deregulation in PCOS patients. Regarding the relationship between vitamin D intake and the reduction of PCOS symptoms, a 2021 review on the topic came to the unclear and non-determinative conclusion that there is insufficient data.

The studies they examined did not produce substantial evidence or definitive results supporting a connection between vitamin D intake and the reduction of PCOS symptoms.[19, 20] The different results in this study about the relationship between vitamin D deficiency and PCOS compared to other populations could be explained by the different degrees of gonadotrophic and metabolic abnormalities that are impacted by multiple genetic and environmental factors interacting.

Conclusion

As the frequency of vitamin D deficiency in women with PCOS is relatively high, we recommend that early identification through screening of the affected patients should be made for proper lifestyle changes or Pharmacological treatment to reduce associated morbidity.

Limitations

The data was collected from a single healthcare facility. This may limit the generalizability of the results.

Recommendations

Vitamin D's role in the pathogenesis and management of PCOS on a larger scale through clinical trials should be explored.

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ORIGINAL ARTICLE

The influence of birth order on anxiety disorders in emerging adulthood: A longitudinal study

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A B S T R A C T

Introduction: The current longitudinal scholarly research analyses the impact of birth order on children's psychological and mental health status.

Objective: The birth order indicates the paramount effect on an individual's psychological, physiological and behavioural transformation.

Methodology: This research study enrolled 150 individuals aged 18 to 25 years to assess their anxiety status in association with birth order. The study applied a mixed-method approach involving structured questionnaires, semi-structured interviews and focal group discussions.

Results: The statistical analysis yields that birth order is statistically inversely related to the level of anxiety, having weak statistical evidence of significance. It predicts that the latterly born (younger) children experience fewer episodes and severity of anxiety as compared to the elder ones.

Conclusion: Family support is a critical factor in buffering anxiety among children. The study suggests the parental consideration of birth order to provide a balance of attention and care to overcome the psychological adverse outcomes among children. Further scholarly attention is required to study the association among these dynamics with multiple approaches for further analysis of associated aspects.

Keywords: *Birth order, Anxiety disorders, Emerging adulthood, Family dynamics, Mental health, Personality traits.*

Introduction

The birth order remained a variable of interest among psychology and psychiatric medicine scholars for having a diversified impact on an individual's development.[1] It pertains to a child's position in the sequence of births within a family, whether they are the firstborn, middle child, or youngest sibling.[2] This dynamic has been linked to differences in personality traits, cognitive development, and social interactions.[3]

However, a relatively underexplored area is the potential impact of birth order on mental health outcomes, particularly in the crucial transitional phase known as emerging adulthood.[4] Emerging adulthood, from late adolescence to the mid-twenties, is a distinct period marked by significant physical, psychological, and social transformations.[5] It is characterized by increased autonomy, exploration of identity, and the pursuit of independence.[6] Simultaneously, it can be a period of heightened vulnerability to mental health challenges, including anxiety disorders.[7] Anxiety disorders, encompassing conditions like generalized anxiety disorder, social anxiety disorder, and panic disorder, can

significantly disrupt daily functioning and hinder the achievement of significant life milestones.[8]

Understanding the potential association between birth order and anxiety disorders in emerging adulthood holds substantial theoretical and practical implications. Such knowledge could shed light on the nuanced interplay between familial dynamics and mental health outcomes during a developmental phase that lays the foundation for future well-being.[9,10] This longitudinal study aims to bridge this gap in the literature by examining how birth order may contribute to the development and prevalence of anxiety disorders in individuals navigating the complexities of emerging adulthood.

This research endeavours to elucidate whether birth order exerts a discernible influence on anxiety levels during this critical life stage. It explores potential mechanisms underlying this relationship, considering factors like family environment, sibling interactions, and individual coping strategies. Additionally, by adopting a longitudinal approach, this study aims to capture the dynamic nature of these associations over time, allowing for a nuanced understanding of how birth order may interact with other life experiences and transitions to shape mental health outcomes.

This research contributes to the growing knowledge of birth order dynamics and their implications for mental health. Focusing specifically on anxiety disorders in emerging adulthood, it addresses a critical gap in the literature, offering insights that may inform targeted interventions and support systems for individuals navigating this pivotal life stage.

Methodology

The study employed a mixed-methods research design to explore the potential impact of birth order on anxiety disorders in emerging adulthood. A diverse sample of individuals aged 18 to 25 was recruited through various channels to ensure representation from different birth order positions. Data collection encompassed questionnaire surveys from 150 individuals, including the State-Trait Anxiety Inventory (STAI) and Birth Order Questionnaire, for quantifying anxiety levels and determining birth order position. Additionally, semi-structured interviews were conducted to obtain qualitative insights into participants' experiences regarding family dynamics and their perceived effects on mental well-being. A validated family assessment tool was employed to gather information on parental involvement, communication patterns, and support networks. Basic demographic data were also collected to account for potential confounding variables. The longitudinal approach, spanning two years, allowed for examining the evolving birth order-anxiety relationship in response to changing life circumstances. Data analysis encompassed descriptive statistics, correlation analysis, and regression models to explore the influence of birth order while considering factors like family environment and socio-economic status.

A thematic study of interview data was conducted to extract meaningful patterns. Additionally, moderation models were applied to investigate potential moderating factors. This comprehensive methodology aimed to provide a nuanced understanding of how birth order may contribute to anxiety disorders in emerging adulthood, offering valuable insights for tailored mental health interventions and support strategies.

Result

The study's descriptive analysis offers a comprehensive overview of the sample's demographic characteristics. The average age of participants was 21.4 years, indicating a relatively narrow age range and a reasonably homogeneous group. Birth order positions were evenly distributed, with 33.3% of the sample being firstborns, middle children, and youngest siblings, respectively, ensuring a representative family position sample. Gender representation was balanced, with 50% identifying as male and 50% as female. Regarding education level, 20% had completed high school, 53.3% held a Bachelor's degree, and 26.7% had obtained a Master's degree, showcasing a diverse educational background within the sample. This information establishes a diverse and representative sample, essential for interpreting and generalizing the study's findings.

The correlation analysis examines the relationship between birth order and anxiety levels in the sample. The correlation coefficient of -0.15 indicates a weak inverse

relationship, suggesting that individuals with higher birth order (middle children or youngest siblings) may experience slightly lower anxiety levels. However, this correlation is weak, indicating that birth order alone is not a strong predictor of anxiety levels. The negative sign implies that as birth order increases, there may be a slight decrease in anxiety levels, aligning with previous research suggesting higher anxiety in firstborns due to greater expectations.

Table 1: Descriptive Analysis of Demographic Variables

Variable	Mean	Std. Deviation
Age (years)	21.4	2.3
Birth Order		
Firstborn	50 (33.3%)	
Middle Child	50 (33.3%)	
Youngest Sibling	50 (33.3%)	
Gender		
Male	75 (50%)	
Female	75 (50%)	
Education Level		
High School	30 (20%)	
Bachelors	80 (53.3%)	
Master's	40 (26.7%)	

The correlation is statistically significant at the 0.05 level, indicating a 5% chance of occurring by chance. Despite significance, the correlation remains relatively weak, emphasizing the need to consider other contributing factors. Overall, this analysis suggests a subtle influence of birth order on anxiety levels, underscoring the importance of examining its interplay with other contextual variables for a comprehensive understanding of mental health outcomes.

Table 2: Correlation Analysis

Correlation	Birth Order	Anxiety Levels
Birth Order	1	-0.15*
Anxiety Levels	-0.15*	1

*Correlation is significant at 0.05 level (two-tailed)

The regression analysis provides valuable insights into the relationship between birth order, family support, and anxiety levels. Let's break down the coefficients: The intercept is -0.28. This represents the estimated anxiety level when all other predictors (birth order and family support) are zero. In this context, it suggests that with no specific birth order or family support, the baseline anxiety level is estimated to be -0.28. The coefficient for birth order is 0.36. This means that for every one-unit increase in birth order position (e.g., from firstborn to middle child), there is a 0.36-unit increase in anxiety levels. This coefficient is statistically significant (t-value = 2.34, p-value = 0.001), indicating that birth order significantly predicts anxiety levels. The coefficient for family support is -0.12. This suggests that for every one-unit increase in perceived family support, there is a 0.12-unit decrease in anxiety levels. Like birth order, this coefficient is also statistically significant (t-value = 4.32, p-value=0.001), highlighting the importance of family support as a protective factor against anxiety.

These coefficients provide valuable information about the relative impact of birth order and family support on anxiety levels. The positive coefficient for birth order suggests that as birth order position increases, anxiety levels tend to grow. This aligns with the earlier correlation analysis, reinforcing the notion that later-born children may experience slightly higher anxiety levels. Conversely, the negative coefficient for family support indicates that increased perceived family support is associated with lower anxiety levels. This finding underscores the critical role of a supportive family environment in mitigating anxiety. Overall, this regression analysis suggests that birth order and family support are both significant predictors of anxiety levels. Understanding these factors can inform targeted interventions to support individuals in managing and coping with anxiety, taking into account their birth order position and the level of family support available to them.

Table 3: Regression Analysis

Regressoin	Anxiety Depression			
	Cof.	Std. Error	t-stat	p-value
Intercept	-0.28	0.01	23.72	0.001
Birth Order	0.36	0.05	2.34	0.001
Family Support	-0.12	0.03	4.32	0.001

Table 4 presents the frequency of specific qualitative themes identified in the study, focusing on the experiences of middle children, firstborns, youngest siblings, family support, and independence struggles. The

Middle Child Experience theme encompasses perspectives of those identifying as middle children, shedding light on their unique roles within the family. Firstborn Experience centres on the responsibilities and dynamics of being the eldest, while Youngest Sibling Experience delves into the position and interactions of the youngest in the sibling hierarchy. Family Support emerges as a prominent theme, underlining its significance in participants' lives, encompassing emotional, financial, and practical support. Independence struggles reflect the challenges participants face in asserting themselves within family dynamics. These themes provide valuable insights into individuals' subjective experiences and perspectives, complementing the quantitative findings and offering a deeper understanding of their lived realities.

Table 4: Qualitative Themes

Theme	Frequency
Middle Child Experience	45
Firstborn Experience	35
Youngest Sibling Experience	30
Family Support	60
Independence Struggles	25

Discussion

The current research study embarked on a quest to unravel the intricate ties between birth order and anxiety levels during the pivotal juncture of emerging adulthood. It sought to shed light on whether the sequence in which one is born within a family might have a bearing on one's anxiety levels during this transitional phase. The study uncovered a delicate yet statistically meaningful inverse correlation between birth order and anxiety levels. Remarkably, those occupying higher birth order positions, namely middle children or youngest siblings, tended to manifest slightly lower levels of anxiety. This finding corroborated prior research that postulated firstborns might grapple with elevated anxiety due to heightened expectations.[11]

Further exploration illuminated the formidable role of family support as a protective factor against anxiety. The meticulous regression analysis pinpointed that heightened perceptions of family support were intimately linked with diminished anxiety levels.[12] This underscored the pivotal role of a supportive family milieu in tempering anxiety amidst the turbulence of emerging adulthood. Delving deeper, the study unveiled that both birth order and family support stood as significant predictors of anxiety levels.[13] A surge in birth order position often paralleled a surge in anxiety levels, while a bolstering of family support was synonymous with a reduction in anxiety levels. This unveiled the urgency for interventions tailored to an individual's birth order and the extent of familial support they could avail. To add depth to the insights gleaned, a qualitative analysis was conducted. It unearthed a treasure trove of subjective experiences and viewpoints from individuals in diverse birth order positions. Themes such as the 'Middle Child Experience', 'Firstborn Experience', and 'Youngest Sibling Experience' offered glimpses into families' distinct roles and dynamics. Additionally, 'Family Support' and 'Independence Struggles' unravelled further layers of the participants' lived realities.[14]

The implications of these findings are manifold. Clinicians and mental health practitioners stand to benefit significantly from this nuanced understanding of birth order's influence on anxiety levels. It equips them to craft interventions that address the unique pressures of being a firstborn. Moreover, recognizing the pivotal role of family support underscores the imperative of involving families in the support and treatment of individuals contending with anxiety disorders. Equipping families with resources and knowledge amplifies their capacity to be adequate support pillars. [9] Anticipating and intercepting anxiety symptoms in individuals, particularly considering their birth order, emerges as a crucial preventive measure. Early identification paves the way for proactive steps to stave off the escalation of anxiety disorders. This could encompass psych education, imparting coping skills, and implementing early intervention programs. [19]

However, it is essential to acknowledge certain limitations in the study. Despite the intention of diversity, the sample was somewhat homogeneous in age, confined to a narrow range of 18 to 25. Consequently, this may circumscribe the generalizability of the findings to a broader demographic. Furthermore, the reliance on self-reported measures for anxiety levels introduces the

potential for response bias. Augmenting the study with objective measures, like clinical interviews or physiological assessments, could fortify the robustness of the findings. Lastly, while associations between birth order, family support, and anxiety levels were discerned, causality remains elusive. There exists the possibility of unmeasured variables exerting influence on the observed relationships. [11] This research venture casts a luminous beam on the interplay between birth order, familial dynamics, and anxiety levels during the tumultuous phase of emerging adulthood. It extols the imperative of comprehensive and bespoke approaches to bolster individuals navigating this critical juncture. Future research endeavours could delve into additional contextual facets and employ diverse methodologies to fathom this intricate relationship further.

Conclusion

This longitudinal study illuminates the intriguing connection between birth order and anxiety disorders during the critical phase of emerging adulthood. While a subtle inverse correlation between birth order and anxiety levels was observed, family support emerged as a decisive protective factor against anxiety. These findings underscore the importance of considering familial dynamics in mental health interventions for individuals navigating this pivotal life stage. Further research in this area promises to refine our understanding and enhance tailored support for emerging adults.

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REVIEW ARTICLE

Unraveling the complexity: A comprehensive guide to subclavian steal syndrome

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A B S T R A C T

Subclavian steal syndrome is a diagnosis that is thought to be relatively uncommon even though its occurrence is not well understood. Some individuals may experience crippling symptoms of arm ischemia and vertebral-basilar insufficiency due to subclavian steal, which is more frequent than the accompanying illness. Patients with uneven arm blood pressure or unilaterally faint pulses should be evaluated for subclavian steal. Although it is not always necessary to check the blood pressure and pulse on both sides, they become significant when these measurements differ and are accompanied by vertebral-basilar or arm ischemia symptoms. Although subclavian steal does not significantly increase the risk of stroke, it is nevertheless essential to recognize and treat asymmetric blood pressure and weak pulses as these may be signs of subclavian steal syndrome. This page thoroughly analyses the aetiology of subclavian steal syndrome, signs, symptoms, diagnosis, and available treatments.

Keywords: *Vertebral-basilar, Subclavian steal syndrome, Stenosis, Blood flow.*

Introduction

There is widespread agreement that subclavian steal syndrome is a relatively unusual diagnosis, while the incidence of the condition is not well established in contemporary literature.[1] With an incidence rate of about 2.5%, subclavian steal syndrome (SSS) is a relatively uncommon disorder. Internal mammary artery (IMA) grafting in coronary artery bypass surgery might occasionally result in the unusual complication known as coronary subclavian steal syndrome (CSSS).[2] Myocardial ischemia caused by decreased blood flow, or flow reversal in the IMA graft, is the medical term for this condition. Most often, this is the result of proximal subclavian artery stenosis, which is hemodynamically severe. Unstable angina, myocardial Infarction, and even abrupt cardiac arrest are all possible clinical presentations. If one is not actively looking for it, CSSS is a problematic entity to diagnose. The clinical diagnosis is frequently challenging, and the disorder's frequency is commonly overestimated.[3] Clinicians have developed diagnostic and therapeutic standards that discriminate between asymptomatic and symptomatic subclavian steal syndrome. [4] The usefulness of subclavian steal syndrome in treating cerebrovascular illness was examined in the 1959 Joint Study of Extracranial Arterial Occlusion. As evidenced by arteriography, 17% of the 6,534 individuals in the study had subclavian or innominate artery occlusions or severe stenosis. Out of these, 168 people were diagnosed as having "true" subclavian steal syndrome.[5, 6]

Early in the 19th century, the idea that vertebral circulation could make up for a blocked subclavian artery was discovered. Harrison first acknowledged the significance of the vertebral-vertebral circulation in subclavian artery obstruction in 1829.[7] Smyth initially noted the reversal of blood flow in the vertebral vasculature in 1866 while treating a traumatic aneurysm with a subclavian artery ligation. In a patient who had no symptoms in 1960, Contorni reported a subclavian steal that had been

angiographically demonstrated. In the case of left subclavian artery obstruction, he documented collateral circulation in which the right vertebral artery was fully anastomosed with the left vertebral artery, causing a reversal of blood flow towards the left subclavian artery and total revascularisation.[8]

Reviech et al. reported cases resembling those Contorni described in 1961. Patients in these cases had vertebro-vertebral collateral circulation and had neurological symptoms such as headaches, scotomas, aphasia, and transient limb paralysis. The origin of these symptoms was determined to be cerebral ischemia brought on by a drop in pressure distal to the stenosis, which led to a decreased pressure gradient in the vertebral artery and a reversal of cerebral blood flow. The name "subclavian steal syndrome" was created by Fisher to describe this disease pattern in an editorial that was published the same year.[9, 10] Steal syndrome has been documented in medical literature since 1960. Blood flows in the opposite direction due to a diseased process, and if vessels supplying the intracranial structures are affected, various neurological symptoms may appear.[11]

According to the Joint Study of Extracranial Arterial Occlusion, Subclavian steal syndrome is more common in men than women, with an average age of 61 and 59 years. The subclavian and innominate vessels rarely have atherosclerotic occlusive disease, which is the cause of this. Additionally, the majority of patients with asymptomatic lesions don't also have concomitant carotid lesions. Additionally, the subclavian and innominate vessels are more slowly affected by atherosclerotic disease than other sites.[12]

ANATOMY:

The internal carotid and vertebral arteries make up the vascular supply of the brain. 80% of the blood flows to the brain through the internal carotid arteries, which divide into the middle and anterior cerebral arteries. [13] The vertebral arteries supply 20% of the blood flow, which unite to form the basilar artery and branch into the posterior cerebral arteries. The circle of Willis, a vascular ring that encircles the diencephalon, is made up of these arteries. When one of the significant blood veins becomes blocked, the circle of Willis assures blood flow between the vertebral-basilar and internal carotid systems.[14] Subclavian steal occurs when one of the subclavian or innominate arteries has stenosis or is blocked, resulting in a higher pressure gradient in the affected vessel and a decreased pressure gradient in the corresponding vertebral artery. The vertebral artery's blood flow is reversed as a result. The posterior cerebral circulation receives less blood due to this reversed flow, frequently called "stealing" (Figure 1). [15]

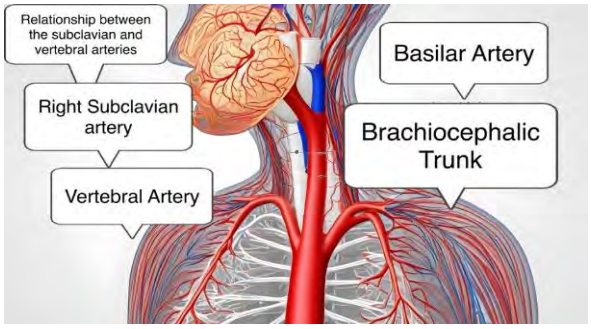

Figure 1: Relationship between subclavian and vertebral arteries[16]

PATHOPHYSIOLOGY:

The proximal subclavian artery can become stenotic or blocked, leading to retrograde flow in the ipsilateral vertebral artery and the subclavian steal phenomenon. The same phenomenon is called subclavian steal syndrome but with additional cerebral ischemia symptoms.[17] Reduced perfusion to the arm and hand on the afflicted side may follow, but symptoms depend on how well the intracranial collateral circulation functions. Patients with sufficient collateral circulation frequently exhibit no symptoms, whereas symptomatic patients may have abnormalities in other regions of the cerebral circulation. Interestingly, those with the left vertebral artery from the aortic arch are not susceptible to the left-sided subclavian steal syndrome.[12]

Blood flow from the brain to the arm is diverted in subclavian steal syndrome, which causes vertebrobasilar insufficiency symptoms (Figure 2). These symptoms are frequently brought on by strenuous arm movements or rapid head movements in the direction of the affected side. The syndrome can be brought on by arteriovenous distal arm shunt disorders or, less frequently, subclavian artery stenosis.[13] Three subclavian steal syndrome severity levels are Grade I: Reduced antegrade vertebral flow (pre-subclavian steal). Alternating flow with the antegrade flow

during the diastolic phase and retrograde flow during the systolic phase. Grade II (intermittent/partial). Retrograde vertebral flow that is persistent and progressive.[14, 15]

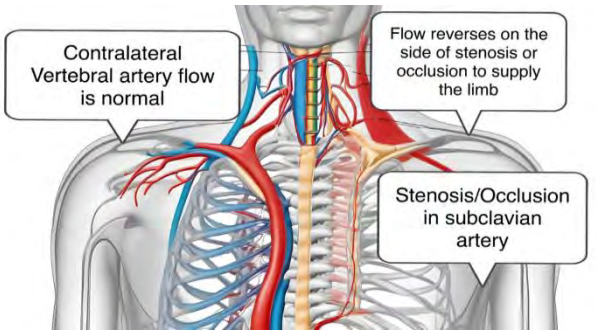

Figure 2: Subclavian Steal Syndrome [16]

CLINICAL PRESENTATION:

The subclavian steal syndrome is hemodynamically linked to proximal subclavian artery stenosis, blockage, and altered vertebral artery blood flow patterns. Retrograde blood flow in a vertebral artery typically doesn't result in symptoms. Except during strenuous arm work, proximal subclavian stenosis or occlusion rarely results in signs of arm ischemia. If arm exercise surpasses the capacity of collateral vessels, the brain may experience symptoms of cerebral ischemia. [17] Symptoms of posterior-circulation cerebral ischemia can include dysarthria, vertigo, syncope, and dizziness. Due to proximal subclavian stenosis or blockage, true subclavian steal syndrome necessitates retrograde flow in a vertebral artery. Blood pressures and pulses in the upper extremities can be used to identify significant subclavian artery lesions. Following surgery to graft the left internal mammary artery, recurrent angina may be a symptom of severe proximal left subclavian stenosis. Consider vertebral artery occlusive disease if posterior circulation symptoms appear with normal blood pressure in the affected arm.[18, 19]

DIAGNOSTICS:

A comprehensive physical examination, including a blood pressure reading and an evaluation of the radial pulse on the affected side, is crucial to determining the severity of subclavian steal syndrome. Additional information can be obtained by measuring the blood pressure in both arms and listening for carotid and supraclavicular bruits.[21] Regular laboratory tests, such as fasting lipid profiles and blood glucose levels, should be requested to evaluate atherosclerosis risk factors. Further evaluation may consider imaging tests like four-vessel cerebral arteriography, computed tomography angiography, duplex ultrasonography, and duplex ultrasonography. Electrocardiography and a thorough history taking are also crucial to recognize neurologic symptoms and arm ischemia. Diagnosed and risk factors for subclavian steal syndrome are evaluated in these tests. The most conclusive diagnosis is made by direct subclavian angiography (DSA). The routine use of DSA before CABG is debatable.[22]

Table 1: Subclavian Steal's Related Symptoms [20]

Vertebrobasilar	Arm Ischemia
Visual disturbances	Muscle fatigue
Vertigo	Claudication
Ataxia	Ischemic rest pain
Syncope	Ulcers
Dysphagia	Digital necrosis
Dysarthria	Atheroembolization
Sensory deficits of the face	
Motor and sensory deficits of the extremities	

A 20 mm Hg difference in systolic blood pressure between the contralateral arms raises the possibility of subclavian steal syndrome and calls for more testing. The afflicted side may have a decreased or nonexistent radial artery pulse. Although the existence of a supraclavicular bruit aids in the diagnosis, its absence does not always rule out the existence of the illness, and its presence does not always signify a major lesion. Nevertheless, the subclavian steal syndrome should be considered in light of these clinical findings.[23] The primary diagnostic procedure for assessing the carotid, vertebral, and subclavian arteries is ultrasonography, particularly duplex US. It can identify occlusive lesions in the carotid arteries and detect retrograde blood flow in the vertebral artery. The neck arteries are routinely examined with a Doppler US to diagnose subclavian steal syndrome. The vertebral artery exhibits early changes, including reduced velocity and biphasic flow, frequently exacerbated by arm activity or blood pressure cuff inflation. It can be challenging to evaluate the proximal subclavian artery; however, the distal subclavian artery often displays particular waveform

patterns. It's essential to comprehend these alterations to diagnose and treat subclavian steal syndrome.[20]

Subclavian artery stenosis or blockage is frequently found during the endovascular intervention. A delayed filling of the ipsilateral vertebral artery indicates insufficient blood supply to the brain and retrograde flow. [21] Other cerebral vascular lesions can also be found with this evaluation. It's crucial to look for severe lesions in the ipsilateral carotid artery. An arch aortogram may be necessary if the brachial artery pressure drops significantly (>20%) from the contralateral side. It has a high sensitivity and specificity and can detect additional abnormalities, so computed tomography angiography (CTA) is the first-line test. A four-vessel cerebral arteriography pinpoints the underlying anatomy of the issue and directs alternative solutions. A different option is magnetic resonance angiography (MRA). However, this method is more likely to exaggerate blockage and produce false-positive results.[17]

TREATMENT:

Because of the underlying atherosclerotic condition, subclavian artery stenosis is linked to higher morbidity and mortality rates. As a cardiovascular risk indicator, it increases the risk of cerebrovascular ischemic events.[7-11] Except in circumstances where a coronary artery bypass graft with an ipsilateral internal mammary artery graft is intended, incidental subclavian stenosis without symptoms does typically not require revascularisation therapy. Treatment focuses on secondary prevention strategies such as blood pressure control, dyslipidemia treatment, smoking cessation, diabetes glycemic control, and lifestyle modifications. Endovascular or surgical revascularisation is the preferred course of treatment, and percutaneous balloon angioplasty with stent support is recommended as the first-line procedure. Despite having a high percentage of success, the carotid-subclavian bypass has been less popular in recent years due to the minimally invasive nature of endovascular techniques.[18]

Treatments for subclavian artery stenosis that are successful and have good long-term results include balloon angioplasty and stenting. Surgical revascularisation, such as bypass surgeries, may be an option for lengthier or farther-reaching occlusions. Axillo-axillary bypass, on the other hand, is usually only used in high-risk patients because of its inferior patency rates.[9] Treatment options for patients with high perioperative risk and unfavourable anatomy include antiplatelet treatment and general cardiovascular preventive measures. Patients experiencing symptoms of subclavian artery stenosis should only be provided treatment, while those without symptoms typically do not need it. Antiplatelet therapy should be used permanently to treat subclavian steal syndrome brought on by atherosclerotic occlusions. Surgery or interventional treatment is advised if retrograde vertebral artery blood flow is the cause of ischemic symptoms. The efficiency of stenting in comparison to angioplasty alone is currently unknown.[10]

Less invasive bypass techniques have primarily replaced DeBakey's 1962 transthoracic approach to subclavian artery endarterectomy. Endarterectomy involves opening the artery, removing the plaque, unhealthy intima, and internal elastic lamina, and removing the occlusive lesions. The aortic arch must be partially occluded to guarantee thorough eradication of lesions. An anteromedial thoracotomy on the left side and a transverse incision on the right side are used to provide surgical exposure while avoiding a thoracotomy.[11-14]

Since subclavian endarterectomy has a mortality rate of 0.5%, extrathoracic carotid-subclavian bypass with a prosthetic conduit has taken its place. Utilizing Dacron or PTFE prosthetic grafts, the surgery calls for a transverse neck incision. An alternative treatment that avoids requiring prosthetic material but necessitates more extensive dissection is transposing the subclavian artery to a new origin on the common carotid artery.[12] When the ipsilateral carotid is unsuitable, an axillary-axillary or axillofemoral bypass can be done. A sequential retro oesophagal carotid-carotid and carotid-subclavian bypass can be performed in severe innominate artery disease cases. Arch aortography is done before surgery to evaluate the health of the distal subclavian and proximal common carotid arteries. An incision is made above the collarbone, the left thoracic duct is avoided, and a prosthetic graft with end-to-side anastomoses to the carotid and subclavian arteries creates a bypass. Postoperatively, brachial blood pressure is compared, and patients are evaluated for neurological impairments.[3-7]

Endovascular therapy is the most popular method for treating lesions of the proximal subclavian artery.

Comparison to open bypass or transposition reveals that it may produce results that are at least as excellent. Technical success rates are high (86–100%), and access site haemorrhage and plaque emboli are more common than nerve damage in terms of consequences. The majority of endovascular operations are performable as outpatients. Retrospective studies have shown that stenting is preferable to balloon angioplasty alone. Perfusion is improved, and subclavian steal syndrome is treated with endovascular recanalization and stenting. Archaortography is done before the procedure, and there are different ways to implant the guide wire. Proper location is crucial to prevent compression of adjacent vessels when using balloon-expandable stents, which are frequently employed. After the surgery, the patients are watched for a few hours while their neurologic condition and blood pressure are assessed.[21-23]

COMPLICATIONS:

Complications from surgical treatment can be cerebral (brain ischemia symptoms) or local (damage to nearby structures). Local problems are rare, although thrombosis or embolism can lead to cerebral issues. The use of a shunt is often not required since cerebral ischemia during common carotid closure is uncommon. The incidence of postoperative stroke ranges from 1.5% to 2.1%.[11] Complications from endovascular therapy can develop at the access site or target vessel. Hemostasis or access site haemorrhage are uncommon. Though less than 4% of instances include them, target vascular thrombosis, dissection, or distal embolization can occur. Transient ischemic episodes have been described in a small number of trials comparing endovascular treatment in patients with subclavian steno-occlusive disease in certain patients during the operation. Long-term recurrent interventions were needed for some patients. Primary 4-year stent patency rates varied, and patients with lengthier stents had a higher risk of problems.[5-8]

LONG TERM MONITORING:

Patients should follow up with doctors three to six months after treatment, then once a year after that. At every appointment, blood pressure in both arms should be measured. Duplex scans should be carried out to evaluate the reconstruction after six months and a year. Usually, patients with subclavian stents are given aspirin and clopidogrel for 6 to 12 months, then a single antiplatelet medication. Aspirin blocks prostaglandins' production, whereas clopidogrel explicitly blocks the binding of adenosine diphosphate (ADP) to platelet receptors. For patients who cannot tolerate or do not react to aspirin therapy, ticlopidine hydrochloride is an option.[9]

SUMMARY:

Subclavian steal syndrome is a very uncommon disorder marked by the reversal of blood flow in the vertebral artery due to stenosis or blockage of the proximal subclavian artery. It may result in vertebral-basilar insufficiency and signs of arm ischemia. Although the prevalence of subclavian steal syndrome is not well known, it is usually acknowledged as a rather unusual diagnosis. Upper-extremity blood pressure readings, pulse rates, and bilateral arm blood pressure measurements can all be used to identify SSS.

Conservative care and revascularisation therapies, including endovascular therapy or surgical bypass techniques, are available treatments for subclavian steal syndrome. The first-line choice is endovascular therapy, such as percutaneous balloon angioplasty with stent support, which has shown promising results in retrospective investigations. In some circumstances, less frequent surgical techniques like carotid-subclavian bypass or subclavian transposition may be explored. Regular follow-up visits, blood pressure tests, and duplex scans to evaluate the reconstruction are also part of long-term monitoring. Antiplatelet therapy may be used to treat patients with subclavian stents. Treatment-related complications are relatively uncommon but can occur and include thrombosis, hematomas, and bleeding at the access site.

In conclusion, the vertebral artery's blood flow is reversed in subclavian steal syndrome, a relatively uncommon disorder. It may result in vertebral-basilar insufficiency and arm ischemia symptoms. Clinical assessment, blood pressure readings, and imaging tests contribute to the diagnosis. Conservative management and revascularisation treatments are available as treatment options. Long-term monitoring is crucial in evaluating therapy effectiveness and identifying potential side effects.

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REVIEW ARTICLE

Nanoparticle's efficacy in the suppression of heavy metals that affect breast cancer progression

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A B S T R A C T

The study aimed to assess the literature to explore the efficacy of different nanoparticles that play a role in suppressing various heavy metals that cause breast cancer. Breast cancer is a prevalent reason of death among females around the world. Heavy metals, including arsenic, beryllium, cadmium, nickel, hexavalent chromium, and much more, play a role in the expansion of various types of cancer, mainly breast cancer. Nanomedicine has unbelievable potential for developing cancer treatment and diagnosis by inventive biocompatible nanocomposites for treatment. Gold nanoparticle's role as an effective treatment is quickly increasing. Silver exhibited significant interactivity among various nanoparticles due to its distinctive characteristics, such as conductivity, stability, catalytic properties, and antibacterial attributes. These can also be used for antimicrobial activities for many microorganisms such as bacteria, fungi, protozoans, and, recently, viruses. The data from various studies was retrieved. The studies on heavy metals and nanoparticles and their role were retrieved and added to this study. This will help people understand the influential role of nanomedicine in suppressing breast cancer. It is concluded that extensive efforts have been devoted to addressing breast cancer by utilizing various nanoparticles, including gold and silver nanoparticles. Silver nanoparticles, gold nanoparticles, and Myr-AuNPs (Gold nanoparticles) demonstrate promise as potent anticancer agents for breast cancer. However, further research is needed to combat the current state of breast cancer effectively.

Keywords: *Breast cancer, Heavy metals, Nanoparticles, Nanomedicine, Gold, Silver.*

Introduction

Breast cancer

Breast cancer is a widespread and important reason for mortality among females around the world, with about 23% of total new cases and 14% of deaths in 2008. Nearly half of these occur in developed countries.[1] According to the latest GLOBOCAN 2018 data from the International Agency for Research on Cancer (IARC), gathered from 185 countries, there were 2.3 million new cases of breast cancer, constituting 11.7% of all cancer cases. The reported mortality rate for breast cancer was 6.9%.[2, 3] In 2019, 76.4% of women aged 50 to 74 indicated that they had undergone a mammogram within the preceding two years.[4] In 2020, breast cancer represented 24.5% of the 19.3 million new cancer cases around the world. Within this, 16.8% occurred in Sub-Saharan Africa (SSA). Additionally, breast cancer constituted 15% of the 9.9 million global cancer-related deaths, with 12.1% of these deaths occurring in Sub-Saharan Africa.[5] Despite experiencing a comparable incidence of breast cancer,

Black women face a 40% higher mortality rate compared to their White counterparts.[6]

Many genes, enzymes, and molecules protect cancer cells against chemotherapy.[7] Owing to its pronounced traits of high metastasis, uncontrolled proliferation, immune evasion, and elevated mortality, current approaches for cancer management encompass surgical intervention, radiation therapy, and the administration of chemotherapeutic drugs.[8] Finally, these pathways were selected for drug treatment, playing a role in suppressing cancer cell propagation.[9]

Role of Heavy metals in breast cancer

Exposure to environmental pollutants such as cadmium, chromium, nickel, and arsenic falls into Group 1 of the International Agency for Research on Cancer's classification of carcinogens. Additionally, lead and mercury are reported as presumed human cancer-causing agents.[10] Many heavy metals play a role in the expansion of various types of cancer (i.e., arsenic, beryllium, cadmium, nickel, hexavalent chromium, and many more). Many studies reported the role of cadmium in cancer development.[11-19]

An epidemiological study unveiled a twofold increase in the risk of Breast Cancer (BC) among women with creatinine-adjusted urine cadmium levels exceeding 0.58 µg/g compared to those with levels less than 0.26 µg/g.[20] Elevated concentrations of cadmium in both breast cancer tissue and the urine of cancer patients, considering cumulative exposure from various sources, including smoking and diet, suggest a potential association between cadmium and breast cancer.

However, it's essential to acknowledge that this conclusion is somewhat tempered by specific methodological issues, such as age differences between the compared groups and a relatively small number of subjects.[21] Evidence shows that the path of contact and the chemical state of the cadmium is vital to developing tumor by contact with environmental pollutants.[22] Cadmium-induced carcinogenesis can be elucidated through various mechanisms: aberrant gene expression, inhibition of DNA damage repair, induction of oxidative stress, and suppression of apoptosis. Foremost among these factors is oxidative stress, primarily due to its role in the induction of abnormal gene expression, inhibition of DNA damage repair, and promotion of apoptosis in response to cadmium exposure.[23]

Previously, the occurrence of heavy metals as a possibly toxic accumulation to inorganic pesticide mixture was discussed. They stated that many metals like cadmium, cobalt, copper, and zinc are at high levels as a mixture in pesticide preparation. High lead, nickel, iron, and manganese levels were detected in other measures.[24]

Nanotechnology

Nanotechnology is a multidisciplinary area currently very favorable in treating cancer.[25] Nanomedicine has unbelievable potential for developing cancer treatment and diagnosis by inventive biocompatible nanocomposites for treatment, which shows a very appropriate method of nanoparticles.[26] In recent years, there has been an unparalleled surge in the utilization of nanocarriers, specifically within the size spectrum ranging from 10 to 100 nm, emerging as a novel therapeutic approach in cancer treatment. The US FDA has approved two therapeutic nanocarriers, liposomes and albumin nanoparticles, for clinical application. Moreover, an illustrative instance of an enhanced permeability and retention (EPR)-guided nano vector application in breast cancer chemotherapy is exemplified by liposomal doxorubicin and albumin-bound paclitaxel (Abraxane).

Current research priorities focus on target-specific drug therapy and early diagnosis methods for various pathologies, with nanotechnology emerging as a pivotal component in addressing these challenges.[27, 28] The data from various studies was retrieved. The studies on heavy metals and nanoparticles and their role were retrieved and added to this study. The previously reported studies were obtained from different sites and well-reputed journals to explore the study thoroughly. Various databases, including Google Scholar, were employed to acquire relevant data. The focus was on retrieving previous studies that investigated the impact of heavy metals and their treatment using nanotechnology.

Specifically, the study aimed to gather data on the effects of heavy metals on breast cancer and the utilization of nanoparticles in its treatment. Data that did not pertain to these specific aspects were excluded from the study.

Nanoparticles to suppress breast tumors:

Recently, a particular focus has been on utilizing nanomaterials as an efficient method for delivering drugs in cancer treatment. Ongoing investigations are dedicated to optimizing this approach to mitigate the adverse effects of conventional methods. Notably, various types of nanoparticles are commonly employed in research for drug delivery in breast cancer (BC) treatment. These include liposomes, mesoporous silica nanoparticles, viral nanoparticles, and polymer-, metal-, or carbon-based nanoparticles. Different drug loading techniques, such as encapsulation, covalent or electrostatic binding, and adsorption, are employed based on the specific characteristics of the nanoparticles.

Nanoparticles are selected for particular areas by surface alterations, which provide precise biochemical contacts with receptors found on targeted cells.[26-29] Another significant role of nanoparticles is the capability to deliver treatments to the targeted areas, crossing many biological blocks like blood-brain barriers.[30-33] The expansion of nanoparticle technique as imaging contrast chemicals also make the manufacture of multifunctional particles capable of selected tumor tomography and distribution of beneficial drugs.[34] The formation of nanoparticles by plants gets attention, principally because of its simplistic method and does not need any process like maintenance of microbial cultures and various cleansing stages.[35]

A simple and environmentally friendly bottom-up synthesis method was employed, utilizing Murraya Koenigii leaf extract as a reducing and stabilizing agent. This process resulted in the production of silver nanoparticles under ambient conditions and gold nanoparticles at 373K. The nanoparticles were thoroughly characterized through UV–vis, transmission electron microscopy (TEM), X-ray diffraction (XRD), and FTIR analyses. This approach allows for the creation of well-dispersed silver nanoparticles, approximately 10nm in size, and gold nanoparticles, about 20nm in size. Silver nanoparticles with a size of about 10nm, exhibiting a symmetric surface plasmon resonance (SPR) band centred at 411nm, were achieved within 5 minutes of adding the leaf extract to the solution of $AgNO_3$ at room temperature.

Nearly spherical gold nanoparticles with a size of approximately 20nm, featuring an SPR at 532nm, were obtained by introducing the leaf extract to the boiling solution of HAuCl4. The crystalline nature of the nanoparticles was confirmed through high-resolution TEM images, selected area electron diffraction (SAED), and XRD patterns. FTIR spectra revealed that the biomolecules responsible for capping differed between gold and silver nanoparticles. A comparative analysis with the author's earlier reports on biosynthesis is also provided.[35] The role of heavy metals in the tumor development and the utilization of gold and silver nanoparticles to suppress their effect (Figure 1).

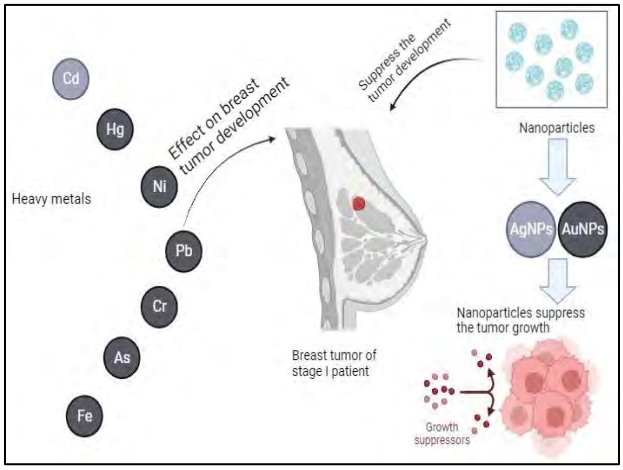

Figure 1: Heavy metals effect and their suppression by nanoparticles

Gold nanoparticles

The importance of gold nanoparticles (AuNP) as a drug delivery system (DDS) quickly increases.[36, 37] Gold nanoparticles exhibit high selectivity against cancerous cells, primarily attributed to their enhanced permeability and retention (EPR) effects.[38] Gold nanoparticles (AuNPs) can be designed in various configurations to sense stimuli, including molecular binding events or changes in ionic concentration. These engineered AuNPs can promptly respond by releasing cargo into cells or tissues, undergoing degradation, or even facilitating the chemical modification of drugs in both in vitro and in vivo settings. Nano-based materials not only hold the potential for integrating multiple therapeutic functions into a single platform but can also be directed to specific tissues.

This enables their reach to sub-cellular compartments or malignancies at different stages, enhancing their precision and effectiveness.[39] Their applications make them very capable of treatment. Precise production of different-sized particles (i.e., 1 to 150 nm) with partial size dispersity has been recognized,[40] and using ligand place-exchange responses,[41] a monolayer performing different functions can be invented. This structural diversity enables particle surfaces to contain many targeted agents.[42-44]

Upon exposure to infrared (IR) radiations, biological systems undergo a sequence of processes categorized into three phases: physical, chemical, and biological, each characterized by varying time scales.[45] In the initial nanoseconds of exposure, during the physical phase, IR interacts with biomolecules, leading to ionization or excitation and the generation of free radicals. DNA is a primary target Among various cellular components, influencing radiobiological effects. If possessing sufficient energy, ejected electrons travel further, colliding with subsequent atoms and initiating a cascade of ionization events. Transitioning into the chemical phase, these highly reactive radicals undergo rapid reactions, either permanently fixing the damage or scavenging reactions to restore cellular charge equilibrium. In the final biological phase, cellular processes are activated to repair radiation-induced damage.

The success or failure of these repair mechanisms determines the cell's fate, with unsuccessful repair eventually leading to cell death over a span ranging from seconds to days or even years. Hydrophobic medicines can be laden on gold Nanoparticles (NPs) by non-covalent relations, which requires no structural change to the medicine for drug release.[46] Also, covalent coupling to the gold NP by cleavable associations can be used to carry prodrugs to cells, and medicine can then be released by exterior[47] or interior[48] response. Regardless of the technique used, the tunability of the gold NP single layer is critical for interior or exterior release processes. Nanotechnology is considered an essential part of treatment design and distribution,[49] and among numerous NPs, gold NPs are highly discriminating for cancer cells generally due to their improved penetrability and retaining effects.[38, 50]

Using the potential poisonousness of particles, NP preparations are used for better imaging of lumps due to their improved acceptance and attention in cancer cells.[51,52] Chemical structure knowledge of NPs allows the binding and transportation of anticancer remedies straight to the lump. The use of AuNPs has also been principally helpful in improving the exposure of tumor-containing cells.[52-54] It is clear that there are beneficial uses for heavy metals like gold to detect tumors in the cell, yet care is required when using other transitional metals.

Silver NPs

Among different NPs, silver nanoparticles (AgNPs) were very interactive in their unique characteristics, like conductivity, stability, catalytic and antibacterial character. Silver and silver-containing materials are used for antimicrobial activities for many microorganisms, such as bacteria, fungi, protozoans, and viruses.[55] The development of Multiple drug resistance (MDR) and the severe disadvantages of many remedies currently cause cancer to become very dangerous and lead to death around the world.

Curcumin, a natural diphenolic compound derived from turmeric (Curcuma longa), has demonstrated its capability to modulate intracellular signalling pathways governing cancer cell growth, inflammation, invasion, and apoptosis, highlighting its anticancer potential. This review focuses on designing and developing various delivery systems to achieve sustained and effective curcumin delivery, including nanoparticles, self-assemblies, nanogels, liposomes, and complex formulations. Additionally, we delve into the anticancer applications and clinical benefits associated with nano-curcumin formulations. While exploring the field, we highlight a limited number of innovative multifunctional and composite nanosystem strategies that provide simultaneous therapy and imaging characteristics. Furthermore, we summarize the challenges inherent in developing curcumin delivery platforms and present current solutions to enhance curcumin bioavailability and maximize its anticancer potential for therapeutic applications.

There is an urgent need to develop treatment strategies for early analysis and treatment with fewer side effects.[56] Current studies have focused on nano oncology that leads

nanoscale particles and beneficial drugs for early judgement and its handling.[57] The practical applications of Gold and Silver Nanoparticles (Table 1).

Table 1: Applications of gold and silver nanoparticles

Sr.	Gold Nanoparticles	Silver Nanoparticles
1	Cancer detection and imaging	Production of reactive oxygen species and oxidative stress, DNA damage, cell cycle arrest
2	Detect biomarkers in the diagnosis of heart diseases	Helps in the induction of tumor cell death by apoptosis
3	Detect cancer types	Inhibit cell proliferation
4	Detect infectious agents	Acts as antimicrobial activity against a wide range of microorganisms like bacteria, fungi, protozoa and viruses
5	Immunoassays	Helpful in anticancer therapy
6	Deliver drugs to specific sites	Applied in the promotion of wound repair and bone healing, or as the
7	Helps in making imaging	vaccine adjuvant
8	Improve anticancer drug bioavailability	Acts as anti-diabetic agent
9	Photodynamic therapy and photothermal therapy	Acts as biosensors

Conclusion

In this study, we explored the efficacy of various nanoparticles, including gold NPs, silver NPs, and Myr-AuNPs, in combatting breast cancer. Much work is done to combat breast cancer by different nanoparticles, i.e., gold NPs, silver NPs and many more. To conclude, silver NPs, gold NPs, and Myr-AuNPs are helpful for BC as a potent anticancer medicine. More research is required to combat the present condition of breast cancer.

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REVIEW ARTICLE

Tuberculosis and scavenger receptors: Exploring their relationship

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A B S T R A C T

Tuberculosis (TB) remains a significant global health concern, particularly in low- and middle-income countries. Several risk factors are associated with TB infection and its progression from infection to disease onset, including host factors, microbial factors, environmental factors, and socio-economic status. Host genetic factors play a significant role in determining susceptibility to acquiring infection, progression to active disease, and the severity of the disease. Innate immunity is essential in the initial defense, advancement, and long-term control of mycobacterial infection. Among various cell surface and intracellular receptors mediating mycobacteria uptake, scavenger receptors play a crucial role in innate immunity. Scavenger receptors are classified into 12 classes, with class B comprising SR-B1 (SCARB-1), SR-B2 (LIMP2), and SR-B3 (CD36). SR-B1 and CD36 are involved in the uptake and phagocytosis of Mycobacterium tuberculosis (Mtb). Scavenger receptors promote cytokine production and modulate cytokine production during antimycobacterial responses. The SR-B1 and CD36 genes contain various single nucleotide polymorphisms in their intronic and exonic regions. These polymorphisms may influence the expression of the genes, leading to changes in Mtb uptake and antimycobacterial response. In this current review, we have explored the importance of scavenger receptors in TB pathogenesis. Additionally, we have summarized SNPs in SR-B1 and CD36 genes and their effect on protein expression.

Keywords: *Tuberculosis, Scavenger receptors, SR-B1, CD36, Single nucleotide polymorphisms*

Introduction

Tuberculosis (TB), caused by a single infectious agent, is the leading cause of death worldwide, surpassing HIV/AIDS. TB remains a significant global health concern, particularly in low-income and middle-income countries. TB can be of different forms, depending on a range of factors, including the site of infection, the immune response of the individual, and the presence of drug resistance. In 2021, there were an estimated 1.4 million deaths among HIV-negative people and 0.19 million deaths among HIV-positive people, for a combined total of 1.6 million.[1] According to the WHO TB Report 2022, 08 countries accounted for two-thirds of the global TB cases in 2021. Mycobacterium tuberculosis (Mtb) is the primary culprit responsible for human TB infections. Mtb is a slow-growing small bacillus, acid-fast, non-motile, rod-shaped, aerobic bacterium that divides every 18-20 hours and possesses a

unique cell wall composition, which includes mycolic acids and lipids. Mtb, also known as Koch's Bacillus, was first identified by Robert Koch in 1882. Mtb can exist in metabolically inactive latent and metabolically active disease states. The bacterium stays dormant and does not actively multiply in the latent form. In contrast, in an active disease state, it actively multiplies and causes clinical manifestations of TB.[2] Approximately 5% of the individuals infected with Mtb rapidly progress to active disease and can transmit the condition.[3] The remaining individuals develop a latent infection and carry a lifetime risk of Mtb reactivation and active TB.

Innate and Adaptive Immunity in TB Pathogenesis

When an individual inhales air contaminated with Mtb, the bacteria can reach the lungs and begin to multiply. The consequences of Mtb deposition in the lungs include the prompt removal of Mtb from the body, the individual's direct commencement of active disease, latent TB infection, disease reactivation, and the emergence of an active disease several years after dormant infection. The pathogenesis of TB can be divided into several stages. The pathogenesis of TB involves a complex interaction between Mtb and the host immune system. When a person inhales aerosols containing Mtb, bacteria reach the lungs and invade the respiratory epithelium. The survival and progression of Mtb depend on its capacity to interact with the host immune system.

To induce infection, Mtb fights and neutralizes both neutrophils and macrophages in the lungs, compromising different lysosomal trafficking pathways. First, alveolar macrophages are infected with Mtb, triggering an innate immune reaction.[4] Various immune cells, including dendritic cells and neutrophils, get involved as the infection progresses. These infected alveolar macrophages travel to the pulmonary interstitium and infect additional macrophages, dendritic cells (DCs), and neutrophils.[5,6]

Infected dendritic cells travel to nearby lymph nodes and initiate the priming of T-cells, activating an adaptive immune response that consequently travels to the location of infection to restrict infection establishment and spread.[7] Mycobacteria use various mechanisms to evade the host immune response and start to multiply, initiating active TB infection. If the immune system cannot keep bacteria under control, Mtb can reproduce quickly, leading to active TB. Unfortunately, 5-10% of infected individuals develop active TB infection and show clinical symptoms of TB.[8]

During the pathogenesis of TB, the bacteria can also trigger an immune response, leading to the formation of granulomas, which can contain both infected macrophages and other immune cells.[9] When an efficient cell-mediated immunological response is established, T lymphocytes, B lymphocytes, and stimulated alveolar macrophages develop a specific granuloma. This protective shell retains Mtb confined and under control, which leads to latent TB infection in approximately 90% of cases.[10] Most of the time, the multiplication of bacteria is stopped, and the inflammatory response diminishes. Patients with latent TB have an adaptive immunological response to Mtb; however, there are no clinical signs of TB.[7] An effective adaptive immune response results in various outcomes, from successful containment of the disease (sterilized infection) to asymptomatic or mild disease (subclinical disease).

Reactivation occurs when the immune mechanism is disrupted, and the control of infection is compromised due to factors such as AIDS, advanced age, inadequate nutrition, and high levels of stress.[11] Reinfection can occur in individuals who have previously had TB, either in the form of LTBI or have been successfully treated with TB.

Role of Host genetics in TB pathogenesis

Several risk factors are associated with TB infection and its progression from infection to disease, including host factors, microbial factors, environmental factors, and socio-economic status. The variability in the clinical outcome of disease among individuals is attributed to the variation in human genes involved in host defence mechanisms.[12] An increasing body of evidence suggests that host genetic factors play a significant role in both susceptibility to acquiring infection and the likelihood of developing severe complications.[13]

Experiments involving transgenic mice demonstrated that overexpression of chemokines made them more susceptible to TB.[14] In another mouse model study, the macrophage-mediated intracellular pathogen resistance gene was identified as a genetic factor crucial in providing innate immunity to Mtb infection.[15] A murine model study

identified the importance of immunoregulatory genes in modulating the inflammatory environment, subsequently facilitating protection against TB infection.[16]

A significant demonstration of the impact of host factors on varying responses to infection was observed in Lübeck when a virulent strain of Mtb was mistakenly administered through the contamination of a locally produced BCG vaccine.[17] More excellent concordance for TB in monozygotic and dizygotic twin pairs suggests that genetic predisposition plays a significant role as a risk factor for tuberculosis susceptibility in humans.[18]

Studies of TB in several ethnic groups have shown that this disease is linked to host genetic mutations. Multiple research groups have reported a significant association between the genes involved in TB immunopathogenesis and TB susceptibility. Some recent studies are quoted here. In the Ethiopian population, polymorphisms in inflammatory cytokines have been identified as significant host genetic risk factors for TB infection.[19] Genetic variations in Th17 pathway genes are crucial for the clinical manifestations of PTB in the Chinese population.[20] Data from different studies suggest a significant association between nuclear receptor polymorphisms and TB susceptibility in Asian populations.[21-23] A comprehensive meta-analysis provided strong evidence supporting the association of polymorphisms in one of the subgroups of PRRs with TB infection across diverse ethnicities, including Asians, Caucasians, and Africans.[24]

Scavenger receptors

Scavenger receptors (SRs) are a family of cell surface proteins (Figure 1) that bind and internalize various ligands. In 1979, Brown and Goldstein first described SRs.[25] SRs as pattern recognition receptors (PRRs) are capable of recognizing damage-associated molecular patterns (DAMPs) and pathogen-associated molecular patterns (PAMPs). They can bind various pathogens, i.e., cell-wall components found in Gram-positive and Gram-negative bacteria, including lipoteichoic acid (LTA), lipopolysaccharide (LPS), and β-glucan present in fungal cell walls.[26] Endocytosis, phagocytosis through adhesion and activation of downstream signalling, is commonly used by SRs to remove degraded or harmful substances.[27]

Classification of SRs

SRs comprise a structurally diverse superfamily of various classes with minimal structural similarity. The primary distinguishing feature among different courses is their ability to bind shared ligands [28] (Error! Reference source not found.2). The classification of SRs is based on sequence alignment of their nucleotide and analyzing their protein structures. According to the proposed nomenclature, there are 12 known classes (A-L) of mammalian scavenger receptors.[29] Class B of scavenger receptors is explained in detail in succeeding paragraphs.

Class B scavenger receptors: SR-B

Class B scavenger receptors comprise the conserved CD36 domain, and its members include SR-B1 (SCARB-1), SR-B2 (LIMP2) and SR-B3 (CD36). This class can bind

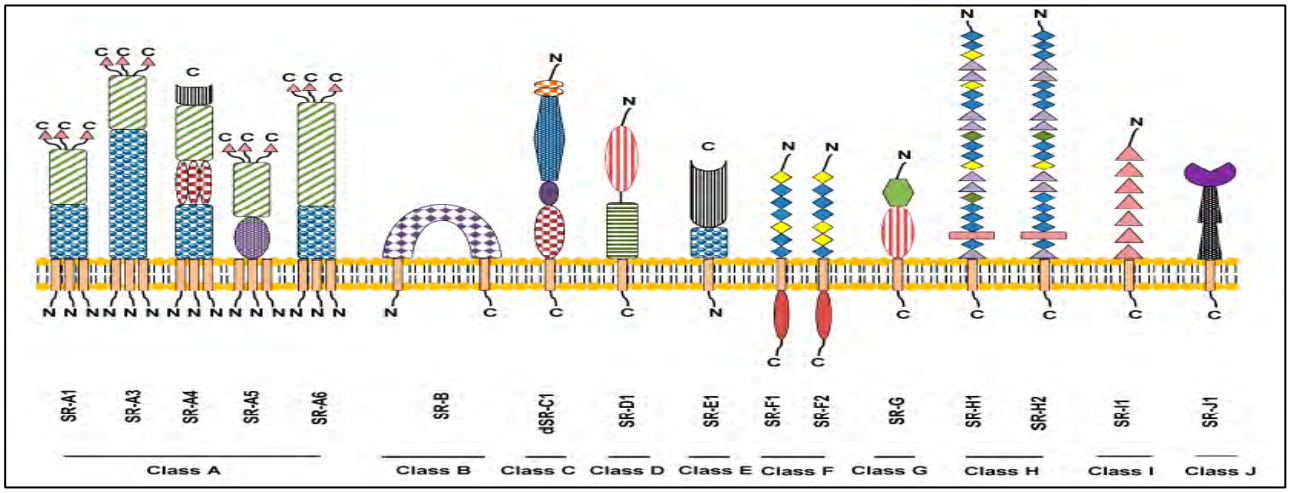

Figure 1: Classification of scavenger receptors [30]

diverse ligands, including viruses, bacteria, and HDL particles.[28] Three members of this class feature two

transmembrane regions positioned near the N- and C-termini, enclosing a central domain of 400-450 residues. This glycosylated main domain is crucial in ligand recognition.[30]

aspects of macrophage biology, including migration, signalling, and inflammatory processes such as foam cell formation.[33] It is also involved in the host's immune response to bacteria and fungi.

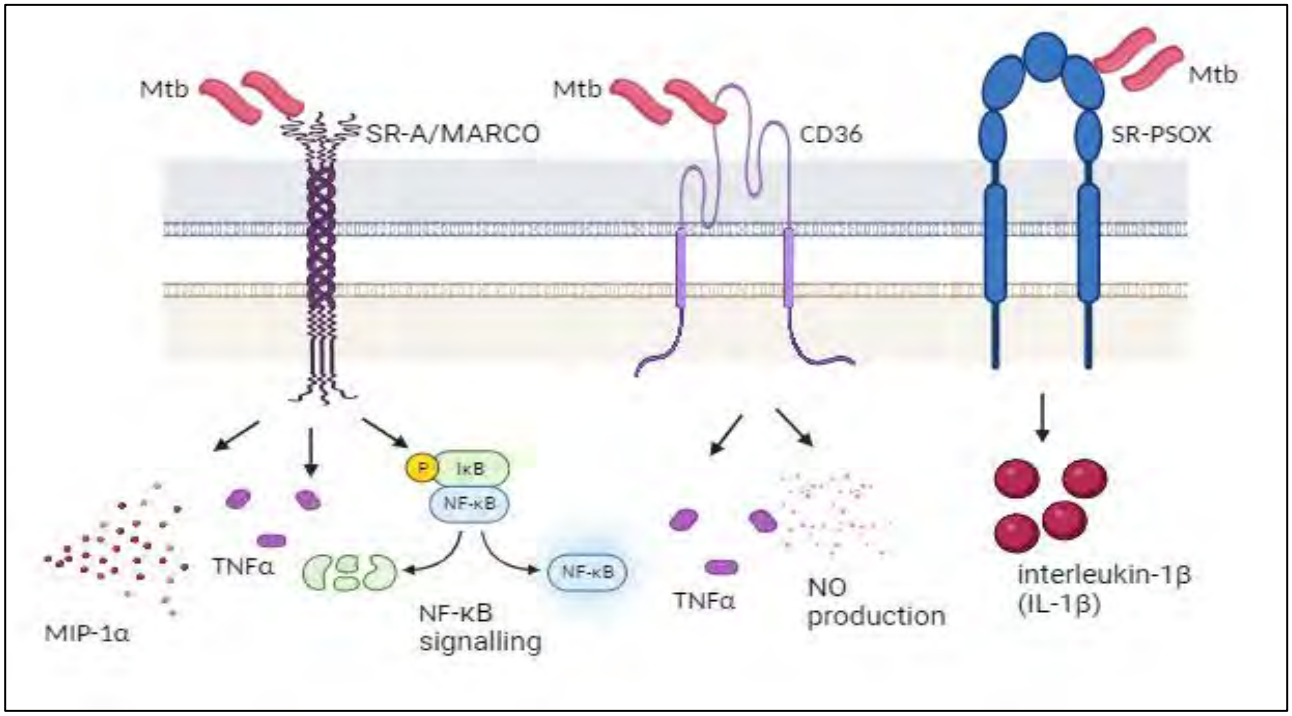

Figure2: Proposed mechanism of the role of scavenger receptors in cytokine production and modulation

SR-B1

This gene, located on human chromosome 12, is the first discovered high-density lipid (HDL) and anionic phospholipid receptor. It facilitates the selective transport of lipids, including cholesteryl esters, from HDL and other lipoproteins to cells.[31] Hepatocytes and steroidogenic cells show the highest expression levels of SR-B1 (Figure 3). It is also present in cells within the arterial wall and macrophages, including those in human and mouse atherosclerotic lesions.[27]

CD36

CD36, located on human chromosome 7, is the most widely studied scavenger receptor. It is expressed in various cell types, including hematopoietic and specialized epithelial cells.[27] Different ligands bind CD36 (Figure 3), including thrombospondin-1, OxLDL, long-chain fatty acids, modified lipid particles, apoptotic cells, and bacterial and fungal pathogens.[32] CD36 is essential in various

Scavenger receptors and innate immunity

SRs play a crucial role in innate immunity because of their ability to specifically bind various ligands and function as PRRs. The identification and characterization of SR genes suggest their role in the host defence mechanisms against foreign and endogenous molecules.[34] They can recognize, engulf, and eliminate various PAMPs on microbial surfaces, such as LPS and LTA. Additionally, SRs can function as co-receptors for other PRRs, primarily Toll-like receptors (TLRs), to detect and phagocytose PAMPs and DAMPs. This cooperation extends to cytokine production, enabling an effective immune response against different pathogens and during inflammatory processes.[26] Non-opsonic phagocytosis of pathogenic microorganisms by macrophages and dendritic cells is the most common function of SRs.[35] Different studies show pathogens often exploit SRs to enter host cells.[36, 37] Genetic screening disclosed that endothelial SRs play role in physiological and pathological processes in innate immunity and infection.[38]

Role of Scavenger Receptors in TB

Innate immunity plays a significant role in antimycobacterial response, the progression and long-term control of Mtb infection. The genes encoding PRRs serve as the primary components of the innate immune system that facilitate the direct molecular interaction between the host and Mtb. Scavenger receptors are one of the various cell surface and intracellular receptors mediating bacteria uptake.[39] This close interaction suggests the possibility of co-evolution between the host immune system and the pathogen over time.

MSCs phagocytose Mtb through SR-B1 and MARCO and exhibit innate control of mycobacterial replication through autophagy. MSCs are found in both human and mouse Mtb granulomas and play a role in TB pathogenesis. They are also involved in mediating macrophage into M1 and M2 phenotypes.[43] The SR-B1 on M cells interact with Mtb EsxA, enabling it to cross airway mucosa and initiate infection. Mtb binding and translocation across M cells reduce if SR-B1 genes are disrupted.[44]

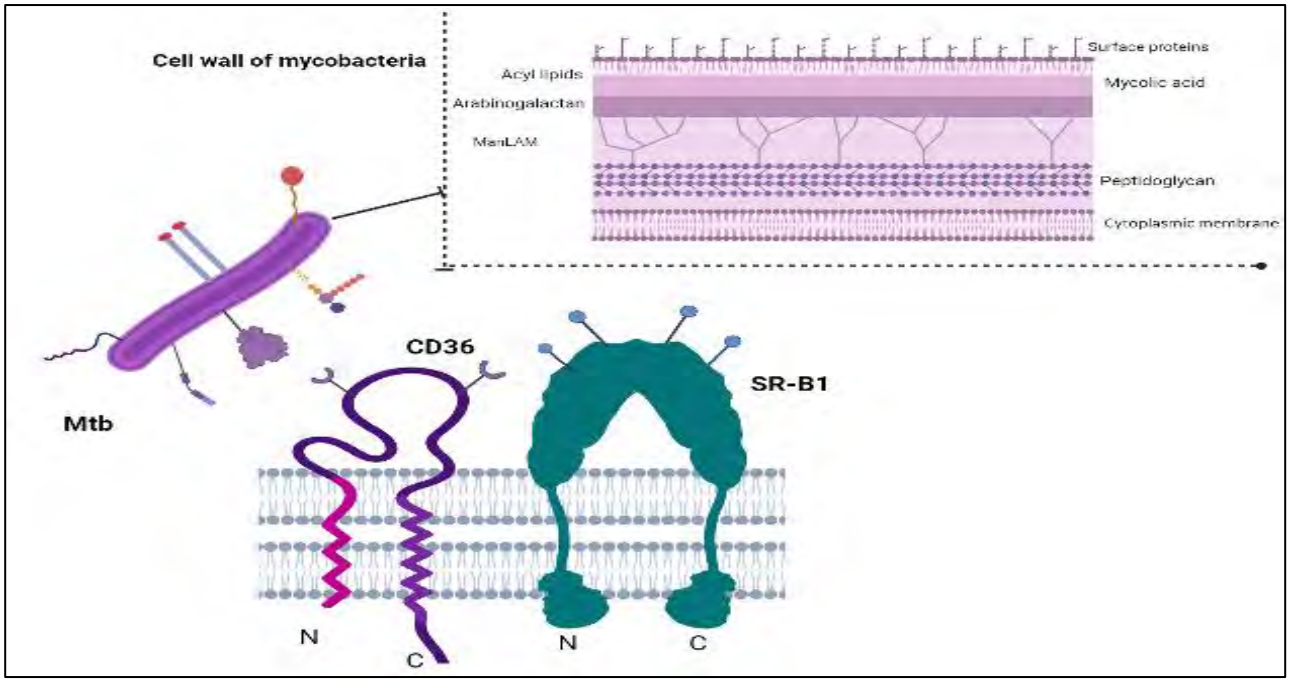

Figure 3: Specific lipoprotein components and lipoglycans in cell-wall of Mtb are recognized by SR-B1 and CD36

Effect on phagocytosis

Scavenger receptors promote the phagocytosis of Mtb through macrophages, dendritic cells, mesenchymal stem cells (MSCs), and airway microfold cells (M cells). CD36 mediates the uptake of surfactant lipids by macrophages, which promotes the growth of Mtb within macrophages.[40] SR-B1, as a receptor on macrophages, is also involved in recognizing BCG. [41] Mtb and BCG binding increases when SR-B1 is overexpressed in macrophages, whereas BCG binding is unaffected by comparable knockout in murine macrophages.[42]

Mice deficient of the ATG7 gene in macrophages express enhanced MARCO and macrophage scavenger receptor-1 (MSR-1), resulting in the increased phagocytic capability of macrophages.[45] In BCG-infected mice, CD36 becomes more abundant in multinuclear phagocytes (MP) during periods of Mtb persistence.[46] A study by Liu et al. indicates higher expression levels of scavenger receptor CD163 on CD16+ monocytes and a higher serum CD163 (sCD163) level in pleural TB patients.[47]

Cytokine production and modulation

Scavenger receptors play a crucial role in TDM-induced MAPK activation and TNF-α production. A study indicates that the expression of MARCO or SR-A enables TDM-induced NF-kB signalling in TLR-transfected HEK293 cells. Furthermore, macrophages lacking MARCO demonstrate

an impaired inflammatory response to Mtb, indicating the significance of SR in an effective macrophage cytokine response against this pathogen.[48] MARCO and CD36 are known to interact with Mtb LAM (lipoarabinomannan) and play a role in its recognition by immune cells. Experimental analysis suggests that CD36 is responsible for mediating the effects of ManLAM (mannose-capped lipoarabinomannan), leading to the release of TNF-α in peritoneal murine macrophages.

Ligands of SRs have similar effects on TNF-α and NO production as observed with ManLAM. Recently, SR-PSOX/CXCL16 has been found to facilitate the production of interleukin-1β (IL-1β) in response to dextran sulfate stimulation in murine peritoneal macrophages infected with Mtb.[49] During Mtb infection, macrophage SR-A (MSR-A) control excessive production of proinflammatory cytokines (TNF-α and MIP-1α/CCL3) by activated macrophages.[50]

Impact on adaptive immune response

During the chronic phase of Mtb infection, SR-A acts as a modulator that inhibits the adaptive immune response. SR-A deficiency in mice led to delayed progression of TB to severe terminal phase, and their prolonged survival was linked to significantly elevated quantities of CD4+ lymphocytes and antigen-presenting cells.[51] CD36 plays a role in the granuloma turnover process and is involved in the expansion of the intracellular reservoir of mycobacteria.[52]

SR-B1 gene polymorphisms

Different genetic polymorphisms can occur within a population, from a single nucleotide change to more significant structural changes in the DNA sequence. Single nucleotide polymorphisms (SNPs) can alter a disease's outcome, influence how individuals respond to an illness and affect the gene expression, function and structure, leading to phenotypic differences. Several SNPs have been reported in SR-B1 genes associated with different diseases and have also been reported to affect the expression levels of the gene. The effect of other SNPs of SR-B1 on its expression levels is summarized in

Table *2*: Effect of various SNPs in CD36 gene on its expression levels

SNP	Location	Nucleotide change	Amino acid change	Effect on expression levels
rs1761667	Exon 1A	18436G>A	None	
rs3211870	Intron 4	60706C>T	None	
rs3211909	Intron 7	67612T>C	None	Decrease [57]
rs3211913	Intron 7	68101A>G	None	
rs3211938	Exon 10	73946T>G	Tyr325Ter	
rs9784998	Exon 1F	36498C>T	None	Increase

A study by Love-Gregory et al. revealed that SNPs in the CD36 gene influence the levels of CD36 protein expression in African Americans. The study investigated the association of SNPs with CD36 expression on the surface of monocytes and platelets. Variants in the gene's coding and non-coding regions impacted the expression levels. The variations in exon 1A and exon 10 were associated with a reduction in monocyte CD36 expression, whereas mutations in intron 7 reduced CD36 expression in both monocytes and platelets. The exon 1F variant was linked to increased platelet CD36 expression, while the intron 4 variant was associated with decreased platelet CD36 expression.

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Mutations at both exonic and intronic regions can alter the SR-B1 expression levels. The mutation at exon 8, which changes the RNA secondary structure and affects protein translation, results in reduced expression and impaired function of SR-B1.[53] At exon 1 and intron 3, mutations were significantly associated with reduced SR-B1 protein translation and expression levels. [54] Similarly, mutations in intronic regions, specifically at intron 7 and intron 11, lowered hepatic SR-B1 expression.[55, 56]

Table 1: Effect of various SNPs in SR-B1 gene on its expression levels

SNP	Location	Nucleotide change	Amino acid change	Effect on expression levels
rs5888	Exon 8	68772T>C	Ala350Ala	Decrease [53]
rs2278986	Intron 3	54151T>C	None	Decrease [54]

rs4238001	Exon 1	5275G>A	Gly2Ser	Decrease [54]
rs3782287	Intron 7	64255G>C	None	Decrease
rs838896	Intron 11	83721G>C	None	Decrease

CD36 gene polymorphisms

Genetic mutations in the CD36 gene give us insight into its impact on health and disease. Several CD36 gene polymorphisms have been identified and extensively studied, representing their ability to influence disease outcomes and induce modifications in the gene. Different studies have demonstrated the impact of genetic variations on expression levels of the CD36 gene Error! Reference source not found..

Table 2: Effect of various SNPs in CD36 gene on its expression levels

SNP	Location	Nucleotide change	Amino acid change	Effect on expression levels
rs1761667	Exon 1A	18436G>A	None	
rs3211870	Intron 4	60706C>T	None	
rs3211909	Intron 7	67612T>C	None	Decrease [57]
rs3211913	Intron 7	68101A>G	None	
rs3211938	Exon 10	73946T>G	Tyr325Ter	
rs9784998	Exon 1F	36498C>T	None	Increase

A study by Love-Gregory et al. revealed that SNPs in the CD36 gene influence the levels of CD36 protein expression in African Americans. The study investigated the association of SNPs with CD36 expression on the surface of monocytes and platelets. Variants in the gene's coding and non-coding regions impacted the expression levels. The variations in exon 1A and exon 10 were associated with a reduction in monocyte CD36 expression, whereas mutations in intron 7 reduced CD36 expression in both monocytes and platelets. The exon 1F variant was linked to increased platelet CD36 expression, while the intron 4 variant was associated with decreased platelet CD36 expression.

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CASE REPORT

An afebrile neuroleptic malignant syndrome with hyponatremia: A case report

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A B S T R A C T

Neuroleptic malignant syndrome (NMS) is a rare, life-threatening situation in response to the adverse reaction of antipsychotic medications characterized by high-grade fever, altered Glasgow coma scale, autonomic dysfunction, and stiffness. We herein present a case with a typical presentation of stiffness and autonomic dysregulations along with the atypical symptoms of urinary incontinence and a history of falls. The patient was afebrile with hyponatremia, showing a similar presentation diagnosed as NMS and treated successfully according to the hospital protocol.

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Introduction

A neuroleptic malignant syndrome (NMS) is a potentially life-threatening medical emergency due to the adverse effects of certain antipsychotic medications. Less likely, it occurs in the rapid withdrawal of antipsychotic medications or resulting in taking low-potency antipsychotic drugs. This condition is characterized by high-grade fever, muscle stiffness, altered Glasgow coma scale (GCS), and autonomic dysregulation. Typical laboratory findings include raised creatinine phosphokinase and leukocytosis.[1]

The global incidence of patients taking neuroleptic drugs ranges from 0.01 to 3.2%. The majority of the cases are reported in young adults. Men suffered more than women, with a ratio of 2:1.[2] However, the incidence rate in Pakistan is still underreported.[3] We herein describe a case of a 31-year-old female with a known case of depression who arrived in the emergency department with drowsiness, generalized stiffness, and a history of falls. She was diagnosed with NMS and was managed accordingly.

Case Presentation

A 31-year-old female patient with underlying depression was brought to the emergency department with abnormal behavior from the past two days, followed by loss of consciousness, generalized body stiffness, urinary incontinence, and a history of falls. Her husband witnessed the first time fall with rapid recovery, and then on the same day, she fell with the associated finding above. The history of seizures was unremarkable.

In detailed history, she was in a usual state of health one year back when she developed behavioral symptoms such as aggressive behavior, excessive talk, and depressive mood. She has been prescribed antipsychotic medications Risperidone 2 mg once a day and Procyclidine 2.5 mg once a day. Upon which half of the symptoms were

relieved. According to her husband, she had stopped the medications two weeks ago, and her symptoms worsened with increased aggressive and abnormal behavior. Upon arrival at the emergency department, she was vitally stable but drowsy, not oriented to time, place, or person, and agitated. On arrival, her vital signs were temperature 36.6 degrees Celsius, respiratory rate 21/min, blood pressure 113/62 mm/Hg, and pulse rate 96 beats/min. On further examination, the patient was well nourished, agitated, not following commands, moving all limbs, and not in respiratory distress with no hidden needle marks. The chest, abdomen, and cardiovascular systems were unremarkable.

On Neurological examination, she was disoriented in time, place, person, pupil bilateral equal, and reactive to light. Glasgow coma scale (GCS) was 13/15 (E4V4M5). She had increased muscle tone throughout the body, reflexes were normal, and bilateral plantar were downgoing with no signs of meningeal irritation. Her initial lab reports showed severe hyponatremia at 121 mmol/l, Potassium at 3.4 mmol/l, and magnesium at 1.3 mmol/l. Furthermore, her creatinine phosphokinase was increased to 3014 mcg/l, and her white blood cell count was also elevated to 17.6 mm3. Moreover, the computed tomography scan (CT scan) of the brain and cerebrospinal fluid detail report (CSF DR) were unremarkable.

The patient was admitted under the internal medicine services with psychiatry on board. Hyponatremia was managed through Intravenous (IV) 3% hypertonic saline, and for CPK, the patient was hydrated. Midazolam 5 mg was given on a need base for agitation. The patient, after that, received broad-spectrum antibiotics ceftriaxone 1 gm once a day, Haloperidol 2.25 mg intramuscular stat, Levetiracetam 500 mg twice a day, Levitirectam 500 mg twice a day as a prophylactic for the seizure but was discontinued on the second day after consulting with the neurology team. Pyridoxine 50 mg once a day, Omeprazole 40 mg before breakfast, and IV hydration. The patient's GCS improved; she tolerated the oral diet and resolved agitation.

Discussion

NMS is a rare but severe medical condition with a mortality rate of 10-30%. It has been classically characterized by high-grade fever, altered GCS, and stiffness.[4] NMS is also seen in patients due to withdrawal of antiparkinsonian medication. At the same time, the typical laboratory findings include elevated serum creatinine kinase. However, atypical or non-specific laboratory findings include leukocytosis, hypo- and hypernatremia, hyperkalemia, hypomagnesemia, hypocalcemia, metabolic acidosis, and mild abnormalities in liver function tests.[5]

Compared to the above literature, our patient falls in rare cases, most probably due to the withdrawal effect, as our patient is on risperidone and procyclidine and has not taken it for the past two weeks. Moreover, in the classical signs and symptoms, our patient has muscle stiffness, altered mental status, and high serum creatinine kinase. It is worth noting that our patient had atypical features, including urinary incontinence, hyponatremia, and raised leukocytosis. However, our patients remained afebrile.

The Diagnostic and Statistical Manual of Mental Disorders, 4th Edition (DSM-IV-TR) states that the existence of two or more of the following findings: hyperthermia and muscular stiffness (significant findings), tachycardia, raised white blood cell count, sweating, altered or generally elevated arterial tension, adjusted GCS, tremor, urinary incontinence, and increased CPK (minor findings) constitutes the diagnosis of NMS.[6]

Conclusion

In conclusion, the presented case study highlighted the critical importance of diagnosing and addressing Neuroleptic Malignant Syndrome as a rare medical severe emergency, particularly in patients who were previously on antipsychotic medications. The sudden discontinuation of antipsychotic medication led to the emergence of aggressive behavior, altered mental status, and other alarming symptoms. The patient's overall clinical conditions improved by promptly providing the recommended care. This emphasizes the vigilance monitoring and use of the proper management techniques in case of withholding antipsychotic medication to reduce the risk of NMS and ensure the best possible outcomes for the patient. The prevalence of mental disorders and the widespread use of antipsychotic medications in Pakistan implies that physicians and nurses must be familiar with the

warning signs, symptoms, and recommended course of care to manage patients promptly and avoid consequences.

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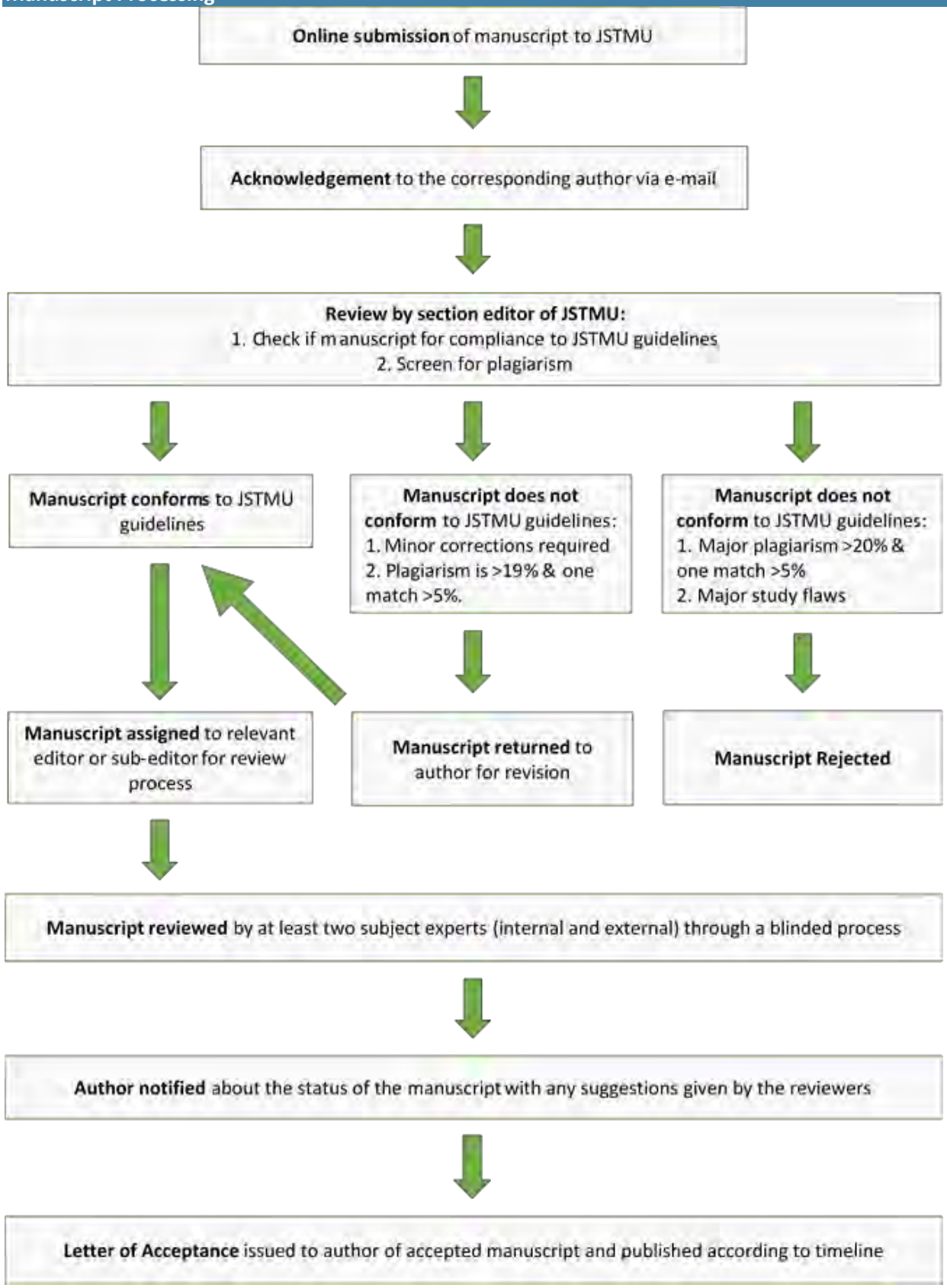

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1. Introduction
2. Objectives
3. Methodology
4. Results
5. Conclusion

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Text must be arranged under the following headings:

1. Introduction
2. Methods
3. Results
4. Discussion
5. Conclusion(s)
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Equal amounts of dietary carbohydrates have variable blood glucose response considerably as a function of specific food ingested.[1]

Bibliography/References Example:

1. Wolever TMS, Yang M, Zeng XY, Atkinson F, Brand-Miller JC. Food glycemic index, as given in Glycemic Index tables, is a significant determinant of glycemic responses elicited by composite breakfast meals. *Am J Clin Nutr* 2006; 83(6):1306–12.
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3. Results
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3. Research question

Methods:

1. Study design
2. Participants, interventions, comparators
3. Systematic review protocol
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2. Study selection and characteristics
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1. Summary of main findings
2. Risk of bias
3. Limitations
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4. Results (1000-1250 words)
5. Discussion (1000 words)
6. Conclusions (2-3 sentences)

Maximum length: **Should NOT exceed 3500 words of text** (not including abstract, tables, figures, acknowledgments, references), with no more than a total of 5 tables and/or figures and no more than 50-75 references.

** For all other information including title page, typing and reference style, please follow the original articles instructions.*

D. Case Reports/Case Series

The journal will consider only those case report/series that represent very rare case(s), or epidemic diseases that are new or emerging, or first observation(s) of some emerging phenomenon or disease. They should have clinical significance and may also include observation of new adverse effect(s) of a drug, vaccine, or procedure or other unique observations, etc. Informed written consent of the patient or next of kin (if patient is not alive or comatose/disabled) should be obtained before submission of the manuscript. A covering letter from the authors that convincingly describe the merits of the case in the light of the mentioned criteria and it's educational or scientific merits should be sent along with the manuscript.

Case Report /case series should contain a single paragraph abstract and text **should NOT exceed 1000 words** (excluding abstract, references, tables and figures) with maximum 10 bibliographic references and either three figures or three tables. Each case report must contain:

1. Abstract (unstructured - should not exceed 120 words)
2. Introduction
3. Case Presentation
4. Discussion
5. Conclusion
6. Competing interest
7. Patient consent

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E. Rapid/Special /Short Communications

Rapid/Special/Short communication should be complete work, such as COMPLETE results of a short RESEARCH study, NOT a preliminary report and **should NOT exceed 1500 words** with one figure and/or one table. An editorial decision will be provided rapidly without reviews.

F. Letters to Editor

Letters should only be written on a specific article in the most recent publication of journal. The letter should be objective and provide constructive opinions offer some academic or clinical interest to the readers.
Letters **should NOT exceed 400 words** of text and 5 references, 1 of which should be to the recent article. It should not have more than 3 authors. The text should include the full name, academic degrees, and institutional affiliation for author and the email address for the corresponding author. Letters considered for publication shall be forwarded to the author of the cited article for possible response. The editor reserves the right to shorten these letters, delete objectionable comments, make other changes, or take any other suitable decision to comply with the style and policies of the journal. For writing and references style, follow the same instructions listed above.

Letter in Reply

Replies by authors should not exceed 500 words of text and 6 references. They should have no more than 3 authors.

G. Editorial

The topics of the editorial are decided by editorial board and/or Editor-in-Chief. Editorial is written either by one member of the editorial board or some expert on that topic invited by the Editor-in-Chief. As a convention, the editorial addresses relevant areas of interest that may pertain to a range of areas influencing health and health care sciences.

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