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Vacuum Assisted Delivery Gone Wrong: A Case Report

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ABSTRACT

Vacuum assisted delivery might not be the first-choice route for delivery but remains a viable option when shortening of the second stage of labour is needed. Incorrect placement of the vacuum device, incorrect technique, prolonged use, and multiple attempts often lead to subgaleal haemorrhage, which is a collection of blood in the space underneath the galea aponeurotica. Here we would like to report a case of an infant that was delivered via vacuum assisted delivery after multiple attempts. The unfortunate infant suffered from subgaleal haemorrhage and was promptly assessed and treated. After spending 1 week in our center, he was allowed to be discharged home, with subsequent follow-up showing remarkable improvement. We would like to emphasize on the importance of this case because even though it does not occur very frequently, the consequences can be fatal if the condition is not identified and treated early.

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Introduction

Vacuum assisted delivery is not a first-choice route of delivery beforehand but remains an option when shortening of the second stage of labour is necessary (1). Scottish Professor James Young Simpson was the first person to use a vacuum instrument in obstetrics in 1849. However, he faced some difficulties with his rubber cup, and it was not until a century later that vacuum extraction regained its popularity, albeit with a stainless-steel cup device at the helm (2).

The soft and semi-soft cups were introduced in the 1970s and disposable cups and handheld pumps became popular in the 1980s (3). As of today, there are a variety of cups made from various materials available in the market. For vacuum assisted delivery, the cup must be placed onto the flexion point, which is situated at the centre of the sagittal suture, roughly three centimetres in front of the posterior fontanelle.

Traction is then applied following the pelvic curve concurrently with uterine contraction and maternal pushing effort.

The fetal head usually starts descending with the first traction. However, incorrect placement of the vacuum device contributes significantly to the development of a subgaleal haemorrhage.

A collection of blood in the space underneath the galea aponeurotica leads to the formation of subgaleal haemorrhage. It easily occurs in this area due to a plethora of emissary veins which connect the intradural venous system with superficial scalp veins (4).

The incidence of subgaleal haemorrhage is estimated to be 1 in 2,000 normal vaginal deliveries but increases to 1 in 200 cases of vacuum assisted deliveries (5).

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Case report

A male infant was born after a gestation of 38 weeks with a birth weight of 2860 g, head circumference of 35cm and length of 45cm, as the child of a nulliparous mother. The infant's mother was 29 years old with underlying gestational diabetes mellitus on diet control. Her latest oral glucose tolerance test showed a reading of 9.7mmol/L. Antenatal blood investigations were normal except for a slightly elevated level of white cell count (11.1 x 109/L). Her viral screening for HIV, hepatitis B and syphilis were unremarkable, but her vaginal culture was however positive for group B Beta-haemolytic streptococcus, for which she was adequately treated with antibiotics (Ampicillin). She had also received two doses of ampicillin during intrapartum.

During labour, the infant was delivered via vacuum assisted delivery due to poor maternal effort and fetal distress. 3 attempts were made using a Kiwi Omnicup before successful delivery of the baby. The Kiwi Omnicup dislodged during the first 2 attempts due to difficulty in determining the position of the baby's head. Only during the third attempt, the kiwi cup was successfully placed onto the flexion point. In total, it took more than 10 minutes to complete the procedure.

The baby was born limp, with no cries and no cord around the neck. He had, however, sustained a skin laceration over the mid scalp measuring approximately 8cm x 2cm with mild bulging of the occipital region of the head. The newborn was then immediately taken to the resuscitation room whereby oronasal suctioning was done. In the resuscitation room he responded well to stimuli and had an oxygen saturation of 100% under room air.

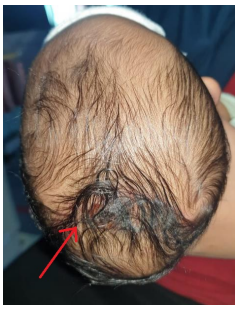

Figure 1: Superficial laceration wound sustained over scalp.

Further examination in the ward demonstrated normal tone with good reflexes, good pulse volume with warm peripheries and a capillary refill time of less than 2 seconds. On top of that, auscultation exhibited good breath sounds with equal air entry bilaterally. Regardless, the baby was given intravenous Benzylpenicillin 280 000 units (100000u/kg/dose) twice a day for 5 days and intravenous Gentamycin 12mg (4mg/kg/dose) daily for 3 days to cover for presumed sepsis. Vitamin K was also administered for 3 days due to increased INR ratio, APTT and prolonged PT. Concurrently, the baby was jaundiced due to an elevated total serum bilirubin, prompting us to start him on phototherapy, with daily monitoring of his total serum bilirubin.

At 4 hours of life, there was an increase in the head circumference of the baby to 37cm with a prominent swelling extending from the left temporo-parietal area to the occipital area. The swelling was soft, tender and boggy. The baby had also vomited 4 times in his first 16 hours of life.

Hence, he was kept fasted for the next several hours before resuming feeding. 2 plain x-rays (anteroposterior skull and lateral skull) were also taken in view of the swelling at the occipital region. The images showed no linear cortical lucency of the skull vault, intact facial bones and no lytic or sclerotic bony lesion.

It did however show opacities exterior to the skull at the parieto-occipital region. Therefore, an urgent ultrasound of the cranium was requested, and the findings are as follows: thick subgaleal anechoic collection at left parieto-occipital region with a maximum thickness of 1.7cm crossing the suture line, left parietal cephalohematoma measuring 1.3cm, normal and symmetrical ventricles with no hydrocephalus.

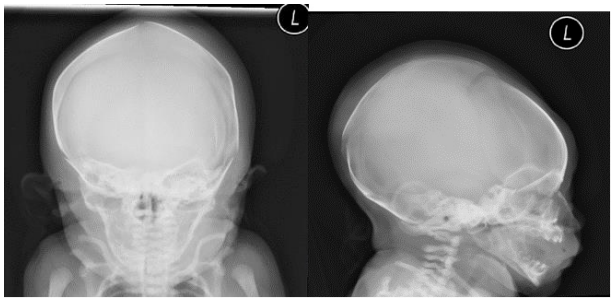

Figure 2: Anteroposterior skull and lateral skull x-rays showing opacities exterior to the skull at the parieto-occipital region

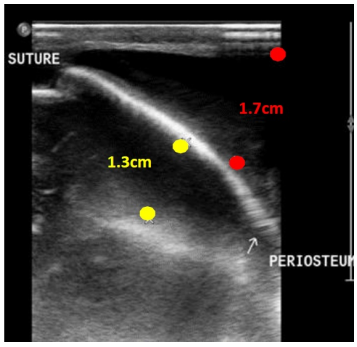

Figure 3: Ultrasound cranium showing left subgaleal hematoma (indicated by red dots) andleft parietal cephalohematoma (indicated by yellow dots)

The plan by the Paediatrics team was for conservative management of the swelling, with close monitoring of the baby and to look out for any neurological deficits or seizure.

This was followed by a referral to the ophthalmology team in view of possible presence of retinal haemorrhage. Their examination revealed normal lids, white conjunctiva with no chemosis, clear cornea, deep anterior chamber, pupils 2mm, round and reactive.

The pupils were then pharmacologically dilated 5mm. Subsequently fundoscopy was performed, exhibiting bilateral cup to disc ratio of 0.3, well defined margins, flat retina, normal macula, no vitreous haemorrhage, no salt and pepper appearance and no roth spots bilaterally.

Unfortunately, the right eye sustained blot hemorrhage below the disc measuring less than ½ of disc diameter in size, whereas the left eye sustained blot hemorrhage superotemporally along the supero temporal vessel measuring 1 disc diameter in size.

The management adopted by the ophthalmology team however was conservative, with an outpatient appointment given 1 week later for reassessment.

The baby was continuously monitored throughout his stay. By day 7 of life, his total serum bilirubin was well below photo level and his head circumference was 33cm with no more scalp swelling. Therefore, he was allowed to be discharged home.

He was however scheduled for a repeat of the ultrasound of the cranium prior to his next visit to the Paediatrics and Ophthalmology clinic.1 week later during his outpatient fundoscopic appointment in the ophthalmology clinic, there was no more retinal haemorrhage with normal vessels appearance, prompting them to discharge him. Upon examination in the Paediatrics clinic, the baby was active, well perfused and pink.

He also had no seizure episodes at home and was tolerating mixed feeding well. He however still had a small swelling over the left parietal area, which was much smaller compared to the initial swelling.

His latest ultrasound of the cranium demonstrated the following findings: smaller subgaleal hematoma at left parietal region measuring 0.4cm and a smaller left parietal cephalohematoma measuring 0.9cm not crossing the suture line.

From the latest ultrasound findings, the baby is on the right track to recovery with a vast reduction in the size of his scalp collection. Thus, we planned to periodically monitor him until the condition fully resolves.

Figure 4: Prominent swelling at occipital region at 4 hours of life.

Figure 5: Resolving swelling at occipital region on day 7 of life.

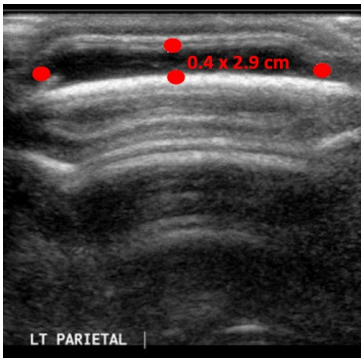

Figure 6: Ultrasound cranium/brain showing reduced left subgaleal hematoma.

Discussion

The American College of Obstetricians and Gynecologists (ACOG) stipulated 3 main criteria in which vacuum delivery is indicated, and they are fetal indication, prolonged second stage of labour and maternal indication (6). Our case fitted 2 out of the 3 criteria mentioned, hence justifying why vacuum delivery had to be applied despite its risks and complications.

The patient was also informed regarding possible complications that can arise from vacuum assisted delivery including scalp injuries, retinal haemorrhage, extracranial haemorrhage such as cephalohematoma and subgaleal haemorrhage, intracranial bleeding, brachial plexus palsy and non-haemolytic neonatal hyperbilirubinemia (1).

One of the most common complications of instrumental deliveries is extracranial haemorrhage. However, it can occur in all modes of delivery, even in utero prior to the onset of labourBased on scalp anatomy and clinical presentation, haemorrhages deep in the scalp and outside the calvarium are categorized into subgaleal haemorrhage, cephalhematoma and caput succedaneum. Table 1 below summarizes several features of these conditions to aid in establishing a diagnosis.

Table 1: Comparison of different neonatal extracerebral fluid collections

Attributes	Subgaleal haemorrhage	Cephalhematoma	Caput succedaneum
Location	Below epicranial aponeurosis, can cross suture lines and may even spread to orbit and nape of neck	Frequently occurs over parietal bones and does not cross suture lines	Occurs at point of contact and can cross suture lines
Features	Firm to fluctuant, ill-defined borders, possible crepitus	Usually unilateral, distinct borders, initially firm but becomes fluctuant after 48 hours	Soft, pitting and superficial edema, ecchymosis over injured area
Blood loss	Can be massive and is often associated with coagulopathy	Rarely severe	Minimal
Prognosis	Mortality rate of 25%	Resolves in 2 to 3 weeks	Excellent, resolves within 72 hours

When shearing forces are applied to the scalp, large emissary veins in the subgaleal space rupture, leading to blood accumulation. As the galea aponeurotica covers the entire cranial vault, the subgaleal space poses a huge potential risk for haemorrhage, from the orbits of the eyes to the nape of the neck and laterally to the temporal fascia. If the haemorrhage is massive, it can even displace the ears anteriorly. Massive haemorrhage can occur because there are no anatomic barriers, such as sutures in this space (8).

Positioning the vacuum device is crucial as incorrect traction may result in descent of only the scalp and not of the infant's entire head. Multiple dislodgments of the suction cup, applications exceeding ten minutes, increased number of pulls, and incorrect manipulation of the vacuum-assisted device also causes subgaleal haemorrhage (9).

Hence, prompt initial identification and assessment of subgaleal haemorrhage by an experienced staff, paediatrician, or neonatologist is of utmost importance. Treatment may include replacing blood volume when needed to maintain adequate organ perfusion, treating neurologic disturbances if present, and managing coagulation disorders to arrest bleeding.

The swelling gradually resolves over several days to weeks once bleeding is controlled. Even though the prognosis is good, it is prudent to have follow-up and monitor the patient closely during the first year of life to detect any residual neurologic deficits (10).

Despite its frequent occurrence, there haven't been many case reports discussing subgaleal haemorrhage and vacuum assisted delivery per se. The main limitation in our case report however is the short duration of follow-up for this patient.

Even though he recovered uneventfully, the risk of developing neurological disorders later in life cannot be disregarded. While this case may only be an isolated case and does not necessarily reflect an entire population, we hope that it will be an eye opener and provide some insight into how things can go wrong when utilizing devices for assistance during delivery.

Conclusion

Neonatal subgaleal haemorrhage is an uncommon but potentially fatal condition that is often linked to vacuum extraction. More similar cases are being encountered with the increase in usage of vacuum extractors for assisted vaginal delivery.

As the saying goes, prevention is better than cure. Hence, measures should be taken to prevent this condition from occurring, such as correct placement of the cup onto the flexion point, maintaining a steady traction in the direction of the birth canal and avoiding rocking movements.

Those involved with the delivery should also be well versed with the vacuum device used and adherently follow the manufacturer's instructions.

However, if this condition does occur, early recognition and appropriate timely management is essential to improve the clinical and neurological outcome, thus decreasing the mortality rate.

Ethics Approval and Consent to Participate

While ethics approval is not applicable in this case report, the principles outlined in the Declaration of Helsinki were strictly followed throughout the entire process to ensure that the authors acted in the patient's best interest when providing medical care while adhering to the ethical guidelines.

Written informed consent for patient information and images to be published was provided by the patient's mother.

Acknowledgment

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Conflict of Interest

The authors declare no conflict of interest

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Psychological Function and Serum Vitamin D Concentration in COVID19- Patients: A cross-sectional study

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ABSTRACT

Introduction*:* The pandemic of COVID-19 created a psychological response. So, the psychological function of COVID-19 patients is an important subject that forces us to follow up with them.

Aim: Assess the correlation between vitamin D serum concentrations and psychological functions such as insomnia, stress, and depression through the COVID-19 pandemic

Methods: In this cross-sectional study, blood samples from 120 COVID-19 patients (61 males and 59 females) who had more than 30 years, were taken. Also, 25(OH)D Serum level of COVID-19 patients was analyzed. The Insomnia Severity Index (ISI), Depression anxiety stress scales (DASS), and the Short Form Health Survey (SF-36) were used to analyze insomnia, anxiety, stress, quality of life, and depression.

Results: The relationship between temperature (p=0.039), PCO2 (p=0.022), and serum vitamin D level was significant. Additionally, there was a significant correlation between stress (p=-0.023, OR=0.389, 95% CI for OR=0.047, 0.843), depression (p=0.012, OR=0.659, 95% CI for OR=0.476, 0.913), and the concentration of serum vitamin D.

Conclusion: This study recommends that vitamin D supplementation improve psychological state in COVID-19 patients.

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Introduction

A cluster of previously unknown pneumonia was reported, in Wuhan, China in December 2019 (1). Since, COVID-19 has spread globally, infecting more than 270 million persons. Also, it caused 5≥ million deaths as of December 2021 (2).

To hinder the fast propagation of COVID-19, social distancing and home-office measures were imposed worldwide, reducing outdoor activities and interpersonal interactions (3). The extreme changes caused by the pandemic have contributed

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contributed to the emergence of a psychological health crisis in many countries, as various studies have demonstrated (4,5). Studies have shown an association between economic stagnation and massive lockdowns due to the pandemic and an escalation in suicide rates, and the prevalence of depressive traits has increased more than three times since the pandemic's beginning (6,7,8).

UNICEF has reported, social isolation as a COVID-19 consequence impairs the psychological health of Australian teenagers in terms of increasing their levels of anxiety (9). Social isolation has also contributed to loneliness, boredom, stress, and fear (9, 10). People with psychological health situations before, are even at higher risk for deterioration or recurrence of their symptoms (11,12).

However, the degree of susceptibility to the psychological distress imposed by the pandemic depends on social support, exposure to mass media, duration of isolation, infection conditions, and lifestyle habits, including nutrition (13). Previously, a relationship between neuropsychological situations like depression and bipolar disorder and vitamin D deficiency was reported in several studies (14,15).

Vitamin D (25(OH)D) is a neuroactive substance that modulates cell growth, inflammation, detoxification, neurotransmitter synthesis, and development in the central nervous system (16, 17). Vitamin D regulates mood via increasing brain serotonin availability by increasing the expression of tryptophan hydroxylase two enzymes. This enzyme is needed for sufficient serotonin production (18). Therefore, low levels of vitamin D causes psychological disorder. Also, vitamin D inadequacy boosts the secretion of pro-inflammatory factors like interleukin-6 by increasing nuclear-factor kappa B expression (19).

Inflammation in the brain increases the risk of mental disorders like depression and anxiety (20). Furthermore, decreased vitamin D level is connected with altered responses to stressors and traumatic events (21,22). A meta-analysis revealed a significant connection between insufficiency of vitamin D and the risk of depression. It recommends that the supplementation of vitamin D could be helpful in depressive patients with hypovitaminosis (23). Additionally, vitamin D supplementation has shown a considerable enhancement in symptoms of individuals diagnosed with depression in comparison to placebo, which could highlight a causal association between reduced vitamin D concentration and depressive traits (24,25).

However, vitamin D function in depression is still debated and requires more study (23,26,27). As vitamin D deficiency is noticeably common among the population, with more than a billion individuals affected by it globally, the importance of investigating its different effects cannot be stressed more at the time of the pandemic (28).

Therefore, we aimed to estimate the correlation between vitamin D serum concentrations and mental function in the COVID-19 pandemic.

Materials and Methods

Study design

In 2021, our cross-sectional study was administered in Imam Reza Hospital in Mashhad, on 120 patients with COVID-19 who were aged >30 years. Without anti-depressant drug treatment, hepatic or renal failure, cancer, metabolic bone disease, and autoimmune diseases throughout the previous six months were the exclusion criteria. Informed written consent was provided by all subjects. The trial was confirmed by the Ethics Committee of MUMS (Mashhad University of Medical Sciences), Mashhad, Iran.

All the participants in the main study who met the inclusion criteria were included in this study based on global sampling (29).

General and clinical characteristics

At first, we collected clinical and demographic characteristics such as smoking status, age, and the data of comorbidity from each subject by professional questioner.

Blood Collection and Biochemical Measurements

Blood samples were collected from all subjects following a 12-hour fasting period in plain Vacutainer tubes. All blood samples were centrifuged at 5000 g for 15 minutes at 4° C to isolate serum. 25(OH)D serum levels were evaluated by commercial ELISA kits (Pishgaman Sanjesh- Iran) using an Awareness/Stat Fax 2100 analyzer.

Depression anxiety stress scales (DASS)

To evaluate mood status, we used DASS (30). DASS is a questionnaire that includes three subscales and consists of 7 questions, generally consists 21 items. Every question is on a four-point (0-3) Likert scale to recognize the intensity of affective disorders like stress, anxiety, and depression.

Every item score should be doubled, as DASS 21 is a summarized version of DASS 42. In DASS, a higher score reveals an increased in negative emotion, and a lower score shows a decreased in negative mood status. The validity and reliability of DASS have been reported in the Iranian population before (31). The scores of stress, anxiety, and depression were separated into two classifications: No or minimal scores, and some degree of affective disorders. The scores received from every item were find out as follows: (≤14, No), (>14, some degree of stress), (≤ 9, No), (> 9, some degree of depression), (≤7, No), (>7, some degree of anxiety).

Insomnia Severity Index (ISI)

The ISI is a self-report tool for determining insomnia that has seven items. The dimensions evaluated are the distress caused by sleep problems, noticeability of sleep disorders by others, early morning waking up problems, interference of sleep problems with daytime functioning, sleep dissatisfaction, severity of sleep onset, and sleep preservation (32).

According to the severity, every item scored on a 0–4 scale. The overall scale ranges from 0 to 28 and is defined as follows no insomnia (0–7), sub-threshold insomnia (8–14), mild insomnia (15–21), and severe insomnia (22–28). The reliability and validity of the Persian version of this questionnaire have been proved in the Iranian population (Cronbach's a>0.8 and intra-class correlation coefficient >0.7) (33).

Quality of Life Questionnaire

We used SF-36 validated questionnaire to assess the general quality of life. SF-36 is categorized into eight subscales, including Mental Health, Role Emotional, Vitality, General Health, Physical Functioning, Role Physical, and Bodily Pain Social Functioning. This questionnaire's scoring ranges from 0 to 100. The SF-36 Persian version was evaluated in a prior study and showed construct validity and good reliability (34).

Statistical analysis

We used the statistical package for social sciences (SPSS) version 16 for analyzing data. The normality distribution of continuous variables was estimated using the Kolmogorov-Smirnoff and Shapiro-Wilk tests. Normally and non-normally distributed variables were presented using mean and standard deviation (SD); were presented using mean and standard deviation (SD); and median and interquartile range (IQR), respectively. The data was double-checked to correct errors regarding outliers and missing variables.

For the remaining missing variables, multiple imputation was performed based on gender, age, and other related variables to the missing variables using the SPSS software. We compared usually distributed and non-normally distributed variables between groups using the independent t-test and Mann-Whitney test, respectively. The chi-square test was performed to compare the distribution pattern of categorical variables between groups.

Also, we used Binary logistic regression to evaluate the relationship between achieving serum vitamin D >30 ng/mL after the intervention as the dependent variable, and the scores of DASS-21 subscales, total SF-36, ISI, and sleep quality scores, as independent variables. The statistical significance level was regarded as $p<0.05$.

Results

One hundred twenty patients (59, 49.1% females and 61, 50.9% males) cooperated in the current study. The mean age of the patients was 60.38±13.61 years old. We separated subjects into two groups; 1) the level of serum vitamin D 30 ng/mL or above, and 2) serum vitamin D below 30 ng/mL. Comparison of the demographic and medical history variables between subjects with levels of serum vitamin D above 30 ng/mL and below 30 ng/mL are presented in Table 1.

Table 1. Comparison of demographic and medical history variables between patients with serum vitamin D levels above 30 ng/mL and below 30 ng/mL

Variable		Vitamin D < 30 ng/mL n=68	Vitamin D > 30 ng/mL n=52	p-value
Gender	Male	35 (57.9%)	26 (42.1%)	0.870
	Female	33 (56.4%)	26 (43.6%)	
Residential status	Male	64 (57.1%)	48 (42.9%)	0.395
	Female	5 (62.5%)	3 (37.5%)	
Hypertension		26 (55.3)	21 (44.7%)	0.721
Diabetes		24 (52.2%)	22 (47.8%)	0.359
CVD		14 (56.0%)	11 (44.0%)	0.884
Smoking		57 (60.0%)	38 (40.0%)	0.146

and In Our study the level of serum vitamin D was 30 ng/mL or above in 52 (42.9%) of the patients. There was an insignificant difference in demographic and medical history variables between patients with levels of serum vitamin D below above 30 ng/mL ($p>0.05$).

A comparison of the clinical variables, DASS-21 subscale, SF-36, and sleep quality scores with the levels of serum vitamin D below and above 30 ng/mL is presented in Table 2.

There was a significant difference between temperature ($p=0.039$) and PCO2 ($p=0.022$) of The relationship between DASS-21 subscales, SF-36, and ISI scores and improved serum vitamin D in the study patients are presented in Table 3.

There was a significant correlation between stress ($p=-0.023$, OR=0.389, 95% CI for OR=0.047, 0.843) and depression ($p=0.012$, OR=0.659, 95% CI for OR=0.476, 0.913) and Vitamin D levels.

Table 2. Comparison of clinical variables and scores in DASS21- subscales, SF36-, and insomnia between patients with serum vitamin D levels above 30 ng/mL and below 30 ng/mL

Variable	Vitamin D < 30 ng/mL n=64	Vitamin D > 30 ng/mL n=48	p-value
Pulse rate (/min)	87.00 (14.50)	90.85±10.46	0.201†
Respiratory rate (/min)	21.96±3.65	27.00±5.63	0.326‡
Temperature	37.00 (0.63)	37.15±0.31	0.039*†
SBP (mmHg)	133.27±20.57	131.77±23.61	0.694‡
DBP (mmHg)	80.15±16.26	79.62±13.85	0.854‡
SPO2 (%)	83.50 (12.75)	89.00 (12.00)	0.320†
O2 saturation (%)	73.15 (6.45)	65.40 (37.25)	0.311†
PaO2 (mmHg)	41.65±13.54	33.10 (24.35)	0.418†
PCO2 (mmHg)	40.72±11.15	48.18±17.67	0.022*†
Depression	9.00 (9.25)	7.00 (3.50)	0.090†
Anxiety	13.00 (9.50)	11.92±3.90	0.491†
Stress	10.50 (9.50)	10.00 (6.50)	0.907†
Quality of life	53.77±18.04	59.32±20.25	0.864‡
Insomnia Severity Index	2.00 (10.00)	1.00 (5.50)	0.665†

SBP: Systolic Blood Pressure, DBP: Diastolic Blood Pressure, SPO2: Blood Oxygen Saturation, PaO2: Arterial Oxygen Pressure, PCO2: Arterial carbon Dioxide Pressure, min: Minute, mmHg: Millimeters Mercury, mEq: Milli Equivalent, L: Liter,

Table 3. Relationship between depression, stress anxiety, quality of life and insomnia scores and improved

Variable	B	Wald	p	OR	95% CI for OR	
					Lower	Upper
Depression	-0.416	6.282	0.012*	0.659	0.476	0.913
Anxiety	-0.105	0.689	0.407	0.901	0.704	1.153
Stress	-0.329	5.191	0.023*	0.389	0.047	0.843
Insomnia	-0.085	1.997	0.158	0.918	0.816	1.033
Quality of Life	-0.009	0.246	0.620	0.991	0.955	1.028

Binary logistic regression was done.

These results revealed that with one point increase in depression scores, the risk of achieving vitamin D levels above 30 mg/mL decreases by 34.1%. Furthermore, with one point increase in stress core, the risk of achieving vitamin D levels above 30 ng/mL decreases by 38.9%. Although we obtained all these results, more studies are required to confirm all of the findings and to determine all the mechanisms that vitamin D affects psychological function.

Discussion

In this cross-sectional study, the correlation between vitamin D concentration and psychophysiological factors among 120 COVID-19 patients was assessed. There was a significant correlation between higher levels of vitamin D and reduced depression and stress in patients. The correlation between vitamin D and mental disorders has been investigated in various studies (35,36,37).

Our data show a significant correlation between the reduced severity of mental effects caused by COVID-19 and 25(OH) D concentrations (at least 30 ng/mL). In line with our study, some experimental studies have shown a significant correlation between increased major depression and vitamin D deficiency (38). Pu et al. showed lower serum 25-OH-D3 levels increase the severity of depression (39). Murphy et al. found that a reduced level of serum 25(OH) D is associated with depression (40).

Also, a meta-analysis of cohort and cross-sectional studies suggested that depressive disorders are related to reduced vitamin D concentrations (41).

It can be due to the extensive impact of Vitamin D on modulating mental function, including neurotransmitter release (42,43,44), neuroprotection (45, 46), maintaining cognitive ability (47, 48), and protection against adverse outcomes of chronic stress (49,50).

Increasing inflammatory factors like TNF-α, IL-1β, and IL-6 change the release and effect of neurotransmitters such as glutamate, serotonin, and dopamine (51).

Vitamin D effectively decreases inflammation and oxidative stress. Selective Serotonin Reuptake Inhibitors (SSRI) are used to reduce the pro-inflammatory cytokine's adverse effects in the brain. (52) Also, oxidative stress is associated with depression by damaging DNA (53). The supplementation of vitamin D increases the gene expression that correlates with antioxidation (glutamate–cysteine ligase modifier subunit and glutathione reductase) (54).

Therefore, vitamin D decreases oxidative stress and improves depression. One of the most COVID-19 outcomes is stress which affects psychological stability (55). Our study revealed that the levels of vitamin D are associated with pressure in COVID-19 patients. Tehrani et al. indicated that adults had higher priority and had lower levels of vitamin D (56).

Another study revealed that higher vitamin D levels reduce stress (57). Also, Trovato et al. found that increased consumption of vitamin D or sunlight exposure is related to lower perceived stress among participants (58). In contrast, insignificant association was found between stress in another study and vitamin D levels (59). Reducing stress may be related to the improvement of depression (57).

So, it helps COVID-19 patient's mental health and decreases stress.

We have some limitations in our study. At first, this is a cross-sectional study that cannot find causality. Also, our study was on Covid-19 patients, which can limit the generalization of the results to other populations. We included patients who had recorded 25(OH) D concentrations. Some confounding factors, like social, economic status and smoking, did not register for all participants and might have a reasonable effect on the severity of COVID-19. Additionally, the RT-PCR test has not been performed on all participants with COVID-19 clinical signs. Second, our study is cross-sectional. Thus, we cannot define the relationship between the sufficiency of vitamin D and the decreased risk of depression or stress among COVID-19 patients.

In conclusion, this study revealed that vitamin D concentrations are related to depression and stress. A higher concentration of serum vitamin D may decrease depression and stress risk among COVID-19 patients. Additional longitudinal large-scale studies are needed to prove our findings. Therefore, these findings might shed more light on the pathophysiology of COVID-19 symptoms.

If these findings are observed in other studies, some of the associated symptoms of COVID-19 may be prevented or improved through nutritional interventions both at the community and hospital levels. Furthermore, physicians might better anticipate of the prognosis of symptoms in COVID-19 patients who present degrees of depression and stress.

Ethical statements

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Availability of data and materials

The datasets collected and/or analyzed during the present study are not publicly accessible due to ethical concerns, but the corresponding author may provide datasets upon reasonable request.

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Mashhad University of Medical Sciences (MUMS)

Reviews in Clinical Medicine

Clinical Research Development Center Ghaem Hospital

A case report of PVOD in a young woman with pulmonary hypertension

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ABSTRACT

Pulmonary veno-occlusive disease (PVOD) is a rare and fatal disease with non-specific clinical presentation often misdiagnosed as group 1 pulmonary arterial hypertension (PAH). The rate of occurrence per one million people is reported to be one-tenth to two-tenths of cases, annually. Our case was a 25-year-old young woman who complained of aggravation of dyspnea during exertion and slight chest pain for two months. Her work-up included pulmonary function test (PFT), an echocardiogram, body box plethysmograph test, diffusing capacity of the lungs for carbon monoxide (DLCO) test, positive ventilation/perfusion (V/Q) scan, computed tomography (CT) scan of chest, cardiac catheterization, and video-assisted thoracopic surgery (VATS). Echocardiography showed high pulmonary artery systolic pressure (PASP). The particular aspect of the present case was that due to the V/Q scan, the patient was diagnosed with chronic thromboembolic PH (CTEPH) and treated with anticoagulant, which did not have a good response. The crucial point is that in PVOD patients, V/Q scan can report segmental and subsegmental defects similar to CTEPH patients that creates a diagnostic challenge in patients. Definitive diagnosis of PVOD was based on VATS. Hypoxia, decreased DLCO, normal V/Q scan, and chest CT findings were used to diagnose PVOD. The patient's treatment with diuretics, bosentan, and tadalafil led to the recovery of the patient's hypoxia, saving her life for further treatment. With respect to the heterogeneous nature of the clinical presentation in PVOD patients, high clinical suspicion and appropriate diagnostic measures are required for diagnosis. The present study showed that PAH specific drugs in addition to diuretics can be used cautiously to control disease progression and save patients for lung transplantation.

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Introduction

Pulmonary veno-occlusive disease (PVOD) is a rare form of fatal pulmonary arterial hypertension (PAH) (1,2) that has clinical and hemodynamic similarities to group 1 PAH (3). PVOD and PAH both show evidence of pulmonary hypertension, characterized by elevated pulmonary artery pressure (equal to or greater than 25 mm Hg at rest) that eventually leads to right heart failure and death (4).

PVOD prevalence is estimated at 0.1 to 0.2 per million people annually (2,5). This disease was first described by Dr. Julius Hora in 1934 by diffuse obstruction of the pulmonary veins by fibrous tissue, pulmonary venous congestion, and associated complications including severe pulmonary hypertension (pHTN), non-cardiogenic pulmonary edema, hypoxia and right ventricular failure (5,6).

In terms of etiology, occupational exposure

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to organic solvents such as trichloroethylene and various chemotherapy agents, especially alkylating agents, bone marrow transplantation, and radiotherapy have been related to PVOD (7).

Biallelic mutations in the eukaryotic translation initiation factor 2 alpha kinase 4 (EIF2AK4) gene are pathogenic and lead to hereditary PVOD (3). The clinical manifestations of patients are usually nonspecific and include shortness of breath that worsens during exertion, fatigue, chest pain, dizziness, cough, and hemoptysis (6). Diagnosis of PVOD is based on clinical presentation and tissue confirmation (2). Although the gold standard for confirming the diagnosis is lung biopsy, due to the risk of bleeding posed by fragile pulmonary veins, biopsy is unsafe in most patients with PAH and is not performed (1,5). Usually, the initial clue to the diagnosis of PVOD is a combined imagine of PAH with concomitant pulmonary edema findings on diagnostic imaging (2,5).

The preferred diagnostic method is non-invasive cross-sectional imaging, e.g., CT (1). The diagnostic process typically includes a high-resolution CT scan of the chest, a pulmonary function test with diffusion capacity, a V/Q scan, an echocardiogram, and cardiac catheterization. The use of PAH-specific therapy for PVOD, which is often misdiagnosed as idiopathic pulmonary arterial hypertension (categorized as PAH class I by WHO) (6), precipitates life-threatening pulmonary edema (3). Unfortunately, PVOD is usually diagnosed late in its clinical course, and has a very poor prognosis (4).

Currently there is no medical treatment to prevent disease progression and lung transplant is the best and final treatment available (6). In the present study, a case of PVOD in a young woman with pulmonary hypertension who finally became a lung transplant candidate is described. The aim of the present study was to provide valuable information regarding the diagnosis of PVOD, its clinical symptoms, and its management. The diagnostic challenge created at the beginning of the patient's treatment and promptly changing the treatment approach was the unique aspect of this study.

Case report

The case subject was a 25-year-old woman who visited the lung clinic due to shortness of breath and a frequent cough. She complained of aggravation of dyspnea during exertion and mild chest pain. SpO2 was 88% at the time of admission, which decreased after brief activity. Cyanosis and clubbing were not identified in the clinical examination. The patient had slight tachycardia and tachypnea. Lung auscultation showed bilateral crackle, particularly in the right lung. The patient complained of worsening symptoms in the last two months. After visiting the doctor, the patient was treated with azithromycin and a respiratory inhaler for about 10 days, but her symptoms did not improve significantly. In the first visit of the patient in our center, the pulmonary function test (PFT) was requested for her, and due to the patient's shortness of breath during exertion, she was referred to a cardiologist for cardiac examination and echocardiography. The spirometry test showed restrictive composition: FEV1: 58%, FVC: 56%, FEV/FVC: 85.

Echocardiography results indicated moderate RV enlargement with mild systolic dysfunction, mild RVH (FAC: 31%), and severe pulmonary hypertension (PASP≥85-90 mmHg). According to the restrictive pattern of lung involvement in PFT, the patient was a candidate for the body box plethysmograph test and diffusing capacity for carbon monoxide (DLCO) test (Table 1).

Table 1. The results of the body box and DLCO tests

Test	Result	Test	Result
FEV1	58%	TGV	98%
FVC	56%	TLC	78%
FEV1/FVC	82	RV	133%
RAW (tot)	55%	RV/TLC	169%
sRAW (tot)	54%	DLCO	46%

FEV1: Forced expiratory volume in the first second; FVC: Forced vital capacity; RAW: Airway resistance; sRAW: specific airway resistance; TGV: Thoracic gas volume; TLC: Total lung capacity; RV: Residual volume; DLCO: Diffusing capacity for carbon monoxide

Considering the high rate of PASP in echocardiography and the severe decrease of DLCO in the body box test, the V/Q scan was requested for the patient. In the V/Q scan, segmental and sub-segmental defects were observed similar to CTEPH patients. Hence, it showed high probability for pulmonary embolism (PE) according to PIOPED criteria. According to the results of the V/Q scan and high PASP, the patient was diagnosed with CTEPH and treated with anticoagulants, but due to the lack of improvement in symptoms and worsening of dyspnea, she finally became a candidate for right heart catheterization (RHC).

RHC results were as follows: Right atria pressure (RAP):8 mmHg, right ventricular pressure (RVP): 50/0-10 mmHg, pulmonary artery pressure (PAP): 50/30(36) mmHg, pulmonary capillary wedge pressure (PCWP):10 mmHg, cardiac output (CO):7lit/min, and cardiac index (Cl):4.7 lit/min/m2. Pulmonary angiography showed no filling defect. Results of imaging (Fig 1) exhibited ground glass opacity (GGO), septal lines, mediastinal lymphadenopathy, and presence of pleural effusion (PE) (Fig 2). With respect to the appearance of septal thickening and GGO mostly in the upper lobes, the

patient became a candidate for VATS. Pathology results revealed pulmonary veno-occlusive disease (PVOD)/pulmonary capillary hemangiomatosis (PCH).

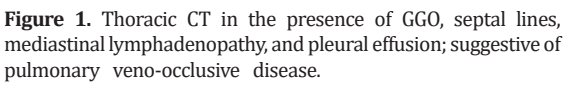

Figure 1. Thoracic CT in the presence of GGO, septal lines, mediastinal lymphadenopathy, and pleural effusion; suggestive of pulmonary veno-occlusive disease.

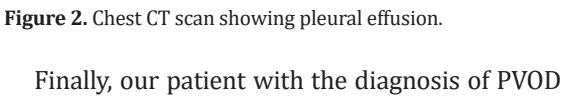

Figure 2. Chest CT scan showing pleural effusion.

Finally, our patient with the diagnosis of PVOD was treated with diuretics, bosentan and tadalafil. At follow-up visits, the patient's hypoxia improved and she was referred to another center for lung transplant evaluation. The measures taken for the patient and the results of the decisions and interventions are shown in Fig 3.

Figure 3. Flow of events with interventions and outcomes

Discussion

PVOD can occur in the first year of life or in the seventh decade, but most cases are reported in children and young adults, with a male to female ratio of 2 to 1 (8). The great similarity in terms of clinical symptoms and hemodynamic characteristics between PVOD and idiopathic PAH can be challenging for the differential diagnosis of PVOD and the possibility of misdiagnosis is high (9). Hence, 5 to 10% of cases initially diagnosed as PAH are actually patients with PVOD (6).

In the present case, the correct and timely diagnosis of PVOD led to partial recovery of the patient and prepared her for the next stage of treatment. A case of PVOD was reported in a 27-year-old woman in Italy, who was misdiagnosed as idiopathic PAH for six months. Like the present report, the case was treated with diuretics and bosentan, leading to the patient's recovery (9).

These two drugs were administered because diuretics are used in the treatment process of RV failure (10) and clinical improvement or stabilization has been reported in a number of patients treated

with oral bosentan (8).

According to a case report from China, two cases of PVOD were misdiagnosed as idiopathic PAH. In these cases, typical findings of PAH were absent and mutation screening revealed the presence of PVOD by identifying the EIF2AK4 gene. These patients had a good response to PAH-targeted therapy (2). However, some PAH-specific drugs may be dangerous in patients with PVOD and can cause fatal pulmonary edema (11).

In fact, treatment guidelines for PVOD are not defined (6) and there are few treatment options other than lung transplant for PVOD (11). Due to the relatively fast progressive nature of the disease and late or misdiagnosis, the prognosis of PVOD is poor and the survival time is short. One-year mortality is estimated at 72% (6).

In our case, GGO, septal lines, and mediastinal lymphadenopathy were seen in the thoracic CT scan images. Bilateral pleural effusions, GGO, hilar and mediastinal lymphadenopathy, and interlobular septal thickening are typically not seen in patients with idiopathic PAH or CTEPH (5).

In the present study, the result of the DLCO test was 46%. In a 57-year-old female of PVOD, RHC showed near normal pulmonary hemodynamics. Lung function was normal, but DLCO was only 42% (12). Similar to our study, Montani et al. also stated that severe hypoxia and severely decreased DLCO, V/Q scan with normal results, severe PH on RHC, and CT scan findings including GGO, lymphadenopathy, and septal thickening along with high clinical suspicion can be extremely effective in the diagnosis of PVOD (9).

Conclusion

In conclusion, regardless of the rarity of PVOD, considering the poor prognosis of the disease and the low chance of survival in case of late or wrong diagnosis, it is necessary to include PVOD in the differential diagnosis of PAH through a comprehensive clinical and diagnostic work-up.

Although the cautious use of PAH-specific treatments along with diuretics to slow down the progression of PVOD and improve the patient's clinical condition is not a definitive treatment for the patient, it can act as a bridge to bring the patient to a lung transplant. This case report can be helpful in future research in the approach of PVOD patients who had a positive ventilation scan in the examinations performed.

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Diagnostic Value of Neck Circumference and Sternomental Distance for Difficult Intubation in Patients Undergoing Cesarean Section

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ABSTRACT

Introduction: Airway safety for difficult intubation or failure to intubate is important during anesthesia. This study assessed the airway before anesthesia, and the diagnostic value of neck circumference (NC) and sternomental distance (SMD) tests was investigated in predicting difficult tracheal intubation during cesarean section.
Methods: In a cross-sectional study, 101 women who were candidates for cesarean section were selected through the convenience and non-random sampling method. The modified Mallampati test (MMT), upper lip bite (ULBT), thyromental distance (TMD), neck circumference (NC), and sternomental distance (SMD) tests were performed to estimate the laryngoscopy problem. The success rate of airway assessment by SMD and NC was evaluated using the Cormack-Lehane score. Data analysis was performed using the software SPSS version 16.0.
Results: TMD (p=0.034) and NC (p<0.001) indicated substantial association with laryngoscopy grades. The sensitivity was 35.29% and 58.82%, and the specificity was 93.93% and 59.09% for NC and SMD. The accuracy, NPV, and PPV of NC was higher than the SMD test (74% vs. 59%, 73.80% vs. 73.58, and 75% vs. 42.55%). The PPV and NPV were 43.63% and 77.77% for TMD. MMT, with high sensitivity (73.52%) and specificity (90.90%), increased the risk of difficult laryngoscopy up to 24-fold when adjusted for TMD, SMD, and NC [p<0.001; OR=24.38 (6.31-94.25)]. Although NC indicated low sensitivity, it had maximum specificity (93.93%) in predicting difficult intubation.
Conclusion: High Mallampati grades increase the risk of difficult laryngoscopy. NC presented low predictive values, and SMD and TMD lack predictive values for difficult intubation.

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Introduction

Maintaining the safety of the patient's airway during anesthesia is a critical principle that must be managed with the least complications and best performance (1). Incomplete or unsuccessful performance of airway control is associated with perioperative morbidity and mortality. Identifying situations and patients at risk for airway management problems is key to optimal care (2, 3). Tracheal intubation is one of the methods for airway control (4). One of the risk factors and a major concern for anesthetists in airway management during surgery, such as cesarean

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birth, is difficult intubation or failure to perform tracheal intubation. Hypoxia, cardiorespiratory arrest, and pulmonary aspiration are dangerous complications during tracheal intubation, sometimes leading to death (5).

Anatomical and physiological changes such as a larger tongue and airway edema in pregnant women cause more problems during intubation than in other patients (6). Anesthesiology trainees are responsible for 2.5% of women's deaths during cesarean section, mostly related to airway control problems and failed tracheal intubation (7). Accurate recognition with laryngoscopy and the diagnosis of specific intubation conditions before anesthesia is very important because it can help the medical staff choose the appropriate equipment and safer techniques for intubation and avoid the complications of unsuccessful performance (8). Preoperative evaluation includes the modified Mallampati test (MMT), measurement of thyromental distance (TMD), sternomental distance (SMD), and neck circumference (NC). Measurement of NC and SMD are high-sensitivity tests that cannot be performed in some cases despite the recommendation to perform them simultaneously (9). In previous studies, the accuracy of these tests was evaluated. Researchers reported the sensitivity and specificity of the NC test to be more than 70%. However, others, like in the present study, showed a 30% sensitivity (10, 11). In addition, the TMD test in some studies showed 100% sensitivity in non-obese people and 80% in obese people (11). The present study also reported this scale at about 70%. The PPV scale in all studies was calculated to be around 30-40%, similar to our results. These results were also true for the SMD test. A previous study found a lower specificity (26%) and NPV (50%) for SMD. However, PPV was higher (59%) in the obese population than in the present study (11). Furthermore, in some studies, its use alone without the need for other tests has been suggested (12). However, the success of this test in obese patients has not yet been determined, and it is recommended not to use this test alone in obese subjects. In this study, in addition to the modified Mallampati test, upper lip bite, and TMD tests, assessment of the airway before anesthesia was performed by two methods, SMD and NC, and the success rate of these tests in predicting difficult tracheal intubation or failure in intubation during cesarean section was investigated.

Materials and Method

Study population

In a cross-sectional study, women candidates for cesarean section who referred to Mashhad teaching hospitals in 2022 were selected using a non-random sampling method.

Inclusion and exclusion criteria

Women over 18-years who had the conditions necessary for general anesthesia for elective surgery were included. Likewise, subjects could sit properly and did not have a history of psychological and neurological diseases and head or neck trauma. Patients were excluded if their diagnosis changed. All patients provided written informed consent before the start of the study.

Study procedure

One-hundred and one women were evaluated to be enrolled in the study, and demographic information such as age, height, weight, and BMI were collected. An expert anesthesiologist measured the sternomental and cervical distance before anesthesia for all subjects.

The SMD (the distance between the upper edge of the sternum and the chin) was measured using a non-flexible ruler with an accuracy of 0.5 cm while the patient's mouth was closed and the head was completely fixed. The SMD size of 12.5 cm was considered the standard for predicting difficult intubation (8). The NC was measured from a point just below the larynx (Adam's apple) and perpendicular to the long axis of the neck in a sitting position. The TMD was measured as the distance between the thyroid notch and the tip of the chin protrusion using a non-flexible ruler.

After receiving propofol (2 mg/kg) and succinylcholine (neuromuscular relaxant, 1 mg/kg), the patients were intubated by another specialist who was not aware of the study. The level of intubation difficulty was evaluated using the Cormack-Lehane (CL) classification system, ULBT, and MMT. CL classification is a gold standard for predicting difficult laryngoscopy and tracheal intubation. CL grades 1 (full view of glottis) and 2 (partial view of glottis or only posterior extremity of glottis seen or only arytenoid cartilages) were considered easy, and grades 3 (only epiglottis seen, none of glottis seen) and 4 (neither glottis nor epiglottis seen) were considered difficult laryngoscopies from the inability to visualize the vocal cords. The ULBT three classes comprise: class I, where a patient can raise the lower incisors above the vermilion line; class II, where a patient can bite the upper lip below the vermilion line; and class III, where a patient cannot bite the upper lip. A difficult airway was defined by grade III in the ULBT. The MMT has five classes: class 0: any part of the epiglottis is visible; class I: soft palate, uvula, and pillars are visible; class II: soft palate and uvula are visible; class III: only the soft

palate and base of the uvula are visible; class IV: only the hard palate is visible. A difficult airway was defined by grades III and IV in the MMT.

Sample size

A sample size of 101 patients was calculated according to the odds ratio of difficult laryngoscopy in patients with big NC [odds ratio (OR): 5.17, 95% CI: (1.05-25.5)] in the Riad study (11) using α=0.05 and β=0.2 and 10% drop out.

Statistical analysis

Data was analyzed using the software SPSS version 16.0 (SPSS Inc., Chicago, Illinois, United States). The sample size was calculated according to the data from the study by Riad et al. (13) and based on OR=6. Data was described by mean± standard deviation (SD), frequency, and percentage for continuous and categorical variables. The Kolmogorov-Smirnov test evaluated the normal distribution. Fisher's exact test or chi-square test tested the association of qualitative variables. Quantitative variables were compared using the independent sample t test. The predictive role of parameters was evaluated using a logistic regression test. Sensitivity, specificity, positive predictive value, negative predictive value, and accuracy were evaluated for all considered measures. A P-value less than 0.05 was considered significant. Diagnostic values of sensitivity, specificity, PPV, NPV, and accuracy were calculated according to the following formulas:

Sensitivity=true positive (TP)/TP+ false negative (FN); Specificity=true negative (TN)/TN+false positive (FP); PPV (positive predictive value)=TP/TP+FP; NPV (negative predictive value)=TN/TN+FN; accuracy=TP+TN/TP+TN+FP+FN.

Ethical approval

Ethical clearance and approval were obtained from the ethics committee of the Mashhad University of Medical Sciences (MUMS) under the number IR.MUMS.MEDICAL.REC.1400.803.

Results

The age range and mean were 17-43 and 31.12 years, respectively. Twenty-six (25.7%) and thirty (15.8%) women had a BMI of less than 30 and more than 35, respectively. Also, NC and SMD mean were measured at 32.63±2.15 mm and 12.68±0.54 mm, respectively. Hypothyroidism or hyperthyroidism was observed in about 10% of subjects. Moreover, the prevalence of cardiovascular diseases and gestational diabetes among patients was 17.8%, and preeclampsia was observed in 12 women. The demographic data of the subjects have been listed in Tables 1 and 2.

Patients were divided into two groups based on the laryngoscopy grade difficulty. Although NC (p=0.585) and SMD (***p***=0.383) means did not show any association between the two groups, the height (p=0.029) and weight (p=0.008) showed significant differences between the difficult and easy groups. The Mallampati (p<0.001) and upper lip bite (p=0.004) grades showed significant differences between the two groups. Moreover, likely laryngoscopy scores, TMD, NC, and SMD were divided into difficult and easy groups. The results showed a substantial association between TMD (p=0.034) and NC (p<0.001) groups with laryngoscopy categorical grades. The results are presented in Table 3.

Gestational diabetes and cardiovascular disease were the most common diseases among

Table 1. Demographic features in the study subjects

Characteristics	Mean±SD	Standard Deviation (SD)	Minimum	Maximum
Age (years)	31.12	6.41	17	43
Height (cm)	161.20	3.67	150	174
Weight (kg)	83.02	9.16	65	110
BMI (kg/m^2)	31.93	3.15	26.45	41.91
Thyromental distance (cm)	6.64	0.40	6.00	7.50
Neck circumference (cm)	32.81	0.86	30.00	34.50
Sternomental distance (cm)	12.68	0.54	12.00	14.00

Table 2. Clinical features in the study subjects

Characteristics	Number	Percent
Diabetes mellitus	2	2.0%
Gestational diabetes	18	17.8%
Cardiovascular disease	18	17.8%
Thalassemia	1	1.0%
Preeclampsia	12	11.9%
Asthma	1	1.0%
Skeletal diseases	1	1.0%
Thyroid disorder	10	%9.9
AIDS	1	1.0%
Hypertension	14	13.9%
Addiction	2	2.0%

Table 3. Association between demographic and clinical characteristics and laryngoscopy classification

Characteristics		Easy (N=66) Mean±SD	Difficult (N=34) Mean±SD	P-value
BMI (kg/m²)		31.23±2.63	33.35±3.63	0.530
Age (years)		31.00±6.13	31.71±6.76	0.430
Thyromental distance (cm)		6.73±0.35	6.47±0.44	0.246
Neck circumference (cm)		32.36±2.53	33.15±0.92	0.585
Sternomental distance (cm)		12.79±0.52	12.46±0.51	0.383
Characteristics		Number (%)	Number (%)	P-value
Modified Mallampati score	0	0 (0.0%)	0 (0.0%)	<0.001
	1	19 (100.0%)	0 (0.0%)	
	2	41 (82.0%)	9 (18.0%)	
	3	6 (21.4.0%)	22 (%78.6)	
	4	0 (0.0%)	3 (100.0%)	
Upper lip bite grade	1	49 (%76.6)	15 (%23.4)	0.004
	2	17 (%47.2)	19 (%52.8)	
	3	0 (0.0%)	0 (0.0%)	
Thyromental distance	Easy	35 (%77.8)	10 (%22.2)	0.034
	Difficult	31 (%56.4)	24 (%43.6)	
Neck circumference	Easy	62 (%73.8)	22 (2%6.2)	<0.001
	Difficult	4 (25.0%)	12 (75.0%)	
Sternomental distance	Easy	39 (%73.6)	14 (%26.4)	0.097
	Difficult	27 (%57.4)	20 (%42.6)	

patients. Data are presented in Table 4. Multivariate logistic regression showed that a higher Mallampati grade significantly increased the risk of difficult laryngoscopy [OR=24.38, 95% CI: (6.31-94.25), p-value <0.001], where it was adjusted for SMD, TMD, and NC. Results are shown in Table 5. Finally, Mallampati indicated maximum sensitivity (73.52%) and specificity (90.90%), with high positive predictive value (80.64%), negative predictive value (86.95%), and accuracy (85.00%). TMD also had a sensitivity of 70.58% and an NPV of 77.77%. However, other values were low. The results are shown in Table 6.

The ROC plot for considered tests is shown in Fig. 1. Area under the curve was 0.33, 0.69, and 0.33 for TMD, NC, and SMD, respectively. The ROC

Table 4. Comparison of underlying diseases in patients with easy and difficult laryngoscopy

Underlying diseases	Easy (N=66) Number (%)	Difficult (N=34) Number (%)	P-value
Diabetes mellitus	1 (50.0%)	1 (50.0%)	0.999
Gestational diabetes	10 (%55.6)	8 (%44.4)	0.410
Cardiovascular disease	10 (55.6)	8 (%44.4)	0.410
Thalassemia	1 (100.0%)	0 (0.0%)	0.999
Preeclampsia	7 (%58.3)	5 (%41.7)	0.536
Asthma	1 (100.0%)	0 (0.0%)	0.999
Skeletal diseases	1 (100.0%)	0 (0.0%)	0.999
Thyroid disorder	7 (70.0%)	3 (30.0%)	0.999
AIDS	1 (100.0%)	0 (0.0%)	0.999
Hypertension	7 (50.0%)	7 (50.0%)	0.225
Addiction	2 (100.0%)	0 (0.0%)	0.547

Table 5. Risk of difficult laryngoscopy in relation to anthropometric indicators

Characteristics	OR	P-value	95% CI	
			Lower	Upper
Mallampati (grade 3 and 4)	24.38	**<0.001**	6.31	94.25
SMD (≤12.5 cm)	0.46	0.265	0.12	1.80
TMD (≤6.5 cm)	2.02	0.271	0.5	7.04
NC (≥33.5 cm)	1.92	0.443	0.361	10.2

TMD: thyromental distance, NC: neck circumference, SMD: sternomental distance, OR: odds ratio, CI: confidence interval, cm: centimeter

Table 6. Diagnostic value of the Mallampati, SMD, TMD, and NC scores for difficult laryngoscopy

Characteristics	Sensitivity	Specificity	PPV	NPV	ACC
Mallampati (grade 3 and 4)	73.52%	90.90%	80.64%	86.95%	85.00%
SMD (≤12.5 cm)	58.82%	59.09%	42.55%	73.58%	59.00%
TMD (≤6.5 cm)	70.58%	53.03%	43.63%	77.77%	59.00%
NC (≥33.5 cm)	35.29%	93.93%	75.00%	73.80%	74.00%

PPV: Positive predictive value, NPV: Negative predictive value, ACC: Accuracy, TMD: Thyromental distance, NC: Neck circumference, SMD: Sternomental distance

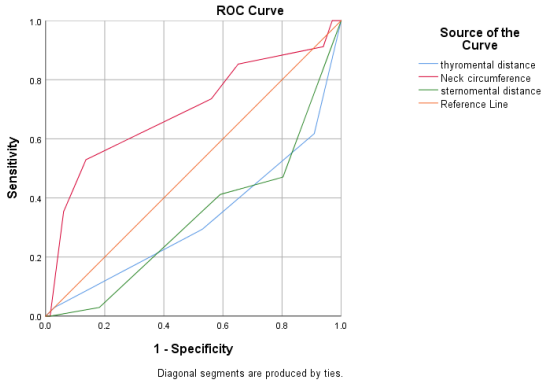

Figure 1. ROC plot for TMD, NC, and SMD measures

plot is shown in Fig. 1.

Discussion

A cross-sectional study investigated the association of anthropometric indicators and difficult laryngoscopy in patients undergoing caesarian section. Results showed that the higher grades of Mallampati increased the risk of difficult laryngoscopy. The specificity, PPV, and NPV of Mallampati in grade 3 and 4 was 90.90%, 80.64%, and 86.95%, respectively.

The effect of anatomical and physiological changes in the airway on the difficulty of intubation is clear. Mallampati et al. predicted difficult intubation in 28 out of 210 cases of direct laryngoscopy (13). These changes during pregnancy place the parturient at increased risk for airway management problems. So, performing a thorough pre-anesthetic evaluation and identifying the factors predictive of difficult intubation is essential. This study found that short height and heavy weight is more common in difficult laryngoscopy groups, and all indicators except SMD had significant differences between difficult and easy groups. Also, due to the high accuracy, specificity, and sensitivity of the Mallampati score, which has a standard limit above 80%, it can be considered the first tool to evaluate intubation status. While the NC test indicated low sensitivity, it could diagnose 93% of true negatives out of all subjects and had significant accuracy. Therefore, like the results of previous studies, this test can effectively predict difficult intubation. Moreover, the SMD and TMD tests indicated low sensitivity and specificity.

Previous studies showed that using a single assessment score decreased the effects of screening tests for difficult intubation (14). Therefore, combinations of tests may add some incremental diagnostic value. Researchers in past studies combined several factors, which is a multivariate system. However, the main problem is the existence of several variables and spending much time. So, using two scores may increase the diagnostic value while not significantly increasing the test limitation16 ,15)). Airway characteristics and changes in pregnant women, such as edema or tongue enlargement, are similar to those in obese patients. According to past studies, NC, TMD, and SMD indicators were selected among the predictors of difficult intubation (2, 17). Our results showed that neck circumference was a better indicator than TMD and SMD. However, multivariate analysis showed no association between NC/SMD/TMD and difficult intubation.

Several studies have been conducted on the association of obesity with difficult intubation in pregnant women and other patients. For example, oropharyngeal anatomy is double in obese pregnant women, and patients have a high risk for airway management problems (6). These women are at increased risk for anesthesia-related morbidity and mortality during cesarean surgery, particularly due to failed intubation during procedures under general anesthesia. Screening the airway condition and proper management by as-

sessment and accuracy tools can greatly prevent these complications (3, 6). In a study, 250 pregnant women scheduled for cesarean section were analyzed for the efficiency of different preoperative difficult intubation tests. The MMT, SMD, and TMD revealed more difficult intubations than the actual number of cases. The results showed that the combination of the upper limb bite test and thyromental distance test is superior to other methods for predicting difficult intubation in pregnant women (8).

Laryngoscopy will be easy or difficult, which may be predicted by using the Mallampati score. Despite diagnostic limitations, it is still a convenient and practical method that can easily be applied in the clinical setting (8). Merah et al. found 87.1% sensitivity and 99.6% specificity in the Mallampati test. They concluded that the MMT could be used to predict difficult intubation18)). However, another study indicated that the Mallampati test produced many false positive results (19). In our study, the MMT had 73.52% sensitivity, 90.90% specificity, 80.64% PPV, and 86.95% NPV, and these results were similar to some previous studies (8). However, the accuracy of this test was higher compared to other indicators.

Head extension is important in predicting whether the intubation will be easy or difficult. Patel et al. indicated that the SMD had a sensitivity and specificity of 91% and 92.7%, respectively. They said that If SMD was less than 12.5 cm, it was considered a predictor of a difficult intubation (20). The results of the sensitivity and specificity of the SMD test in the present study were lower than in previous studies (21). It was proved that it was not a useful test for predicting difficult intubation. The difference in results can be related to the size of the examined samples. For example, in a study conducted by Prakash et al., they enrolled 610 patients to evaluate LD by the SMD method. Finally, they reported sensitivity and specificity of 66% and 60%, respectively (22). However, in the present study, only one-hundred patients participated.

An accurate tool for estimating overweightness and obesity in people is the neck circumference size. A neck circumference ≥32 cm in women should be considered the cutoff point for being overweight. The relationship between the NC size and intubation conditions has been investigated and it has been proven that in several studies more patients with larger NC were in the difficult intubation group. For example, Riad et al. found that neck circumference >42 cm (p=0.044) was an independent predictor of difficult intubation. Also, in the present study, NC had a significant association with the laryngoscopy easy/difficult category (22).

Although the high specificity (94%) of the TMD test was remarkable in our study, Jimson et al. reported that TMD ≤7 cm was not a good predictor of difficult intubation preoperatively, as it had a low sensitivity (32%), and high specificity (80%). On the other hand, Patel et al. reported that TMD (<6.5 CM) had a sensitivity and specificity of 100% and 75.8%, respectively (20). There is disagreement that it is the best test for predicting hardship intubation.

Since a single test is insufficient to predict difficult intubation, it was reported that a combination of tests would obtain the most accurate results. In a study, the MMT, TMD, and SMD tests in single form were weak regarding sensitivity, specificity, and PPV. When MMT was combined with TMD or SMD, the sensitivity decreased, and the NPV remained at 93%. They found that the specificity for the MMT with the TMD increased from 89% to 100% and increased from 27% to 100% with SMD (23). Furthermore, Patel et al. indicated that combining MMT, SMD, and TMD increases the assessment validity of difficult intubation in adults compared to individual tests (20). Although the safe outcome of anesthesia is an important goal for every anesthesiologist during cesarean sections, there is still no test or group of tests predicting 100% of difficult laryngoscopies. However, our findings alongside previous reports highlight the importance of the modified Mallampati test as a valuable test for the prediction of difficult laryngoscopy for the management of patients under cesarean surgery.

Like other studies, this project had some limitations that should be acknowledged. The number of patients was one of the limitations of the present study, and more studies with larger populations should be conducted to increase the power. Underlying diseases such as diabetes or gestational hypertension might affect the results, so homogenous samples concerning underlying diseases should be selected in the subsequent studies. It is also better to research male or female patients undergoing other surgeries so that the results are comprehensive.

Conclusion

Although the big NC, short TMD, and high grades of ULB and Mallampati were associated with difficult laryngoscopy, patients with grades 3 and 4 of the Mallampati score had 24 times greater risk of difficult laryngoscopy. NC indicates low predictive value and SMD and TMD lack predictive value, and the modified Mallampati is a valuable test for the prediction of difficult laryngoscopy because of its high specificity, PPV, NPV,

and accuracy. These findings could assist clinical professionals choose valuable and precise tests to predict laryngoscopy statuses, which could increase the quality of patients' safety during anesthesia.

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Reviews in Clinical Medicine

Clinical Research Development Center Ghaem Hospital

Prolonged Fever and Coronary Artery Involvements: Kawasaki Disease or Systemic Juvenile Idiopathic Arthritis?

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ABSTRACT

Introduction: The symptoms and laboratory findings of Kawasaki disease (KD) and systemic-onset juvenile idiopathic arthritis (SoJIA) may overlap in the early phases. Coronary artery lesions are common complications seen in KD.

Cases Presentation: In this article, we report three cases of SoJIA (two males and one female) with prolonged relapsing fever and coronary artery involvement. Initially, all three cases were presumed to have KD and were treated with IVIG. All three cases had arthritis and lymphadenopathy, and one of them had a skin rash. After 3-8 weeks, fever and main clinical symptoms returned. In the second evaluation, they met the criteria for SoJIA and were treated with methylprednisolone, ibuprofen, and methotrexate. High ferritin levels were observed in all three cases (mean=6024 ng/ml).

Conclusion: Coronary artery involvement may rarely be seen in the early phases of SoJIA. Continuing or relapsing fever, late-onset arthritis, and increased serum ferritin levels may help distinguish SoJIA from KD.

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Introduction

Kawasaki disease (KD) and systemic-onset juvenile idiopathic arthritis (SoJIA) are two febrile inflammatory illnesses in children that exhibit similar clinical and laboratory manifestations in the early phase of the disease, such as prolonged fever, lymphadenopathy, rashes, arthritis, and increased inflammatory markers (1). However, the presence of splenomegaly, generalized lymphadenopathy, and frequent febrile episodes may suggest SoJIA over KD, making the definitive diagnosis challenging at times (2). Although coronary artery lesions are a known complication of KD, they are rarely reported in patients with SoJIA (3).

Prolonged fever, along with increased inflammatory markers and coronary artery involvement, is usually diagnosed as incomplete KD and treated with intravenous immunoglobulin (IVIG). However, patients with KD who are IVIG-resistant will eventually improve with methylprednisolone, which is an effective treatment for SoJIA. Moreover, early administration of methylprednisolone pulses could prevent macrophage activation syndrome (MAS), a life-threatening complication of rheumatologic and inflammatory disease that is much less frequent in KD than in SoJIA (4). Transient response to IVIG and recurrent episodes of fever favor a diagnosis of SoJIA (1, 2, 5, 6). Some manuscripts have

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also described a combined diagnosis of KD and SoJIA, which is not relevant to our study (7). In this manuscript, we report three cases of SoJIA that were initially diagnosed as KD.

Case Presentation

Clinical, laboratory, and echocardiographic findings of the patients are summarized in Table 1.

Case 1

A four-year-old boy presented to our rheumatology clinic with a high-grade fever for seven days and an ill appearance, followed by generalized maculopapular rashes, right-sided cervical lymphadenopathy, arthralgia, and left knee arthritis. His medical history revealed that he had a short period of isolated and self-limited fever four months ago. The initial evaluation revealed a normal blood leukocyte count, anemia (Hb=8.6 g/dl), thrombocytosis (PLT=426×109/L), elevated ESR (115 mm/hour), and CRP (55 mg/L) levels, normal urine analysis, normal AST, ALT, and Alb levels. Septic arthritis with normal left knee arthrocentesis was excluded. More specific tests such as parvovirus B19 IgM, anti CCP, PANCA, CANCA, anti dsDNA, ANA, anti ASO titer, and brucellosis tests were also within the normal limits. Ferritin level was 9948 ng/ml. Left main coronary artery (LMCA) ectasia and an abnormal tapering of the right and left coronary arteries (RCA and LCA) were found in the echocardiography test.

He was treated with 2 g/kg IVIG and high-dose aspirin (ASA) with the diagnosis of incomplete KD. The fever and other complaints were resolved two to three days after initiation of therapy, except for left knee arthritis. He was discharged with low-dose ASA. In the first outpatient follow-up (one month after discharge), reduced LMCA size was found. However, he still had knee swelling and no finger desquamation. In the second follow-up (three months after discharge), the LMCA ectasia was improved and RCA was normal, but the arthralgia had progressed with mild swelling in the other joints, including wrists, elbows, knees, and ankles. Elevated ESR and CRP levels (93 and 96, respectively) were also found. So, the diagnosis of SoJIA with coronary artery involvement was raised, and the patient received IV methylprednisolone. The treatment was followed by oral prednisolone (1 mg/kg/day), ibuprofen (30 mg/kg/day), and methotrexate (MTX) (10 mg/m2/weekly). Systemic symptoms were controlled one month after initiation of treatment, and the arthralgia and arthritis subsided after six months. After three months, prednisolone was tapered off, and ibuprofen and methotrexate were continued for the next six months and then gradually tapered off. He was symptoms-free in three years of follow-up.

Case 2

A three-year-old girl was referred to us with fever and arthritis in her knees and right wrist for a week, which led to limping. One month ago, she was admitted to another pediatric hospital due to an isolated prolonged fever (20 days). She was diagnosed with incomplete KD because of fever, increased ESR and CRP levels, and severe brightness of coronary arteries on the echocardiography examination and had received a standard treatment protocol for KD, including IVIG and ASA. In the current admission, we found elevated ESR and CRP levels (71 and 148,

Table 1. Comparison of the clinical manifestations, laboratory, and echocardiographic findings of the patients

	Case 1	Case 2	Case 3
Gender	Male	Female	Male
Age	4	3	8
Fever duration in the current attack, days	7	7	10
Conjunctivitis	No	No	No
Skin rash	Yes	No	No
Arthritis	Yes	Yes	Yes
Lymphadenopathy	Yes	No	Yes
WBC, ×10³/ µl	7.5	12.5	18.2
Hemoglobin, g/dl	8.6	7.9	11.3
Platelet, ×10³/ µl	426	647	560
ESR, mm/h	115	93	85
CRP, mg/l	55	96	65
Ferritin, ng/ml	9948	5626	2500
Echocardiography findings	LMCA ectasia, RCA, and LCA abnormalities	LMCA aneurysm	LAD ectasia, pericardial effusion

respectively), mild leukocytosis (WBC=12500 with 65% PMNs), anemia (Hb=7.9 mg/dl), and thrombocytosis (647×100). Other laboratory data were within normal ranges, including Wright, 2ME, ANA, RF, anti CCP, AST, ALT, and Alb. Ferritin level was 5626 ng/ml. In the ultrasonography, prominent effusion and synovial thickening of the left knee and mild effusion of the right knee and right wrist were reported. The tri-phasic bone scan showed polyarthritis in the knees, left elbow, right wrist, and right hip. In the echocardiography test, an aneurysm in LMCA (5mm) was revealed. Therefore, the diagnosis of SoJIA presenting with an unusual pattern was made. Prednisolone, MTX, and low-dose aspirin were administered. The signs and symptoms improved after a few weeks. In the follow-up visits, the LMCA size was reduced to 3 mm and then normalized completely. The maintenance treatments were tapered off based on standard protocols. However, in long-term follow-up, she had a disease flare-up after one year.

Case 3

The last case involved an 8-year-old boy who presented with a 10-day fever, knee arthritis, and submandibular lymphadenopathy. The symptoms had started three months ago with prolonged fever, generalized lymphadenopathies, and arthritis. He was admitted to a tertiary pediatric hospital and underwent a diagnostic work-up. He had increased ESR and CRP levels and thrombocytosis along with cardiac involvement, mild LAD dilation, and mild pericardial effusion. He was treated with IVIG, a pulse dose of methylprednisolone, and ASA with a diagnosis of KD. The symptoms subsided until the fever started again 10 days ago. In the current admission, the laboratory findings revealed leukocytosis and neutrophilia (WBC=18200, PMN: 72%), thrombocytosis (PLT=560×109/L), elevated ESR (85 mm/hour) and CRP (65 mg/L) levels, and serum ferritin equal to 2500 ng/ml. The bone marrow aspiration and biopsy were normal. The diagnosis of SoJIA was made as a diagnosis of exclusion. The signs and symptoms were resolved after three pulses of methylprednisolone. He was discharged with a maintenance dose of prednisolone and ibuprofen. In the follow-up visits, the complaints improved, but he had two disease flare-ups in the three-year follow-up.

Discussion

The diagnosis of KD and SoJIA is typically based on clinical and laboratory criteria, the clinical suspicion of the clinician, and the exclusion of similar diseases; there are no specific diagnostic tests. Table 2 compares the clinical manifestation, laboratory, and echocardiographic findings of Kawasaki Disease, SoJIA, and MAS.

Fever is a main characteristic in both diseases that tend to be acute self-limiting in KD and chronic relapsing in SoJIA (7). In Dong et al.'s study, the incidence of presumed patients with KD with a subsequent diagnosis of SoJIA was estimated at 0.2%. They were predominantly caucasian and experienced more MAS compared

Table 2. *Comparing clinical manifestation, laboratory and echocardiographic findings of Kawasaki Disease, SoJIA *, and MAS***

		Kawasaki Disease	SoJIA	MAS
Clinical Manifestation	Fever	Almost/ Always	Almost/ Always	Almost/ Always
	Skin Rash	Common (Morbilliform)	Common (Salmon rash)	Uncommon
	Conjunctivitis	Common	Rare	Rare
	Changes in extremities	Common	Rare	Rare
	Lymphadenopathy	Cervical	Generalized	Generalized
	Visceral involvement	Rare	Common	Common
	Arthritis	Uncommon	Always	Common
	Serositis	Rare	Common	Common
	Koebner phenomenon	Rare	Common	Common
Laboratory findings	WBC	↑	↑	↓
	Platelet	↑	↑	↓
	Hb	↓	↓	↓
	ESR	↑	↑	↓
	CRP	↑	↑	↑
	Ferritin	↔↑	↔↑	↑↑
	Liver enzymes	↔↑	↔↑	↑↑
	Triglyceride	↔↑	↔↑	↑↑
Cardiac involvement	Myocarditis	Uncommon	Uncommon	Common
	Pericarditis	Uncommon	Common	Common
	Coronary artery abnormalities	Common	Rare	Rare

*Systemic onset juvenile idiopathic arthritis
** Macrophage activating syndrome

to patients with KD (1). So, when fever relapses, SoJIA should be considered, as well as MAS (4).

Mucous membrane involvement, especially conjunctival injection, is a frequent manifestation of KD, vasculitis of medium and small size vessels. Oxidative stress, endothelial dysfunction, and neutrophil infiltration in the wall of the small vessels in the early phase of KD lead to these mucocutaneous manifestations (8, 9). Conjunctivitis was reported infrequently in KD patients with a subsequent diagnosis of SoJIA (1), which is in line with our study.

Arthritis is present in both diseases. In KD, arthritis is divided into two categories: early-onset polyarticular arthritis in the acute phase and late-onset oligoarticular arthritis in the sub-acute phase. The inflammatory markers in KD with early-onset arthritis are significantly higher compared to KD without arthritis. In pre-IVIG literature, cardiac outcomes such as coronary artery aneurysms and early-onset arthritis were more frequent (1). In the acute phase of KD, the arthritis is symptomatic and painful with notable inflammatory reactions in synovial fluid and most likely will be resolved after IVIG administration. Otherwise, it will be resolved spontaneously 2-4 weeks later in the sub-acute phase (6). In the subacute phase of KD with oligoarticular arthritis, there is more inflammation in the tissues compared to in the systemic circulation (10, 11). Therefore, late-onset arthritis especially unresponsive to IVIG, even in the presence of coronary artery involvement, favors SoJIA over KD. The innate immune system has a critical role in the acute phase of KD. Activated monocytes secrete IL1, IL6, and TNFα, and macrophages cause the acute phase manifestations of KD (12). The number of monocytes/macrophages and the level of IL1, IL6, and TNFα are directly related to coronary artery involvement in KD. In patients with KD and coronary artery involvement non-respond to IVIG, the level of IL10, IL6, INF-y, and TNFα was demonstrated to be higher than the other cytokines (12, 13). IL1 and IL6 are two important cytokines in the pathogenesis of SoJIA, and IL6 also has a critical role in the pathogenesis of vasculitis. Therefore, the pathogenesis of coronary artery involvement in SoJIA and the acute phase of KD may be the same. Observed benefits from the IL-1 receptor antagonist anakinra in both relapsing KD and SoJIA support this finding (1, 14, 15).

In the sub-acute phase of KD, the elastin degeneration of coronary walls progresses to the aneurysm due to vascular inflammation, activation of the acquired immune system, and lymphocytic infiltration. TNFα and its receptor have been shown to be at the highest levels in IVIG-resistant patients with coronary artery aneurysms. Indeed, the polymorphism of TNFα has been demonstrated in this group (16). The genetic variations and super-antigen specifications may play a critical role in this phenomenon.

Inflammation and increased cytokines stimulate macrophages and result in elevated ferritin levels. In SoJIA and KD, especially in IVIG-resistance cases and high TNFα, ferritin levels could be elevated (16, 17). In SoJIA, the innate immune system, macrophages, and cytokines have a more pivotal role in the pathogenesis of the disease than KD (1, 17). In Mizuta et al.'s study, measurement of serum ferritin levels has been suggested as a useful diagnostic marker to differentiate SoJIA from KD, as higher ferritin levels favor the diagnosis of SoJIA (17). Our three cases also showed high ferritin levels (mean=6024 ng/ml). So, the higher level of ferritin, especially in the early phase, should be considered important and should lead the physician to another differential diagnosis including SoJIA.

In conclusion, systemic inflammation in KD and SoJIA may be caused by similar cytokines derangements. Recurring fever, late-onset and IVIG-resistant arthritis, and high ferritin levels in patients with KD should raise the possibility of SoJIA.

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Reviews in Clinical Medicine

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A Case Study and a Brief Review on Dermatopathological Drug Reaction in Major Thalassemia

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ABSTRACT

Introduction: Thalassemia consists of a variety of genetic hemoglobinopathies. Thalassemia-major causes anemia in early age. Those suffering from thalassemia need frequent life-long blood transfusions to survive, resulting in iron overload in the body and many health problems. Much improvement has occurred in predicting the course of Thalassemia major thanks to iron chelation therapy. Edible iron chelating agents are the standard of the chelating process. Deferasirox is a newly developed orally active iron chelating tablet which is used on a daily basis. Th present case study investigated severe dermatopathological reactions to the Iranian made product of Deferasirox.

Case presentation: We present a case of adverse drug reactions in a thalassemic patient who was started on Deferasirox orally after receiving Deferoxamine injections for several years with no serious reactions. The patient experiences generalized maculopapular, deep red- blue partially purpuric itchy skin rashes throughout her body. The histopathological biopsy found superficial perivascular or dermatitis with low-grade vasculopathy, few eosinophils, and mild psoriasis form-supraglottic-lichenoid epidermal reactions associated with Drug Reaction diagnosis.

Conclusion: With regard to inherent features, caution must be applied to start the Deferasirox for the patients who will undergo the oral chelation process with a smooth increase in the daily dosage for a few weeks in order to create improved tolerance.

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Introduction

Thalassemia is the worst clinical case of genetic global hemoglobinopathies (1- 4), and the most widespread genetic hemoglobin (Hb) condition across the world. Patients suffering from β-thals assemia major (TM) or transfusion-dependent thalassemia (TDT) require lifelong blood transfusions to achieve a pretransfusion Hb >9.0 g/ for normal growth. This disorder leads to iron overload, causing complication in several organs including hepatic impairment, endocrine glands dysfunction, heart failure, skin hyperpigmentation, and diabetes mellitus (DM). Therefore, receiving an iron chelation regimen is indispensable to minimize the complications associated with iron excess (5-6).

Thalassemia is among a class of genetic blood disorders which are caused as a result of decreased (β+) or nonexistent (β0) synthesis of the hemoglobin beta-globin chains, resulting

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in reduced red blood cells (RBC) as well as anemia (4). The phenotypes of inherited heterozygous compound beta-thalassemia comprise thalassemia major and thalassemia intermedia (TI). Patients suffering from thalassemia major experience severe anemia in early age, which necessitates lifelong transfusion of blood and iron chelating medications for survival while patient with thalassemia intermedia may not need them (1, 4, 7).

As an adverse effect of regular blood transfusion, vital organs including the heart, kidneys, liver, and tiny endocrines undergo hemosiderosis, which damage the tissues and leads to organ dysfunction. Although iron chelating agents considerably improve the rate of survival depending on blood transfusion, multi-organ hemosiderosis occurs frequently (7- 9).

Deferasirox (DFX) is a newly developed edible iron chelating agent prescribed to be used on a daily basis. The commonly observed complications of Deferasirox include gastrointestinal disorders (15.2%), skin rash (10.8%), as well as a brief rise in serum creatinine and increases in the levels of liver enzyme (38%) (10-13).

Numerous longitudinal research projects have shown the safety and effectiveness of DFX. This medication has been shown to result in maculopapular rash in almost one in ten patients. There have been reports of effective desensitization to DFX in delayed drug hypersensitivity reactions (DHR), including maculopapular rash and erythema multiforme. In these reports, it took many days to determine the desirable dosage. Few studies have reported rapid hypersensitivity reactions (10-14). Thus, we report an instance of immediate dermatopathological drug reactions in a patient suffering from thalassemia after having been prescribed Deferoxamine (DFO) combined with Deferiprone (DFP) without any serious undesirable reactions.

Case report

This case presentation was approved in Ethics Committee of Biomedical Research in Royan Institute IR.ACECR.ROYAN.REC.1401.032. Our case was a 44-year-old female with beta thalassemia, who had received consistent transfusions from the age of five after being diagnosed with the disease. She has been constantly transfused with an interval of 21days. She had been previously prescribed chelating with DFO and DFP. The ferritin level in her body oscillates in the range of 800.0 and 1300 ng/mL (mean 1149ng/mL). Her weight and height are currently 64kg and 164cm, respectively. She has had healthy growth with no adverse effects in the liver or heart . Her latest clinical lab examination results are presented in Table 1.

She has received an Iranian made generic DFX which is an oral iron-chelator as the original DFX has been unavailable. She stopped receiving her usual iron chelating treatment and was started on oral DFX tablets (360 mg), with dosage based on 20 mg/kg/day, two tablets daily, morning and night, and the dosage being increased to three, for the subsequent weeks. Nine days after getting started on the tablets, she complained of deep red-blue partially purpuric itchy skin rashes (maculopapular eruption) and received treatment at (Figure 1). The rashes began in the face and neck, expanding downwards to affect all the body. Based on her history, she had only experi-

Table 1. Patient's clinical data at the time of adverse reaction

Parameters	At referred time	Reference range
Ferritin (ng/mL)	1149	Male: 12 to 300 ng/mL Female: 12 to 150 ng/mL
Cardiac MRI t2* (ms)	39.8– Normal	>20 ms
Hepatic MRI t2* (ms)	10.95– mild Hemosiderosis	>17 ms
LIC (dry weight mg/g)	2.820779	<1.8dry weight mg/g
WBC (10^9/L)	5.6	4.5 to 11.0 × 10^9/L
Hb (g/dL)	9.5	Male: 13.2 to 16.6g/dL Female: 11.6 to 15 g/dL
Platelets (10^3/L)	454	150 to 450 10^3/L
PT (sec)	15.4	
Activated PTT(sec)	36.8	28-44
Glucose (mg/dL)	91	Adult: 74-100mg/dL

ng/mL: nanograms per milliliter
;WBC: white blood cell count
;Hb: hemoglobin
(MRI T2: magnetic resonance imaging (cardiac> 20 ms; normal, Hepatic>17 ms: considered normal
LIC: Liver iron content

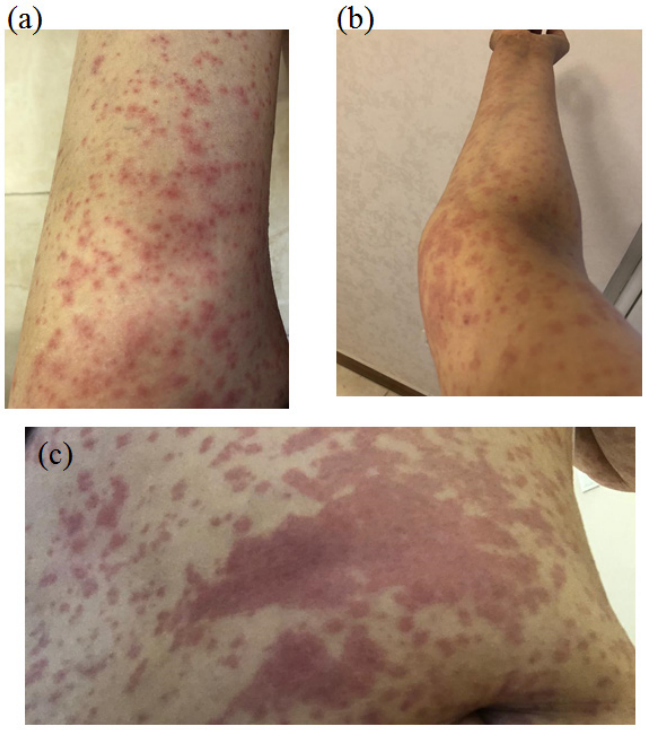

Figure 1. Drug reaction severity (a) leg, (b) arm, and (c) abdomen lesions on the day of referring to the clinic

enced a rise in the number and severity of skin lesions, without any breathlessness, shortness of breath, or losing consciousness.

Further examination revealed that the condition was maculopapular eruption, deep red- blue partially purpuric itchy skin rashes throughout her body. No other organs showed any complications upon physical examination. Laboratory examinations showed a low level of Hb (9.5g/dL), average WBC and platelet count, PT, and activated PTT. The functions of the liver and kidneys were found to be normal. The patient stopped taking oral DFX and, based on the dermatologist's prescription, and was started on oral high dose steroids (one stat Betamethasone LA IM, and 15mg/day for three days and gradual decrease), topical Clobetasol ointment as well as oral antihistamines. The rash started to subside and complete recovery was achieved within two weeks of DFX discontinuation. However, an ecchymotic lesion was seen on the left leg on the healing maculopapular rash (Figure2). To establish the cause of hypersensitivity and its type, skin biopsy was carried out after obtaining the patient's consent upon her first visit. A specimen was taken in formalin which comprised a piece of punch skin biopsy which measured 0.2x0.2cm in terms of surface area and 0.2cm in terms of thickness.

The results are presented as a microscopic description and diagnosis as follows in the next section.

Microscopic Description

A small part of the skin tissue showing mild basket weave keratosis, focal parakeratosis, Irregular mild epidermal acanthosis, slight spongiosis as well as small foci of vacuolar degeneration of basal keratinocytes along with individual cell apoptosis scattered around.

The dermis underneath shows slight RBC extravasation with a mild infiltrate of lymphocytic inflammatory cells and few eosinophils around blood vessels with prominent endothelial cells mostly in the superficial portion of the skin.

Microscopic diagnosis (Skin biopsy of body lesion)

Superficial perivascularor dermatitis with low grade vasculopathy, few eosinophils and mild psoriasiform-spoaglotic-lichenoid epidermal reactions which are associated with Drug Reaction.

After this adverse drug reaction was treated by corticosteroids and the patient returned to a normal and stable situation, she was started on iron chelation therapy again based on DFPO combined with DFP. The drug administrator was informed about the adverse complication.

Since there was a doubt that this might be an adverse reaction to the intrinsic molecule of DF, two months later, the patient accessed the original brand medicine of DFX with a gradual increase of the dose to the prescribed one. The treatment response was accurately monitored

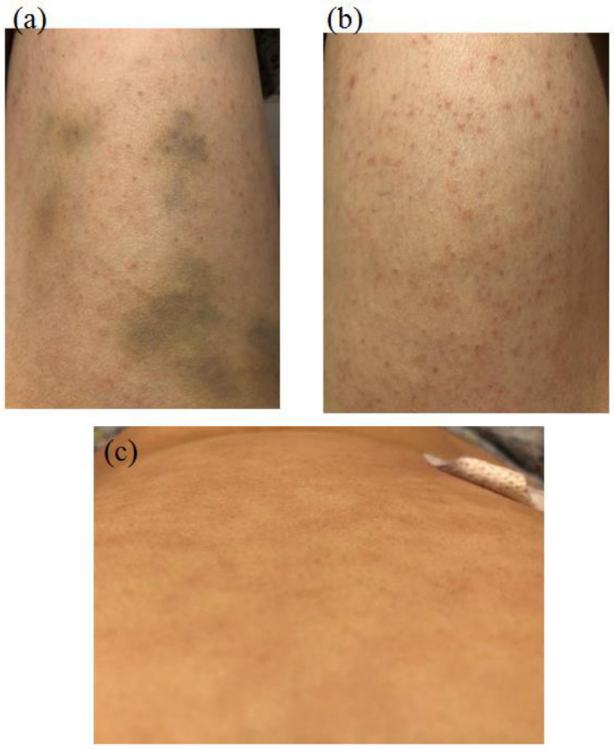

Figure 2. On the fifth day of medical therapy (a) left leg, (b) right leg, and (c) abdomen, oral steroid therapy (to 45mg), note the ecchymotic lesion on the left leg at the site of healing maculopapular rash

under the supervision of dermatologist and hematologist. There was no drug reaction to the intrinsic DFX molecules at the time interval of the appeared drug reaction of generic medicine (Figure 3).

Discussion

Following an extensive review of the literature, several similar case reports of thalassemia patients were found. We observed skin rash occurring in 7-11% of thalassemia patients who re-

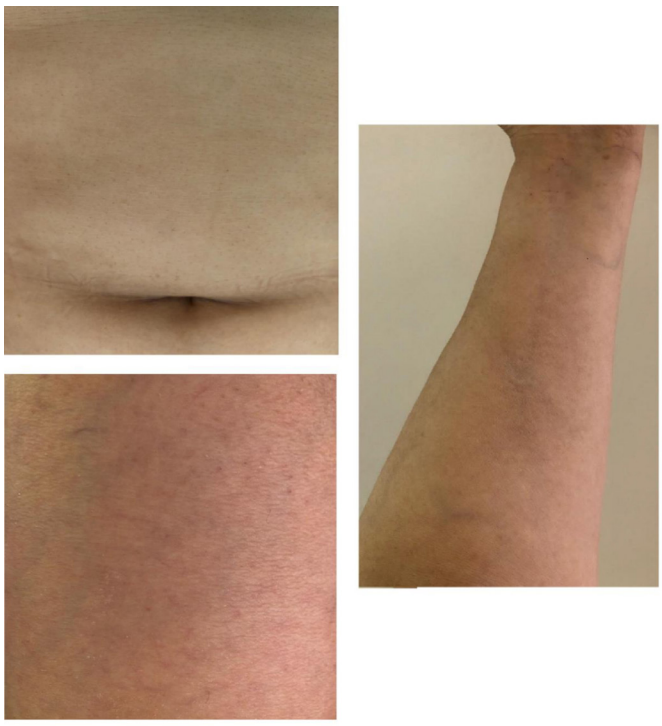

Figure 3. Abdomen, leg, and arm skin 9 days after initiation of original brand tablets DFX, 360 mg

ceived DFX (1).

A case report of challenge-proven immediate adverse drug reaction associated with the use of DFX emerged in 2020 (10). The researchers used graded challenge and treated through the reactions, which included ill-defined erythematous macules and lip angioedema, by administering H1-antihistamine. The patient in the study finally showed increased tolerance to the drug as H1-antihistamine was discontinued (10).

Another case report was related to an Indian patient who showed adverse skin rashes once she was started on DFX. Then, she received DFX at a dose of 750 mg daily. Six days after the therapy, she presented with pruritic skin rashes on the neck which later affected the whole body (14).

In a case report published in 2010, a ten-year-old boy suffering from ß-thalassemia in Turkey was started on 20 mg/kg/day DFX therapy. He showed pruritic skin rashes, starting from the neck and affecting the whole body within seven days of the treatment. His complaints included lesions which were erythematous, and raised skin lesions which became pale after palpation. These lesions were more noticeable on the upper extremities, upper body, and on dorsal areas (15).

Our patient recovered from adverse drug effects and discontinued the generic preparation of DFX. After accessing the brand molecule, original DFX, and initiating the oral chelation again, she was monitored for 10 days and gradually increased the dose to the prescribed one with no dermatopathologic complications.

Last but not least, there is no doubt the reaction to the DFX was not due to the intrinsic characteristic of this medicine. Since there was no recurrence with the original brand, it may be plausible to consider the presence of impurities in active pharmaceutical ingredients (AIP).

Conclusion

Since there is no transient available data about API analysis used for generic products, we are not able to be fully determined this issue. The noticeable point is that it seems reasonable for the food and drug administration to make available more clear data for AIP of the medicine. Or, it is wiser and more cautious to apply this medicine from low dose, increase it definitely smooth for controllable tolerance. Finally, for moderate to severe reactions, treatment should be stopped under the supervision of medical specialists to be sure there is no threat for the patients about the adverse effects.

Declarations

Ethical Approval

This case presentation was approved by the Ethics Committee of Biomedical Research in Royan Institute IR.ACECR.ROYAN.REC.1401.032.

Conflict of interest

Authors declare that they have no conflicting interests.

Consent for publication

We obtained informed written contest from the patient.

Authors' contributions

Leila Ataie Fashtami contributed to the study by designing and conducting the clinical case report presentation; Afshan Shirkavand was responsible for the literature review and drafting; Azita Azarkeivan and Zohreh Zahedi contributed to this research by reviewing the data and the manuscript; all of the authors collaborated in writing and editing the manuscript, as well as reviewing the manuscript.

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None to declare.

Availability of data and materials

To preserve the patient's privacy, this is not applicable.

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Reviews in Clinical Medicine

Clinical Research Development Center Ghaem Hospital

Oxidative Stress in Relapsing-remitting Multiple Sclerosis Patients

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ABSTRACT

Introduction: In multiple sclerosis (MS), oxidative stress (OS) plays a vital role in the neurodegeneration process. Cholesterol and lipids in the myelin sheath supplied by low-density lipoprotein (LDL) are also vital for nerve cells. In OS, lipid peroxidation occurs in LDL.

To investigate the OS biomarker such as prooxidant-antioxidant balance (PAB), malondialdehyde (MDA) and their correlation with LDL and oxidized LDL (Oxi-LDL) in patients with relapsing-remitting MS.

Methods: Blood samples from 18 patients with relapsing-remitting MS and 18 healthy subjects were collected to measure the OS biomarkers.

Results: In the patients' group in comparison to the control group: PAB, white blood cells (WBC), and neutrophils significantly increased ($P<0.05$), but there was no difference between the relapsing and remitting phase; MDA significantly increased in the relapsing phase ($P=0.013$) but was marginally significant in the remitting phase ($P=0.068$). There was no significant difference in LDL and Oxi-LDL between the two groups. Only the lymphocytes were different between the relapse and remission phases.

Conclusion: The importance of OS in the process of MS disease was confirmed and a PAB assay can be used to determine OS levels.

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Introduction

Multiple sclerosis (MS), a chronic autoimmune disorder of the central nervous system (CNS), is one of the most prevalent disabilities in young adults, identified by oligodendrocyte loss, demyelination, inflammation, and axonal damage (1).

MS can present in different forms, like primary progressive (PP-MS), relapsing progressive (RP-MS), secondary progressive phenotypes (SP-MS), and relapsing-remitting (RR-MS), which is the most prevalent form (80% of cases) (2). In MS patients, myelin in the CNS is damaged, and a large majority of myelin-producing oligodendrocytes are lost (3). Progressive loss of myelin and deterioration of its component proteins may further inflame the autoimmune response (4). As myelin consists of 70% lipids, human serum lipoproteins are implicated in the transportation of lipids, modulation of membrane lipid distribution, and regulation of signal transduction in CNS (5). Under normal conditions, elevated low-density lipoprotein (LDL) levels are present in CNS to transport across the brain-blood barrier (BBB) (6). Dyslipidemia may contribute to inflammatory processes, leading to the generation

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of adhesion molecules and the recruitment of leukocytes. The recruitment of immune cells in the activated endothelium of the BBB is critical in MS pathogenesis (7). Shreds of evidence on oxidative stress and clinical involvements have shown that the formation of free radicals lead to oxidative stress, which performs a role in neurodegeneration pathogenesis (8). In a healthy condition, the prooxidants and antioxidants remain in a balance status (9). Oxidative stress (OS) is an imbalance status between antioxidants and prooxidants in favor of the prooxidants that damage cellular ingredients, including proteins, lipids, and DNA. For ROS generation, the major exogenous factors are environmental pollution, radiation, cigarette smoking, certain foods, and drugs. The major endogenous factors are mitochondrial respiratory chain and various intracellular enzymes (10).

Reactive oxygen species (ROS) induce peroxidation of biological molecules, particularly lipoproteins that are involved in the pathogenesis of MS (11). The CNS is sensitive to oxidative stress because of the brain's high oxygen consumption, rich lipid content, and lack of antioxidant agents (12). Since many studies have demonstrated that oxidative stress has a main role in multiple sclerosis (8,12), in this study, prooxidant-antioxidant balance (PAB), malondialdehyde (MDA), Oxi-LDL, as markers of OS, and LDL, were measured in relapsing-remitting MS (RR-MS) patients; and their correlations were evaluated, which may provide evidence for diagnostic and therapeutic implications.

Materials and Method

In this case-controlled study, following informed consent, 18 RR-MS patients, and 18 control subjects were enrolled from Qaem hospital, Mashhad. RR-MS patients had been diagnosed to be in the secondary progressive phase and referred to Qaem hospital for corticosteroid therapy. Since this study is the first study to determine PAB in MS patients, therefore, sample size was determined with at least 18 participants in each group for this pilot study. Exclusion criteria were the use of corticosteroids within the past 30 days, the presence of infections or fever in the past 30 days, pregnancy, use of vitamin supplements, obesity, diabetes, thyroid dysfunction, and renal disorders. A 5 cc blood sample was obtained in the relapsing phase before corticosteroid therapy in Qaem hospital. Plasma was isolated from red blood cells by centrifugation at 2500 rpm, 4°C, and 15 minutes. Aliquots of supernatant (0.5–1 mL) were immediately frozen at -20°C and not thawed until analysis. Three months later, another blood sample was taken from the same patients who were in the remitting phase in the same situation. The control group consisted of 18 subjects from the identical geographic region, who did not show either laboratory or clinical attributes of autoimmune, liver, heart, or renal disorder. Also, the control subjects expressed that they were not consuming any antioxidant supplements or anti-inflammatory drugs. The patients' nutritional status did not vary from the control group, and none of the subjects were under a particular diet. Parameters like age, ethnicity, sex, body mass index (BMI), and smoking were matched in the patient and control groups.

Biochemical parameters

Prooxidant-antioxidant balance (PAB) method

The PAB assay was done according to the method explained by Alamdari et al. (13). A low PAB value indicates that AO exists at greater concentrations than prooxidants (OX); a high level of PAB indicates more prooxidants exist than AO.

Serum Oxi-LDL Evaluation

Oxi-LDL was measured by the ELISA kit (EASTBIOPHARM, CK-E10869) using anti-Oxi-LDL monoclonal antibody FOH1a/DLH3, the capture antibody, and an anti-human apolipoprotein B (apoprotein B) monoclonal antibody labeled with horseradish peroxidase.

MDA Measurement

Samples were added to the reaction mixture including phosphate buffer and $FeCl_3$ (pH=7.4). The reaction was arrested by adding 10% trichloroacetic acid (TCA), followed by 0.67% TBA, and the tubes were placed in boiling water for 20 minutes. The tubes were then transferred to an ice bath, and the contents were centrifuged for 10 minutes. The amount of MDA formed in each of the samples was evaluated by measuring the supernatant's optical density using tetra ethoxy propane (TEP) as a standard. MDA content was indicated as $nmol.mg^{-1}$ protein.

Serum LDL Measurement

Serum LDL level was measured by a biochemical autoanalyzer (BT3000, Parsazmoon, Iran) through an enzymatic reaction using cholesterol esterase and peroxidase. The procedure was carried out based on the manufacturer's instructions, and the results were shown in mg/dL.

Hematology analysis

CBC count was performed by the Sysmex XS800i, a hematology analyzer with fluorescence technology (Diamond Diagnostics-USA).

Statistical analysis

The data were assessed by the statistical analysis software SPSS version 16. Descriptive statistics were used to analyze data. The distribution of sex, smoking, and ethnicity was analyzed using a chi-square test. Comparisons between the control group and MS patients were done with the Mann–Whitney and independent t-test (for non-parametric and parametric variables, respectively). Comparisons between MS patients in the relapsing and remitting phase of the disease were performed using the Wilcoxon test and paired t-test (for non-parametric and parametric variables, respectively). All the results were considered meaningful when $p<0.05$.

Results

After neurological examinations, RR-MS was diagnosed in 18 patients. The mean age of participants was 29.21 (22-42) years. The demographic characteristics of RR-MS patients and the control group are presented in Table 1.

The mean PAB value in MS patients was 157.550±12.31 in the relapse phase, 156.766±13.81 in remission, and 118.539±9.58 in the control group. A significant increase in PAB value in both phases of MS was seen in comparison to the control group (Table 2).

MDA increased significantly in the relapsing phase (0.314±0.089) in comparison to the control group (0.119±0.043, P=0.013), but was marginally significant in the remission phase (0.218±0.054, P=0.068). There was no meaningful difference in MDA between the two phases (Table 3).

The LDL in MS patients was 81.89±3.087 in the relapse phase, and 82.17±3.037 in remission, which is significantly less than in the control group (112.96±7.321). There was no significant difference in LDL in the relapse and remission phases (Table 4).

There was no significant difference in Oxi-LDL among patients in the relapse phase, remission phase, and control subjects. The Oxi-LDL was 3573.978±584.397 in relapse and 3932.897±647.158 in remission and in the control group 3677.669±626.268 (Table 5).

There was no correlation of PAB with MDA, LDL, and Oxi-LDL.

White blood cells (WBC) were significantly increased in the relapse phase 7.956±0.472 and the remission phase 8.500±0.557 in comparison to the control group 6.522±0.371 (P<0.05), but there were no significant differences between the relapse and remission phase (P>0.05).

The neutrophils (4.900±0.438) in the relapse and remission (5.467±0.477) were significantly more than the control group (4.200±0.325), but there were no meaningful differences between the relapse and the remission phase (P>0.05). There was no significant difference in lymphocyte (2.483±0.217) in the relapse phase, but significance existed in the remission phase (2.928±0.223), in comparison to the control group (2.300±0.140). There was no meaningful correlation of PAB with WBC, neutrophils, and lymphocytes (P> 0.05) (Table 6).

Table 1. Characteristics of the RR-MS patients and healthy controls

		Controls	RR-MS patients	P-Value
Age	y 20> y 20-30 y 30-40 y 40<	% 6.0 % 55.0 % 33.0 % 6.0	% 5.9 % 47.0 % 35.3 % 11.8	P>0.05
Sex	Male Female	% 22.5 % 77.5	% 22.2 % 77.8	P>0.05

RR-MS: Relapsing Remitting- multiple sclerosis.

Table 2. Mean level of PAB in MS and control group

Comparison	PAB, Mean ± SEM	P-value
MS (relapse) **Control**	157.550±12.31 118.539±9.58	0.017*
MS (remission) **Control**	156.766±13.81 118.539±9.58	0.029*
MS (relapse) **MS (remission)**	157.550±12.31 156.766±13.81	0.955

*Statistically significant, MS: Multiple Sclerosis, PAB: Prooxidant- Antioxidant Balance

Table 3. Mean MDA in MS and control group.

Comparison	Mean ± SEM	P-value
MS (relapse) **Control**	0.314 ± 0.089 0.119 ± 0.043	0.013*
MS (remission) **Control**	0.218 ± 0.054 0.119 ± 0.043	0.068
MS (relapse) **MS (remission)**	0.314 ± 0.089 0.218 ± 0.054	0.112

*Statistically significant, MDA: Malondialdehyde

Table 4. Mean LDL in MS and control group.

Comparison	LDL, Mean ± SEM	P-value
MS (relapse) **Control**	81.89 ± 3.087 112.96 ± 7.321	0.0001*
MS (remission) **Control**	82.17 ± 3.037 112.96 ± 7.321	0.0001*
MS (relapse) **MS (remission)**	81.89 ± 3.087 82.17 ± 3.037	0.927

*Statistically significant, MS: Multiple Sclerosis, LDL: Low Density Lipoproteins

Table 5. Mean Oxi-LDL in MS and control group

Comparison	Ox-LDL, Mean ± SEM	P
MS (relapse) Control	3573.978± 584.397 3677.669± 626.268	0.945
MS (remission) Control	3932.897 ± 647.158 3677.669± 626.268	0.963
MS (relapse) MS (remission)	3573.978± 584.397 3932.897 ± 647.158	0.349

Multiple Sclerosis, Ox-LDL: Oxidized Low Density Lipoproteins

Discussion

In this study, the increased markers of oxidative stress (PAB and MDA), WBC, and neutrophils were seen in both phases of the disease (relapsing and remitting) in comparison to the control group but it did not differ significantly between both phases. There was no significant difference in lymphocytes in the relapse phase, but significance existed in the remission phase in comparison to the control group. There was no significant difference in LDL, or Oxi-LDL among patients in the relapse phase, remission phase, and control group. No correlation of PAB was seen with MDA, Oxi-LDL, LDL, WBC, neutrophils, and lymphocytes.

About 85% of MS patients are in the RR-MS phase at the time of the diagnosis (14). The etiology of MS is unclear although numerous investigations have proposed that oxidative stress is a significant etiology of MS (15). Additionally, autoreactive lymphocytes are the primary inflammatory causes of CNS that begin the disorder process (16). Inflammatory signs were observed in biopsied plaques, including lymphocytes and macrophages, and the MS patient's serum, including myelin reactive T lymphocytes (17). Microglia cells are present in inflammatory situations by releasing cytokines, oxidative products, and free radicals, which are toxic to myelin (18). Shreds of evidence illustrate mitochondrial dysfunction and oxidative stress as critical factors of common progressive neurological disorders (19). Antioxidants are a promising treatment for decreasing and preventing the disease's progress (20). ROS damages lipids, proteins, and nucleic acids and renders them to cell death. Their generation elevates through various pathological situations (21, 22). ROS, by its possible role in tissue damage in MS, provokes inflammatory responses (23).

Oxidative stress causes neurodegeneration through bioenergetic failure, depletion of antioxidant defenses, damage of bio-molecules, microtubular disruption, ion channel activation, demyelination, neuroinflammation, mitophagy impairment, and apoptosis of the neuronal cell, in which these events contribute to MS pathogenesis (24). Although various mechanisms are engaged in the demyelination and neurodegenera-

Table 6. White blood cell (WBC) count and WBC differentiation

	MS patients (relapse)	MS patients (remission)	Control
WBC count	7.956 ± 0.472[a]	8.500 ± 0.557[b]	6.522 ± 0.371
Neutrophils	4.900 ± 0.438	5.467 ± 0.477[c]	4.200 ± 0.325
Lymphocyte	2.483 ± 0.217	2.928 ± 0.223[d]	2.300 ± 0.140

a, b, c and d: significant difference compared with control group (independent T-test), MS: Multiple Sclerosis

tion in MS, multiple research shows that oxidative stress has a vital role in MS pathogenesis related to myelin and oligodendroglia degeneration that ultimately causes neuronal death (25). Notably, high concentrations of prooxidant agents in the serum of MS patients are found (26). A study has shown a remarkably lower capacity ($p<0.001$) of total antioxidants in the serum of MS patients in comparison to healthy subjects (27).

Evidence implies that infiltrated macrophages are among the primary ROS sources in CNS inflammation in patients with MS (28). Infiltrated macrophages through ROS lead to neuronal damage via their interaction with lipids, proteins as well as nucleic acids, and disruption of membrane integrity of neurons (29). Therefore, high ROS generation is among the most critical factors in inflammation and neuronal damage, and there is a mutual correlation between oxidative stress and inflammation wherein they boost each other (30).

White blood cells are known as recourses of oxidative stress in inflammatory diseases (31) and the role of neutrophils in the pathogenesis of MS is complicated (32). They can play dual effects by omitting damaged myelin particles and secreting growth factors and on the other hand, they can adversely affect the disease by producing pro-inflammatory cytokines (33). It has been reported that lymphocyte levels are higher in MS patients and they are considered to be correlated with axonal injury (34). In our study, there were more lymphocytes in MS patients than in healthy controls, but just in the remitting phase it was significant in comparison to the control group.

Mariani et al. showed that lipid peroxidation products alter cell membrane permeability and induce cell dysfunction, and oxidation of lipids by prooxidants could perform a role in the pathogenesis of MS (35). Therefore, the product of lipid peroxidation such as MDA can be predictive of the disease stage. Our results showed MDA increased significantly in the relapsing phase but was marginally significant in the remitting phase.

The limitations of this study are the small sample size and conducting the research in one academic center. Hence, it is suggested that additional studies be run in multiple centers to substantiate the finding of this study. The strengths of study are the cost effectiveness, generalizability, and reliability of the PAB method, which could be done easily in every clinical laboratory.

Conclusion

Oxidative stress plays a main role in MS patients and PAB assay can be used to determine oxidative stress levels.

Statement of ethics

The procedures done in this study were approved by the Mashhad University of Medical Sciences (MUMS); project no.: 930202.

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Conflict of interest

The authors declare that there is no conflict of interest

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Reviews in Clinical Medicine

Clinical Research Development Center Ghaem Hospital

Challenges of the Management and Resource Allocation during Coronavirus Disease 2019 Outbreak: Experience from an Internal Medicine Centre, Iran

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ABSTRACT

The potency of health systems to effectively respond to crises varies between high- and low-income countries. The COVID-19 pandemic has presented numerous challenges for hospitals worldwide. In this context, the resilience of health systems and the capacity of health institutions and populations play a key role in mounting an effective response to crises.

We gathered data on the condition and resilience of health systems in the two main hospitals in Mashhad, Iran, during three peaks of the COVID-19 pandemic. The results highlighted the fact that health systems officials and managers need to consider the consequences of COVID-19, such as the need for more beds and trained healthcare workers. Hospitals should take into account the impact of the COVID-19 pandemic across all wards and departments and prioritize the well-being of healthcare workers since they are at the forefront of the fight against this pandemic.

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Introduction

Due to the lack of pre-existing scientific data, the coronavirus disease 2019 (COVID-19) epidemic has spread worldwide. As of March 2021, more than 1.7 million cases of COVID-19 have been reported in Iran, with over 60,000 deaths (1). The potency of health systems to effectively respond to crises varies depending on the income levels of countries (2). The COVID-19 outbreak has presented many new challenges for hospitals (3). In this regard, the resiliency of health systems, as well as the capacity of health institutions and populations, are crucial for giving effective responses to crises (4).

The first positive case of COVID-19 in Mashhad, Iran, was reported on February 25, 2020. During the following week, the number of reported positive cases increased to 40 individuals. It should be noted that due to the lack of RT-PCR diagnostic kits, diagnoses were made based on clinical signs and CT scan findings in the first week of the pandemic in Mashhad, Iran.

Due to the rapid spread of the disease, emergency task forces were established to respond to the outbreak, and managers offered plans to manage this pandemic in Mashhad,

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Iran. Here, we gathered data on the condition and resilience of health systems in two main hospitals in Mashhad, Iran, during three peaks of the COVID-19 pandemic.

Adaptation to real-time and clinical management of COVID-19 patients

The management of the first patients infected with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was based on scientific data and experiences obtained from previous outbreaks. Real-time data on SARS-CoV-2 was crucial to provide new guidelines promptly. Quick notifications and dissemination of the guidelines to healthcare workers was a significant challenge. To address this challenge, data communication sessions were held regularly either face-to-face or via the intranet.

Multidisciplinary management has played a vital role during epidemics. Initially, the responsibility of managing COVID-19 patients fell on infectious diseases and emergency departments. However, with the increase in the number of infected cases with SARS-CoV-2, internal medicine departments took action to support these two departments (i.e., Emergency and Infectious Diseases departments). Additionally, non-COVID-19-related activities, including non-urgent surgical interventions, had to be stopped or limited in line with similar observations in other centers worldwide (5-7). Microbiology services were also expanded for SARS-CoV-2 detection and monitoring.

Source of the information

During the three peaks of COVID-19 in Mashhad, Iran, Imam Reza and Ghaem hospitals managed the first cases of patients diagnosed with COVID-19 on February 25, 2020. To date, these two hospitals have given medical services to more than 70,000 COVID-19 patients admitted by the Internal Department. Imam Reza Hospital, affiliated with Mashhad University of Medical Sciences, is a 610-bed university hospital with nine floors with an area of 52,000 square meters. It is worth mentioning that this hospital has the largest hospital system in the northeast of Iran, with more than 3,400 staff. Furthermore, it is one of the reference centers in Iran for patients with suspected or confirmed emerging infectious diseases. On March 15, 2020, more than 100 COVID-19 patients were admitted to Imam Reza Hospital. In general, there were three peaks of COVID-19 in March, May, and September 2021. Professors and assistants planned to visit Imam Reza and Ghaem hospitals. The 610-bed Imam Reza University Hospital had to evacuate patients from other wards. The second basement in Ghaem Hospital was assigned to taking care of COVID-19 patients. During the first peak of the pandemic, all faculty members of the Internal Department visited COVID-19 patients. In the next peak, the majority of visits were conducted by Pulmonology and General Internal Medicine specialists. About 60 faculty members (professors in other fields and internal medicine specialists) and 26 internal assistants from Emergency (n=6) and other wards (n=20) were present in our center; however, there were only six internal assistants in the center after the first peak of the pandemic.

Moreover, 500 general staff (nurses and assistant nurses) have been involved in this process. In total, approximately 500 nurses provided services to COVID-19 patients in the inpatient ward. In the wards, one nurse was responsible for every five to six beds, and in the ICU, one nurse was responsible for providing nursing care to each patient. The workload was heavy during the midnight, and 200 patients were visited daily by the health workers of the internal ward.

In Imam Reza Hospital, COVID-19 patients on the 1st and 6th floors were visited by infectious disease specialists, while those hospitalized on the 4th and 5th floors were visited by internal specialists. The 2nd and 3rd floors (ICUs) were dedicated to patients with severe symptoms. However, the ICU staff visited patients hospitalized on these floors as well. Emergency medicine workers were also present at the screening sites and front line. All subspecialty wards were closed, and emergency patients were referred to the general wards of Ghaem Hospital. The only active subspecialty ward was the hematology ward in Imam Reza and Ghaem hospitals.

A specific night duty service was established, which was initially managed by six assistants and overseen by three assistants and senior consultants. In general wards, patients were visited by professors (n=10) and internal assistants (n=10). Since the beginning of the outbreak, interns have been on-call and responsible for visits in non-COVID-19 and non-infectious wards. Non-resident interns specializing in Dermatology, Gynecology, Urology, Surgery, and Cardiology had to take night shifts in COVID-19 wards.

General visits were performed by the Rheumatology and Endocrinology fellowships. In addition, Gastroenterology, Hematology, and Nephrology fellowships visited patients related to their field of study. This program was run under the supervision of the internal group manager.

Table 1 presents the key elements of the response to COVID-19, including challenges and strategies, following the experience of our center.

Taking care of the Healthcare Workers and Staff

Healthcare workers were at the forefront of the fight against the COVID-19 epidemic which posed many challenges to the healthcare system, including the difficulty in recruiting healthcare workers and bed shortages. Vacations were put on hold, working hours increased, and we even had to call in temporary nurses to deal with the pandemic. In this regard, it was essential to support healthcare workers who played a key role during the epidemic. A total of 300 healthcare workers and 75 faculty members and internal assistants were infected with COVID-19, nine of whom were hospitalized. Training sessions were run remotely through virtual classes in the first

Table 1: Challenges encountered by the internal medicine ward and local solutions

Challenges	Preparations
Management of COVID-19 patients	Training frontline healthcare workers, including the provision of practical exercises within different departments (emergency, infectious, and internal wards; as well as ICU and microbiology laboratory). Performing technical supervision by trained and experienced workers. Identifying facilities of the hospital. Systematic supervision of the patients' transportation.
Prediction of the new items	Predicting the suspicious cases in each unit and developing plans to deal with it. Setting up a special unit in the emergency department for visiting outpatients. Determining the required medical equipment (by the logistics department).
Preparation of the healthcare workers	Identifying the required professions. Inviting nurses, laboratory technicians, and ICU staff to collaborate on relevant trends and plans. Increasing the number of trained healthcare workers
Adaptation to COVID-19 Outbreak condition	Performing regular crisis meetings for all healthcare staff and workers. Compatibility with national and international strategies and protocols in managing the pandemic. Adapting real-time data to investigate epidemiology and novel scientific knowledge.
Diagnosis and treatment	Having access to RT-PCR. Training laboratory technicians Training point-of-care testing at the bedside.
Emergency department considerations	Training the emergency department staff. Providing protocols for the management of the calls. Regular communication between the hospital and ambulance services.
Management of the healthcare workers	Focusing on effective management strategies. Regular communication between healthcare workers and hospital staff (using the communication software). Providing psychological support. Providing real-time information to the healthcare workers. Ensuring a rotation of healthcare workers' shifts
Equipment	Ensuring the availability of beds. Providing protective equipment for healthcare and staff. Providing therapeutic devices, such as medicines and oxygen masks.
Development of research projects and teaching activities	Identifying the research purposes. Creating coordination between clinical research and patient care. Maintaining proper teaching activities through online training classes. Presenting educational webinars. Equipping the students with outbreak management skills.

peak and the first months of the second peak of the epidemic. About 16 apprentices and interns were infected with COVID-19 during the third peak.

All healthcare workers in the hospital had to wear surgical masks following the instructions from the Internal Department. Some psychological support was provided for healthcare workers and staff, especially those who were anxious and felt threatened by the disease. To control rumors that might have affected healthcare workers, information was shared via the Internet on a daily basis. Moreover, internal communication was performed through conferences that were open to all healthcare workers (8, 9).

Resource Allocation

The internal medicine center had to adapt to the rapidly growing medical demands and provide personnel with the necessary treatment equipment. The task of providing personal protective equipment for interns was undertaken by Mashhad University of Medical Sciences, Mashhad, Iran. It should be noted that the cost of providing equipment to assistants and professors of the Internal Department was covered by supporting groups and donors. At the workload peaks, there was a dire shortage of beds and medicines. Disinfectants, disposable face masks, filtered masks, and gowns were the main personal protective equipment shortages, which were most noticeable in the first weeks of the pandemic onset.

Education and training

During the COVID-19 outbreak, all proposals on COVID-19 offered by internal groups were approved in collaboration with the Ethics Committee and Research Deputy of Mashhad University of Medical Sciences, Mashhad, Iran. Education, training, and practices have been regularly organized for frontline healthcare workers. From April 4, 2020, virtual training was started for interns and stagers in WhatsApp groups. Moreover, various webinars on COVID-19 were conducted through Camtasia or the university's virtual education system. In addition to visiting COVID-19 patients, internal professors performed their educational duties as well. So far, the Internal Department has organized 62 webinars out of 400 prepared webinars at Mashhad University of Medical Sciences, which was the second group following the Neurology Department. (10-12).

Conclusion

During the pandemic, health structures faced an increasing number of patients to deal with. Therefore, leaders and managers of the health systems should consider the consequences of this widespread pandemic, such as the need for more beds and trained healthcare workers. Hospitals have to consider the consequences of COVID-19 on all departments, and it is of utmost importance to take special care of the healthcare workers who are at the forefront of the fight against any pandemic.

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