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RESEARCH ARTICLE

Measurement of Serum Ceruloplasmin, Lipid Hydroperoxide Level and Prolidase Activity in Children with Primary Headache

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Abstract:

***Introduction*:** Primary headache is a significant health problem in children as it remarkably negatively affects the child and his/her family. Migraine and tension-type headaches constitute the majority of primary headaches in childhood. Studies regarding adult migraine patients suggest that oxidative stress has a significant role in the pathogenesis. This study aimed to investigate the relationship between primary headache in chidhood and the levels of oxidative stress markers.

***Materials and Methods*:** Pediatric patients diagnosed with primary headache and healthy controls in the pediatric age range were recruited. Data regarding age, gender, height, weight, and body mass index (BMI) were recorded. The levels of ceruloplasmin, lipid hydroperoxide, and prolidase activity were measured in plasma using the ELISA method. Statistical analyses were conducted using the SPSS 11.5 statistical program. A p-value of less than 0.05 was considered significant.

***Results*:** The study included 76 patients with primary headache and 61 healthy controls. The mean ages of the patients and healthy controls were 14.4±3.2 and 13.6±2.9 years. The patient and control groups were similar in terms of gender distribution (p=0.948), age (p=0.079), and BMI (p=0.196). Migraine accounted for 35.5% (n=27), while tension-type headache accounted for 64.5% (n=49) of the patients. Serum ceruloplasmin (p=0.033), lipid hydroperoxide (p<0.001), and prolidase (p=0.010) levels were higher in patients compared to the control group. Lipid hydroperoxide (p=0.021) and prolidase (p=0.013) levels were higher in migraine patients than in tension-type headache patients, while ceruloplasmin levels were similar between patients with different headache types (p=0.581).

***Conclusion*:** In this study, oxidative stress markers were shown to be increased in pediatric patients with primary headache. These findings support the hypothesis that patients with primary headaches are exposed to oxidative stress. Future studies may elucidate the role of oxidative stress in the etiopathogenesis of childhood migraine and other headache types.

Keywords: Headache, Oxidative stress, Migraine, Tension-type, Ceruloplasmin, Lipid hydroperoxide, Prolidase.

1. INTRODUCTION

Headache is a common health problem in both young children and adolescents [1-3]. The prevalence of headache increases throughout childhood and peaks at 11-13 years old [4]. Migraine and tension-type headaches (TTH) frequently constitute the primary headaches (PH) specific to the nervous system [5].

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Migraine has been reported to occur in 6.1-13.6% of children and TTH in 9.8-24.7%. Although the prevalence is estimated to be high, clinical data on PH in childhood are very limited. Most of the available data are compiled from studies on adult headaches.

Childhood headaches should be considered a significant health problem as they significantly negatively affect the child and his/her family [6,7]. Compared to children without headaches, these patients are more likely to miss school, have poorer peer relations, and have a lower quality of life [5].

Factors defined as risk factors or triggers associated with migraine and TTH include obesity, sleep disorders, behavioral and psychiatric factors, and dietary causes [8-10]. In addition to these triggers, oxidative stress has recently been thought to be associated with PH.

The oxidant-antioxidant balance is of great importance for maintaining homeostasis [11]. In physiological conditions, reactive oxygen radicals are continuously produced in all aerobic organisms and used for physiological purposes. At the same time, the antioxidant system triggered by oxidants keeps this balance under control. If the oxidant-antioxidant balance is disturbed in the direction of the oxidant system, oxidative stress emerges and leads to several disease processes.

Ceruloplasmin, involved in copper metabolism, is frequently associated with Wilson's disease [12]. However, it has been reported to be involved in plasma redox reactions and inhibit lipid peroxidation. Therefore, elevated plasma ceruloplasmin levels are accepted as an indicator of increased oxidative stress.

Since the literature has not adequately evaluated the relationship between oxidative stress and PH in the pediatric age group, our study aimed to compare prolidase activity, lipid peroxidation, and ceruloplasmin levels in children with PH and healthy controls.

2. MATERIALS AND METHODS

This descriptive study was conducted with patients younger than 18 who were diagnosed with PH in the Department of Pediatric Neurology at Harran University Faculty of Medicine and a healthy control group. Ethics committee approval for the study was obtained from the Harran University Faculty of Medicine Scientific Research Ethics Committee (21.12.2016/16217). Children whose families did not consent to the study, patients diagnosed with secondary headache, patients with chronic morbidities in addition to PH, and individuals with an acute disease when the blood sample was taken for the study purposes were omitted. Healthy controls were selected among children brought to Harran University Faculty of Medicine, Healthy Children Outpatient Clinic.

Sociodemographic information such as age, gender, height, weight, body mass index (BMI), and anthropometric characteristics of all participants were recorded in an electronic database. The PH type (migraine or TTH) and the frequency of attacks were also included in the database.

Venous blood samples were collected from all study participants to analyze serum ceruloplasmin, lipid peroxide, and prolidase activity. After the venous blood samples were centrifuged at 3500 rpm for 10 minutes, the shaped elements were discarded with the tube, and the remnants were stored at -800 C for analysis.

2.1. Measurement of Ceruloplasmin Level

In our study, ceruloplasmin levels were evaluated using the ELISA method. The analysis was performed according to Elabscience (CP) Ceruloplasmin ELISA Kit protocol: The lyophilized standard was centrifuged at 10.000xg for 1 min, 1ml Reference Standard & Sample Diluent was added and kept for about 15 min to be completely homogeneous. The standards were diluted 7-fold by serial dilution method (40-20-15-2.5-1.25-1.25-0.63-0 µg/mL). Prepared standards and serum samples were added 100µl to each well and incubated at 37°C for 90 min. After incubation, the liquid was removed and Biotinylated Detection Ab. (1:100) was added and incubated at 37°C for 60 min. All wells were washed 3 times with washing solution carefully. 100 µl HRP Conjugate (1:100) was added and incubated at 37°C for 30 min. All wells were carefully washed 5 times with the washing solution. 90 µl Substrate Reagent was added and

incubated at 37°C for 15 min (in the dark). 50 µl Stop Solution was added to stop the enzyme activity, and absorbance at 450nm was measured.

2.2. Measurement of Lipid Peroxide Level

The lipid peroxide levels were evaluated using the ELISA method. The analysis was performed according to the Cusabıo (LPO) Lipid Peroxide ELISA Kit protocol: The lyophilized standard was centrifuged at 10.000xg for 1 min, 1ml Standard Diluent was added and kept for about 15 min to be completely homogeneous. Standards were diluted 7-fold by serial dilution method (1000-500-250-150-125-62.5-31.25-15.6-0 ng/mL). 100µl of prepared standards and serum samples were added to each well and incubated at 37°C for 120 min. After incubation, the liquid was removed, and Biotin-antibody 1X was added and incubated at 37 °C for 60 min. All wells were washed 3 times with washing solution carefully. 100 µl HRP Avidin 1X was added and incubated at 37 °C for 60 min. All wells were washed 3 times with washing solution. 90 µl TMB Substrate was added and incubated at 37 °C for 15-30 min (in the dark). 50 µl Stop Solution was added to stop the enzyme activity, and absorbance at 450nm was measured.

2.3. Measurement of Prolidase Activity

The prolidase activity was analyzed using the ELISA method. The analysis was performed according to the Elabscience (PEPD) Peptidase D ELISA Kit protocol: The lyophilized standard was centrifuged at 10,000xg for 1 min. Then, 1 ml of Reference Standard & Sample Diluent was added and kept for about 15 min to make it completely homogeneous. The standards were diluted 7-fold by serial dilution method (200-100-50-25-12.5-6.25-3.13-0 ng/mL).

100µl of the prepared standards and serum samples were added to each well and incubated at 37 °C for 90 min. After incubation, the liquid was removed and Biotinylated Detection Ab. (1:100) was added and incubated at 37°C for 60 min. All wells were washed 3 times with washing solution carefully. 100 µl HRP Conjugate (1:100) was added and incubated at 37 °C for 30 min. All wells were carefully washed 5 times with the washing solution. 90 µl Substrate Reagent was added and incubated at 37 °C for 15 min (in the dark). 50 µl Stop Solution was added to stop the enzyme activity, and absorbance at 450nm was measured.

2.4. Statistical Analysis

Statistical analyses were performed using the SPSS version 20.0 (IBM® Inc, Chicago, USA) package program. Descriptive data were given as numbers, percentages, means, and standard deviations. The conformity of the variables to normal distribution was examined using visual (histogram and probability graphs) and analytical methods (Kolmogorov-Smirnov, Shapiro-Wilk tests). The numerical variables were compared between two groups using the Student t-test, and the One-Way ANOVA test was used to compare three groups. The homogeneity of variances was evaluated using Levene's test. Post-hoc analyses were performed with the Bonferonni test when significant differences were found. Pearson and Spearman correlation tests were used in correlation analysis. Numerical variables that did not show normal distribution were compared between two groups using the Mann-Whitney U test, and three or more groups were compared using the Kruskal Wallis Test. Chi-square analysis was used to compare ordinal data. A p-value below 0.05 was considered statistically significant.

3. RESULTS

Power analysis indicated that the sample size should be at least 120 patients. A total of 76 patients, 27 (35.5%) males, and 49 (64.5%) females were included in the study (Table **1**). The male/female ratio was 1.8:1. The control group comprised 61 healthy individuals, 22 (36.1%) males and 39 (63.9%) females. The male/female ratio was 1.7:1. The mean age was 14.4±3.2 years in the patient group and 13.6±2.9 years in the control group. The mean BMI was 19.1±2.4 kg/m2 (median 19.3, range 14.8-25.4) in the patient group and 18.5±2.9 kg/m2 (median 17.8, range 14.3-25.8) in the control group. There was no statistically significant difference between the patient and control groups in terms of gender, age and BMI

(p=0.948, p=0.079, p=0.196). While 35.5% (n=27) of the patients with headaches had migraines, 64.5% (n=49) had TTH.

Table 1. Demographic data.

-	Patient Group	Control Group	p Value
Age (year)*	14.4±3.2	13.6±2.9	0.079
Height (cm)*	147±17	142±15	0.081
Body weight (kg)*	43±13	39±14	0.104
Body-mass index*	19.1±2.4	18.5±2.9	0.196
Gender **	-	-	-
Male	35.5%	36.1%	0.948
Female	64.5%	63.9%	-

Note: *Independent t-test
**Chi-square test

The frequency of headache attacks was 10 or more per month in 30.3% (n=23) and less than 10 attacks per month in 69.7% (n=53) of the patients.

The serum ceruloplasmin level was 23.2±9.1 µg/mL in the patient group and 16.7±5.4 µg/mL in the control group. The ceruloplasmin level of the PH patients was statistically significantly higher than that of the control group (p=0.033) (Table **2**).

Table 2. Comparison of serum ceruloplasmin, lipid hydroperoxide and prolidase levels between two groups.

-	Patient Group	Control Group	p Value
Ceruloplazmin* (µg/ mL)	23.2±9.1	16.7±5.4	0.033
Prolidase* (ng/ mL)	94.2±12.3	58.8±11.5	0.010
Lipid hydroperoxide* (ng/ mL)	798.9±16.7	419.6±14.3	<0.001

Note: *Student t-test was used

The mean serum prolidase activity was 94.2±12.3 ng/mL in the patients and 58.8±11.5 ng/mL in the control group. The serum prolidase activity of the PH patients was statistically significantly higher than that of the control group participants (p=0.010).

The mean serum lipid hydroperoxide level was 798.9±16.7 ng/mL in the patients and 419.6±14.3 ng/mL in the control group. The serum lipid hydroperoxide level of the patients was statistically significantly higher than the control group (p<0.001).

There was no difference in serum ceruloplasmin levels between migraine and TTH (p=0.581). However, serum prolidase and lipid hydroperoxide levels were significantly higher in migraine headache group than in TTH group (p=0.021, p=0.013).

In migraine patients with a high number of attacks (≥10 attacks per month), serum ceruloplasmin level was 23.7±9.4 µg/mL, lipid hydroperoxide level was 939±25 ng/mL, and prolidase activity was 99.2±12.3 ng/mL; in migraine patients with a low number of attacks (<10 attacks per month), serum ceruloplasmin

level was 25.2±8.4 μg/mL, lipid hydroperoxide level was 723±23 ng/mL and prolidase activity was 84.7±9.7 ng/mL.

In patients with TTH with a high number of attacks (≥10 attacks per month), serum ceruloplasmin level was 28.2±10.4 μg/mL, and lipid hydroperoxide level was 756±23 ng/mL. Prolidase activity was 89.8±8.3 ng/mL in patients with TTH with a low number of attacks (< 10 attacks per month), serum ceruloplasmin level was 26.9±8.9 μg/mL, lipid hydroperoxide level was 723±18 ng/mL and prolidase activity was 86.7±9.2 ng/mL.

When the patients were grouped according to the frequency of attacks, the levels of lipid hydroperoxide and prolidase were higher in migraine patients with a high frequency of attacks than in migraine patients with a low frequency of attacks; however, ceruloplasmin levels did not differ ($p<0.001$, $p=0.036$, $p=0.354$). In patients with TTH, ceruloplasmin, lipid hydroperoxide, and prolidase levels were similar between patients with more and less frequent attacks ($p=0.668$, $p=0.656$, $p=0.913$).

4. DISCUSSION

Headache affects a significant number of children as well as adults [13]. By the age of 20, headache has been reported in 58% of the population. It is also the most common reason for referral to neurology clinics. Despite this fact, it may be neglected by families, teachers, and primary caregivers. Neglecting causes problems in social communication and school life and decreases quality of life [14]. Therefore, diagnosis and effective treatment of the disease is important. Although it is a common clinical entity, data on the pathogenetic mechanisms underlying PH are limited.

Although many studies have been conducted on the etiology of migraine, its pathogenesis still needs to be fully elucidated [15]. It has been suggested that oxidative stress, which occurs when the balance between the production of reactive oxygen products and antioxidant defense mechanisms is disrupted, is associated with various headache disorders, such as migraine [16].

Previous studies examined the potential role of oxidative stress in PH [17,18]. In most of these studies, oxidative stress levels were evaluated using various oxidant-antioxidant markers. Most studies were conducted in the adult age group, while studies evaluating oxidative stress levels in childhood headaches are limited [19].

Therefore, our study examined serum ceruloplasmin and lipid hydroperoxide levels in migraine and TTH. Their distribution in different PH types was also evaluated and compared with the control group. Prolidase enzyme activity, which has a vital role in collagen metabolism, was also evaluated in the patient and control groups [20]. The first striking finding of our study was that serum ceruloplasmin and lipid hydroperoxide levels and prolidase activity were higher in patients with PH compared to the control group. In addition, there was no difference in serum ceruloplasmin levels between patients with migraine and TTH. In contrast, migraine patients had higher serum prolidase activity and lipid hydroperoxide levels.

Lipid hydroperoxide is one of the most common lipid peroxidation products and an essential oxidative stress marker [18,21]. The most important effect of lipid peroxidation is the disruption and destruction of cell membranes. The brain is more sensitive to products released due to lipid peroxidation than other organ systems [22]. Studies investigating the role of oxidative stress in the etiology of headaches have shown high levels of malondialdehyde (MDA), the end product of lipid peroxidation [17,23,24].

Data on the level of lipid hydroperoxide in migraine patients are minimal [18]. In our study, lipid hydroperoxides were thought to be associated with PH, and lipid hydroperoxide levels were found to be higher in PH than in the control group. In light of our findings, it can be stated that lipid peroxidation increases in migraine patients, and oxidative stress, which is the expected result of lipid peroxidation, is at a higher level in these patients.

Ceruloplasmin, which is primarily involved in copper metabolism, controls lipid peroxidation [25]. Therefore, increased ceruloplasmin levels are an indicator of oxidative stress load [25,26].

The relationship between PH and serum ceruloplasmin was not examined before. In our study, the serum ceruloplasmin level was higher in PH than in the control group, which was thought to be an indirect indicator of oxidative stress. However, our findings should be confirmed by prospective controlled studies.

In a study by Erol *et al.,* antioxidant enzyme levels were evaluated in pediatric migraine patients [27]. This study found that catalase and glutathione peroxidase activities were lower in migraine patients than controls. As a result, it was concluded that oxidative stress played a significant role in the pathogenesis of pediatric migraine.

In a study by Gupta *et al.,* oxidative stress levels were evaluated in migraine and TTH patients and compared with the control group [17]. This study used FRAP (ferric reducing activity of plasma) and MDA as oxidative stress markers. The authors observed that MDA and FRAP levels were higher in migraine patients compared to the other two groups, while no difference was observed between TTH patients and the control group. In our study, oxidative stress levels were found to be higher in patients with migraine than in patients with TTH.

In a study by Vurucu *et al.,* 38 children with chronic daily headaches were evaluated [28]. The study showed that SOD, catalase, MDA, and GPx levels were higher in children with chronic daily headaches compared to controls.

In a recent study by Bernecker *et al.,* MDA and 4-hydroxy-2-nonenal (HNE) levels, which are lipid peroxidation products, were evaluated in 96 migraine patients [29]. While MDA levels were not found to be different, HNE levels were found to be higher in migraine patients than in controls.

It was also reported by Shimomura *et al.,* Ciancerelli *et al.,* and Tozzi-Ciancerelli *et al.* that oxidative stress levels were higher in migraine patients compared to controls [23,30,31].

On the other hand, some studies reported contradictory results regarding the potential association between migraine and oxidative stress [16,19,32]. A study by Geyik *et al.* analyzed the total oxidant level, total antioxidant level, and oxidative index in 50 migraine patients [16]. This study concluded that the oxidative stress level was not different from that of controls. Similarly, Eren *et al.* examined the same parameters in 141 migraine patients, but no difference was found between migraine patients and the control group [32].

Our study also analyzed the relationship between the frequency of attacks and oxidative stress. Lipid hydroperoxide and prolidase levels were higher in the group with a higher frequency of attacks. These results suggest that these markers can be used not only to diagnose disease but also as an indicator of disease severity.

Prolidase, a member of the metalloproteinase family, plays an important role in collagen synthesis [33]. It is found in leukocytes, erythrocytes, and keratinocytes, as well as in plasma. In their study conducted in 2017, Aslan *et al.* reported that serum prolidase activity was associated with oxidative stress [33]. However, to our knowledge, the role of prolidase in PH was not examined before. Based on its association with oxidative stress, serum prolidase activity was evaluated in PH for the first time in our study, and serum prolidase activity was higher in PH patients than in the control group.

Our study has some limitations. First, the number of patients included in our study is relatively small. On the other hand, most studies analyzed the levels of oxidative markers such as MDA, FRAP, total antioxidant level, total oxidant level, oxidative stress index, or HNE to elucidate the relationship between oxidative stress and migraine [16,17,29]. In our study, prolidase, ceruloplasmin, and lipid hydroperoxide, which have limited data, especially for pediatric patients, were preferred as the studied oxidative stress markers.

In our study, it was shown that oxidative load was higher in migraine patients. However, with these results, it cannot be fully understood whether increased oxidative stress causes migraine or migraine causes oxidative stress.

CONCLUSION

Oxidative stress is a function the human body requires to maintain its physiological life. It is kept under control by the antioxidant system. Disruption of this balance in favor of oxidants constitutes oxidative stress, blamed for numerous disease processes.

In our study, we found that prolidase, lipid hydroperoxide, and ceruloplasmin levels increased compared to controls. In addition, lipid hydroperoxide and prolidase levels were higher in migraine than in GTB. In light of these findings, it can be stated that oxidative stress has an important role in PH, especially in migraine type.

AUTHORS' CONTRIBUTIONS

The author confirms sole responsibility for the following: study conception and design, data collection, analysis and interpretation of results, and manuscript preparation.

CONSENT FOR PUBLICATION

Not applicable.

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None.

CONFLICT OF INTEREST

The author confirms that this article's content has no conflict of interest.

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CASE REPORT

A COVID-19 Case: Isolated and Persistent Headache

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Abstract: COVID-19 effects many systems such as respiratory, nervous, renal and hematologic system. Third of patients have experienced neurological symptoms such as headache, anosmia, ageusia and dizziness. Headache has been reported as the most common neurological manifestation but cases just headache are extremely rare. This case is a Covid-19 case with no symptoms other than sudden onset headache. The result of the nasal swab PCR sampling was negative however local infiltration areas with ground glass density in the periphery of the middle lobe, lateral segment of the both lungs were detected in the thorax CT.

Keywords: Covid-19, headache**,** pain, infection.

1. INTRODUCTION

Coronavirus disease 2019 (COVID-19) is caused by the novel beta coronavirus, severe acute respiratory syndrome coronavirus 2 (SARS-CoV2) and declared as a pandemic by the World Health Organization on March 11th 2020. COVID-19 effects many systems such as respiratory, nervous, renal and hematologic system. In severe disease, patients experience respiratory failure, acute renal failure, and ultimately multisystem organ failure.

COVID-19 is characterized by fever, cough, dyspnea, sore throat, myalgia, fatigue, diarrhea [1] and over a third of patients (36,4%) have experienced neurological symptoms such as headache, anosmia, ageusia and dizziness. Headache is the most common neurological manifestation [2]. The onset of headache associated with COVID-19 is typically within 24 hours of infection and lasts an average of 7 days. However, 13 percent of patients may develop persistent headaches lasting more than 1 month [3]. In a study by Caronna *et al.*, they reported that headaches continued 6 weeks after admission in 28 of 74 COVID-19 patients. The headache is usually bilateral, long lasting, and likely to be analgesic resistant [4].

Toptan *et al.* reported an isolated COVID-19 headache series consisting of 13 patients. In these some cases other symptoms appeared within 2-3 days following the diagnosis, such as diarrhea. Unlike our case, all of these patients were PCR positive and none of them developed persistent headache. In 70% of the cases, the headache ended within 3 days [5]. Asif et al reported a case with isolated headache in COVID-19, but in this case the cause of headache was sinus vein thrombosis [6]. In our patient, headache was the only symptom of COVID-19 and was persistent. Also in our case, asymptomatic pneumonia was present at the time of diagnosis, there were no other symptoms were observed during the treatment course. Our case is the only reported case with no other symptoms, but headache with pneumonia in thorax CT.

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2. CASE REPORT

56-years-old female patient initially admitted to the emergency department with complaint of a sudden headache. The pain started from the neck and spread to the entire head. The characteristic of the pain was throbbing on the first day. The next day it turned to a feeling of pressure in the head. The initial pain was very severe, sharp and different from the headaches she has experienced before. There was no accompanying nausea, photophobia, phonophobia, osmophobia, tearing-redness of the eyes, runny nose, fever, cough, sore throat, dyspnea, diarrhea, musculoskeletal pain, chest pain, anosmia and ageusia. The neurological examination was normal. There was no response to paracetamol, but a small relief with the non-steroidal antiinflamatuar drugs (NSAIDs).

The patient did not have any comorbidities and no previous diagnosis of migraine or any other headache syndrome. On the first day, cranial computed tomography (CT) and cranial CT angiography, cervical CT angiography and brain diffusion MRI were performed in the emergency department and reported to be normal.

Blood analysis revealed fibrinogen: 691,67 (180-350mg/dL), D-dimer: 0,97 (<0,55 mg/L), WBC:14,0 (4,5-11*10^3/uL), Neutrophils:11.1 (2-8 10^3/uL), CRP:3,84 (0-0,8 mg/dl), LDH:258 (120-246 U/L). The result of the nasal swab PCR sampling was negative. To rule out COVID-19, a chest CT was performed despite the absence of symptoms. However local infiltration areas with ground glass density in the periphery of the middle lobe, lateral segment of the both lungs were detected in the thorax CT (Figs. **1** and **2**). Bacterial pneumonia was ruled out as the procalcitonin level was normal and the patient was quarantined at home with the suspicion of COVID-19 pneumonia.

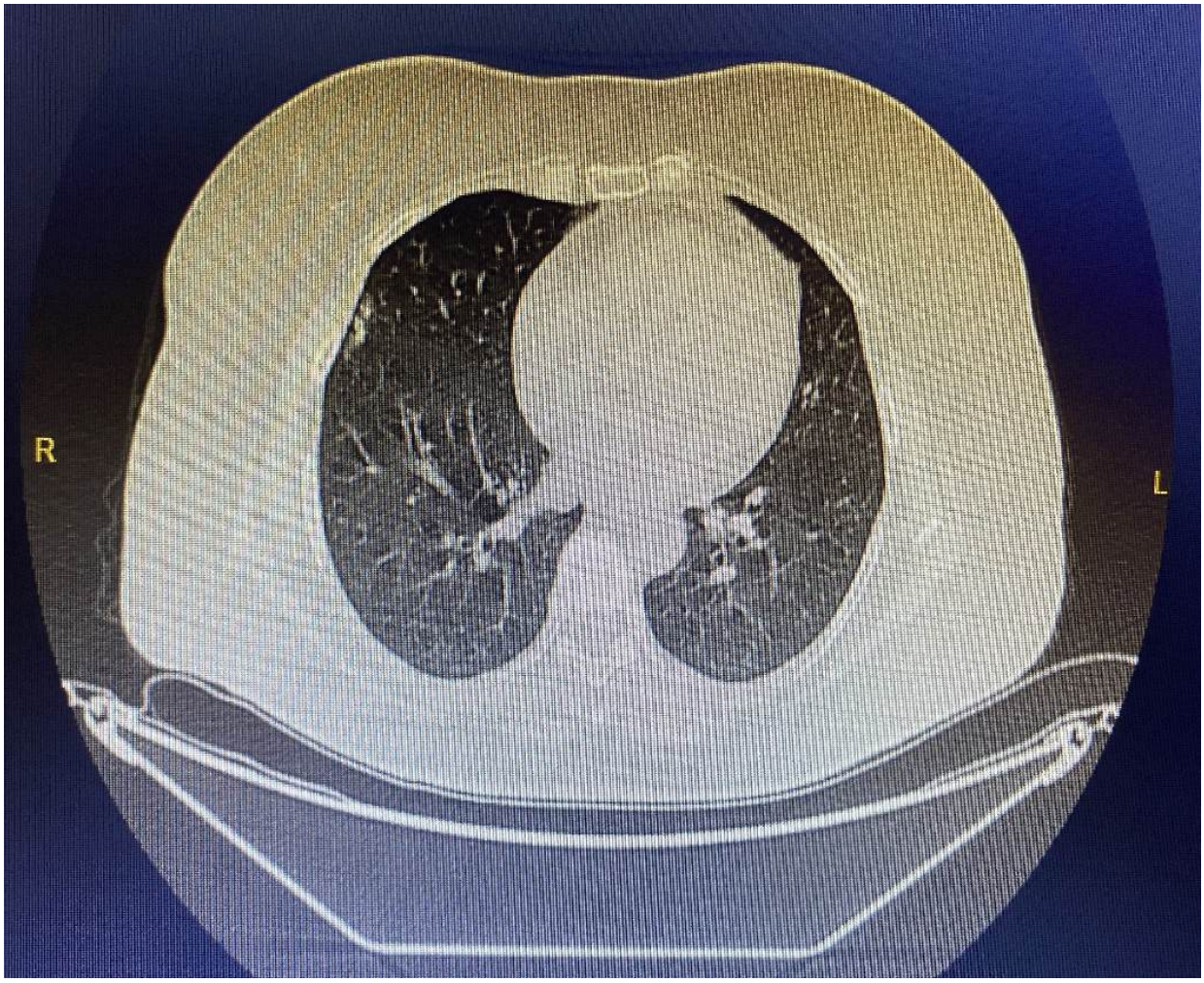

Fig. (1). Thorax CT: Small infiltrative area in middle lobe lateral segment.

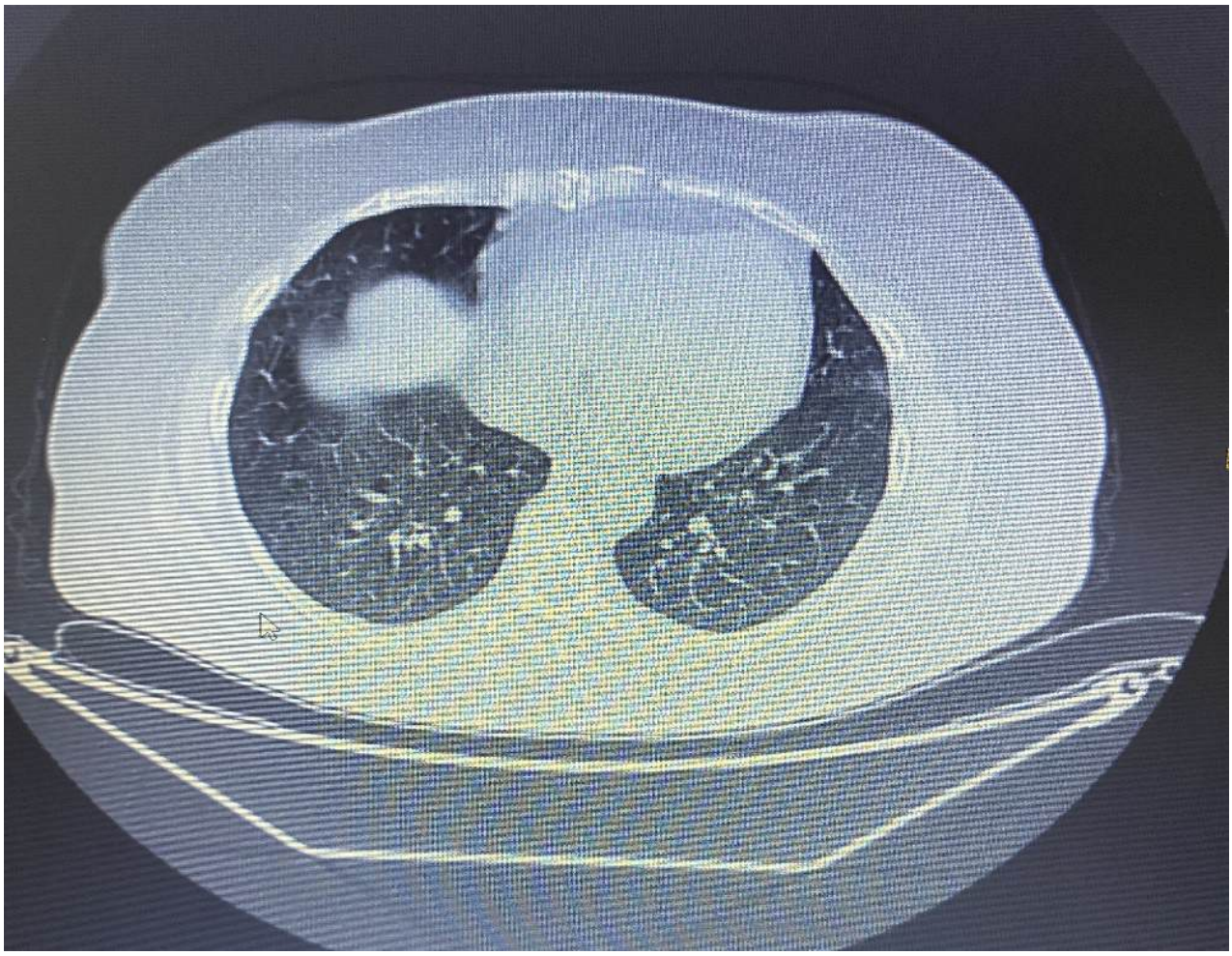

Fig. (2). Local infitration areas of both lung.

She was prescribed Hydroxychloroquine 200 mg tb oral every 12 hours for 5 days, Favipiravir 1600 mg oral every 12 hours on the first day, then 600 mg every 12 hours for the next 4 days, Famotidine 40 mg every 12 hours, Enoxaparin 6000 IU subcutaneously once a day. For her headache, she was prescribed Paracetamol 500 mg every 8 hours. On second day visit at home her complaints were still continuing, so paracetamol was replaced with Tramadol 100 mg every 8 hours for the first 7 days, then it was continued 50 mg every 8 hours for the following 3 days. The patient was followed up by phone calls to evaluate headache and other COVID-19 symptoms. She did not develop additional symptoms and the severity of the headache decreased approximately in 7 days. Therefore, additional tests and imaging were not performed. Mild persistent headache remained for about 2 months with paracetamol 500 mg three times in a day.

3. DISCUSSION

The pathophysiological mechanism of COVID-19-associated headache is still unclear. However, activation of trigeminal nerve endings, overproduction of pro-inflammatory cytokines, hypercoagulation, and hypoxia have been suggested as possible mechanisms [7]. SARS-CoV-2 uses the transmembrane angiotensin-converting enzyme type 2 (ACE2) receptor to enter mammalian cells. The ACE2 receptor is found on a variety of cells in humans, including lung epithelial cells, vascular endothelium, pericytes and smooth muscle cells, neuronal cells in the trigeminal ganglion, olfactory bulb, and other cortical and subcortical areas. Viral neuroinvasion is suggested to occur *via* synaptic transmission from infected cells, penetration into the brain *via* the olfactory groove, or perivascular lymphocytic infiltration [8].

There is evidence of a prolonged proinflammatory response (cytokine storm) in COVID19 patients, which can lead to rapid hyperactivation of T cells, macrophages, and natural killer cells and overproduction of more than 150 inflammatory mediators [9]. The cytokine storm triggers an atypical response of mast cells, a dramatic increase in interleukin-6 (IL-6) levels, and overexpression of angiotensin-converting enzyme 2 (ACE2) in the central and peripheral nervous systems [10, 11]. The same mechanisms play a role in migraine and tension-type headache. It is possible that this cytokine storm leads to hyperexcitability of the trigeminovascular system and triggers headache.

Molina-Gil *et al.* reported that only trigeminal neuralgia developed as a neurological symptom in a COVID-19 case. In this patient, as in our case, the PCR test was negative, but the rapid test showed positive IgM and IgG serologies for SARS-CoV-2. Again, as in our patient, an increase in D dimer was observed in this patient. Unfortunately, we could not perform a rapid test because it was not available in our hospital at that time [12].

At the beginning of the epidemic, due to Covid-19's similarities to SARS-CoV, many researchers recommended the use of hydroxychloroquine and chloroquine on the new virus [13,14,15]. At the same time, Wang and colleagues tested the effects of various Food and Drug Administration-approved antiviral drugs on the virus *in vitro*. In these studies, Chloroquine showed efficacy at the entry and post-entry level, whereas remdesivir was effective only at the post-entry level [16]. Yao and colleagues also tested the effect of hydroxychloroquine and chloroquine *in vitro* [17]. They found that hydroxychloroquine was more effective than chloroquine *in vitro* for both prophylaxis and treatment. As a result of these studies, hydroxychloroquine became one of the first agents used at the beginning of the COVID-19 epidemic. We believe that by using hydroxychloroquine in our patient, we benefited from the anti-inflammatory effect of the drug.

The International Classification of Headache Disorders third edition (ICHD-3) lists "Headache attributed to systemic viral infection" [18]. COVID-19 is clearly associated with headache and the character of COVID-19 headache was defined in a study [19]. This study included 130 adult patients. 97 patients had experienced headache as a COVID-19 symptom (74.6%). 19.6% patients had a history of episodic migraine and no patient had a history of chronic migraine. 37 patients had holocranial pain and the quality of pain was pressing and throbbing (68 and 19 patients, respectively). Nausea and vomiting (25,77%), worsening with movement (12,37%), photo/phonophobia (10,3%), vertigo (4,12%) and subjective neck stiffness (3,09%) were reported by the patients. 24 out of 97 patients had severe headache, 73 had mild-moderate pain, specifically analyzing migraine-like features. 74 of the patients with headache could be contacted after 6 weeks, 37.8% (28/74) still had headache. In our patient, headache was in the form of throbbing and pressure sensation and lasted more than 8 weeks.

There is a case with headache lasting more than 85 days reported in the literature [20]. The patient had been using naproxen and sumatriptan for the treatment of headache attacks. NSAIDs are not recommended as first choice for managing of COVID-19 disease [21]. Long term use of NSAIDs have been associated with higher rates of myocardial infarction, heart failure and stroke [22]. Acute respiratory tract infections are also associated with increased risk of myocardial infarction and stroke and short term use of NSAIDs during the illness is associated with further increases in risk [23]. The WHO declared to press that there is no evidence of an increased risk of death with the use of NSAIDs in COVID-19. Even so, we did not prefer to use NSAIDs for our patient. If paracetamol is inadequate, tramadol can be the second choice.

According to WHO, COVID-19 disease diagnosis is achieved with clinical manifestations, thorax CT and real-time reverse-transcriptase polymerase chain reaction (rRT-PCR). Our patient is included in the CT positive group [24,25,26]. In addition according to Pakdemirli and collegues, lung parenchymal changes due to COVID-19 can be clearly seen on chest CT, despite repeated RT-PCR negative results [27]. They described five patients with typical COVID-19 findings on CT scan despite two negative RT-PCR results. Also Brogna and collegues reported three cases, in which a chest CT was performed, showing lung changes characteristic of COVID-19 with multiple negative RT-PCR tests and positive serology for SARS-CoV-2 [28].

In a study, 87 patients underwent both CT scan and rRT-PCR to diagnose COVID-19 disease. 36 patients were diagnosed with COVID-19 pneumonia. The distribution of the CT lesions were 72,2% peripheral and 27,8% central. Peripheral distribution was more common than central distribution. According to this study, the sensitivity of CT was found to be 97,2% and the sensitivity of rRT-PCR was 83,3%. This may be related to collection of the samples at upper respiratory tracts. Additionally, the sensitivity of the rRT-PCR kit can also contribute to false negatives [29].

Higher or lower blood leukocyte count, higher neutrophil count and percentage, lower lymphocyte count and percentage, lower platelet count, higher C-reactive protein level, higher D-dimer level, higher alanine aminotransferase and aspartate aminotransferase activity, higher α - hydroxybutyrate dehydrogenase activity, higher lactate dehydrogenase activity and higher creatine kinase activity were related to severe 2019 novel coronavirus pneumonia [30].

In our case bilateral peripheral ground-glass opacity was defined in the thorax CT imaging. This was compatible with COVID-19. Additionally our patient's laboratory results were compatible with COVID-19. However rRT-PCR testing was negative. The negative result with pharyngeal or nasal swab technique in patients with pneumonia can be repeated by taking samples from the lower respiratory tract. Unfortunately, we did not make a second PCR sample in our patient.

CONCLUSION

In conclusion, the pathophysiology of COVID-19-associated headaches remains unclear, with some authors proposing direct viral invasion of the central nervous system *via* ACE2 receptors and retrograde spread through trigeminal nerve terminals, while others suggest an indirect mechanism involving activation of the trigeminal-vascular system due to a cytokine storm and elevated systemic inflammatory markers like calcitonin gene-related peptide. Given these varying hypotheses, further research is required to elucidate these controversial aspects. Clinicians should consider COVID-19 infection in patients with sudden onset of severe headaches, even in the absence of other symptoms, and pursue diagnostic evaluation with PCR testing and lung CT, particularly when cranial CT and CT-angiography results are normal.

AUTHORS' CONTRIBUTIONS

All authors contributed the study.

CONSENT FOR PUBLICATION

Written consent was obtained from the patient that the procedures to be carried out were photographed, including the appropriate parts of the body for medical, scientific, research or educational purposes, and that he accepted the record, provided that his identity is not disclosed in the images or in the article.

CONFLICT OF INTEREST

Authors have no conflicts of interest to declare.

FINANCIAL DISCLOSURE

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CASE REPORT

Delayed Diagnosis and Late Presentation of Primary Hyperparathyroidism in Somalia: A Case Report and Literature Review

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Abstract: Primary hyperparathyroidism (PHPT) is a rare endocrine disorder characterized by elevated serum calcium levels due to overproduction of parathyroid hormone (PTH). While parathyroid adenomas are the most common cause, they can present diagnostic and management challenges, especially in resource-limited settings. We present the case of a 51-year-old Somali female with a six-year history of generalized weakness, fatigue, and nonspecific abdominal pain. Laboratory investigations revealed elevated PTH levels (231 ng/ml) and hypercalcemia (14 mg/dl), consistent with PHPT. Cervical ultrasound identified a hypoechoic hypervascular solitary lesion suggestive of a parathyroid adenoma. The patient underwent a successful parathyroidectomy, resulting in the normalization of serum calcium levels and symptomatic relief. Histopathological examination confirmed the diagnosis of parathyroid adenoma. This case underscores the importance of early recognition and intervention in PHPT, particularly in underserved regions where healthcare resources may be limited. Efforts to raise awareness, provide training for healthcare workers, and improve access to diagnostic and treatment modalities are crucial in optimizing outcomes for patients with PHPT.

Keywords: Primary Hyperparathyroidism, Hypercalcemia, Somalia.

1. INTRODUCTION

An endocrine disorder termed primary hyperparathyroidism (PHPT) is characterized by elevated serum calcium levels because of parathormone oversecretion and is most often caused by parathyroid carcinomas, hyperplasia, and parathyroid adenomas, which together account for most instances. Although parathyroid gland adenomas are uncommon, they can be difficult to surgically treat [1]. Parathyroid adenomas, or PTAs, typically have a size of less than 2 cm and a weight of less than 1 g [2]. It is crucial to identify hyperparathyroidism early on in order to prevent problems that could harm the kidneys (nephrolithiasis or nephrocalcinosis) and bones (osteitis fibrosa cystica and osteoporosis) [3].

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Primary hyperparathyroidism (PHPT) is a common endocrine disorder characterized by excessive secretion of parathyroid hormone, leading to hypercalcemia and associated complications. In high-income countries, PHPT is often diagnosed early due to routine biochemical screening; however, in low-resource settings like Somalia, delayed diagnosis and late presentation are prevalent due to limited access to healthcare, lack of awareness, and insufficient diagnostic facilities. This case report aims to highlight the challenges of diagnosing PHPT in Somalia, where patients frequently present with advanced disease and complications such as severe bone disease, renal calculi, and neuropsychiatric manifestations. The rationale for this study lies in the need to raise awareness among healthcare providers about the atypical and advanced presentations of PHPT in resource-limited settings, emphasizing the importance of early recognition and intervention. By reviewing the existing literature and detailing a representative case from Somalia, this report seeks to contribute to the limited body of knowledge on PHPT in sub-Saharan Africa, thereby advocating for improved diagnostic strategies and healthcare resources to mitigate the burden of this condition in underserved populations.

We present a case involving a 51-year-old Somali patient from a rural area who experienced weakness and nonspecific abdominal discomfort for six years before being diagnosed with primary hyperparathyroidism due to a parathyroid adenoma, resulting in elevated parathyroid hormone and serum calcium levels.

2. CASE REPORT

A 51-year-old Somali female patient from a remote region was admitted to our internal medicine department because of generalized weakness, fatigue, constipation, and vague abdominal pain for the past 6 years. The patient had weakness in both legs and arms and had tenderness in the abdomen which was revealed by physical examination. There were no other remarkable findings. The vitals were also stable with no abnormality.

3. INVESTIGATION AND DIAGNOSIS

Parathormone and serum calcium levels were elevated, with PTH levels of 231ng/ml and calcium 14 mg/dl. Other laboratory investigations demonstrated normal range, hematocrit, and a euthyroid state, with TSH, T3, and T4 levels within the normal limits and normal biochemistry results. Ultrasound of her neck revealed a normal-sized thyroid gland, while a 1.6x1.2 cm in size hypoechoic hypervascular solitary lesion was located in the posterior inferior right thyroid lobe (Fig. **1**). Laboratory examination and cervical sonographic features revealed parathyroid adenoma as the cause of hyperparathyroidism.

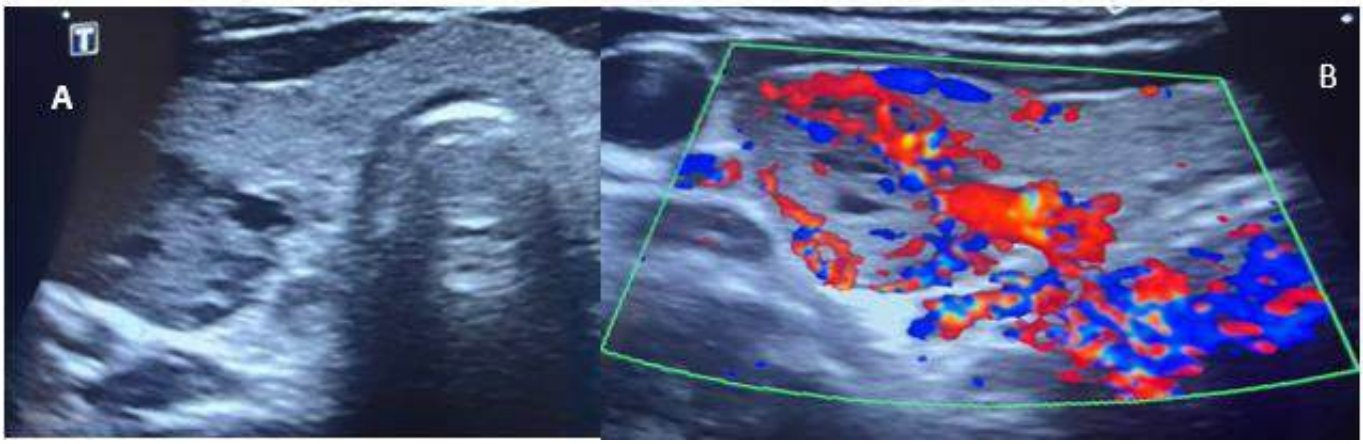

Fig. (1). Posterior inferior to the right thyroid lobe 2cm sized hypoechoic lesion compared to the thyroid tissue (**A**) with vivid vascularization in color Doppler examination (**B**).

4. INTERVENTION AND TREATMENT

The patient was admitted to the internal medicine department for fluid and electrolyte optimization and then transferred to the surgical department for parathyroidectomy. The patient was then transferred to the operating room after written consent was obtained. A resection of the right parathyroid gland was performed by an experienced general surgeon through a Typical MIP incision approximately 2 cm in length, with successful parathyroidectomy. The excised 1 cm specimen was removed, and intraoperative PTH was sent according to the vein criteria and more than 50% drop in pth levels (pre-op PTH 231pg/ml intraoperative PTH 38pg/ml). The surgical pathology specimen sent for pathological examination showed areas of hemorrhage and focal endocrine atypia (low-power view, high-power view) and histopathological confirmed parathyroid adenoma (Fig. **2**).

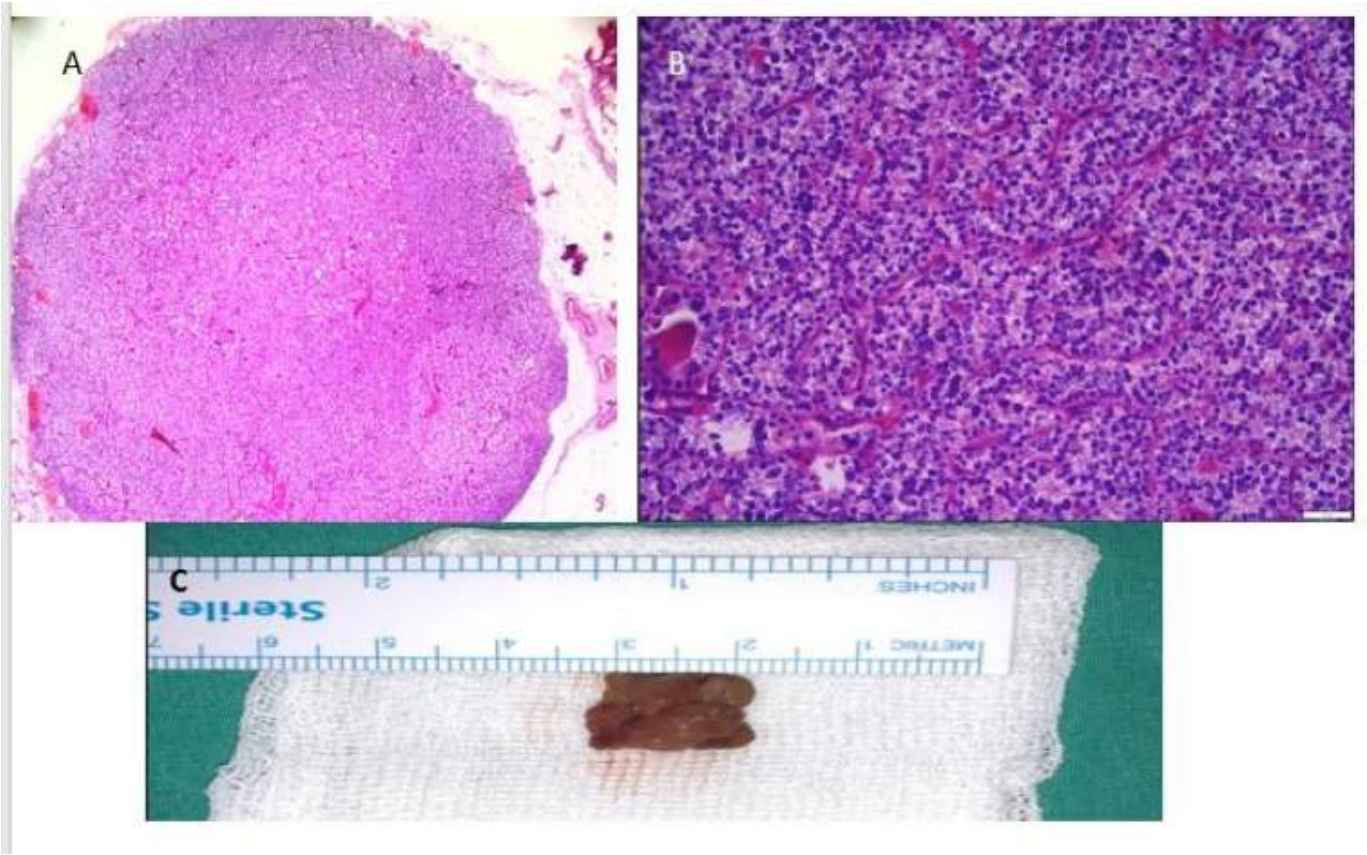

Fig. (2). Parathyroid adenoma, parathyroidectomy. Parathyroid adenoma (Chief cell adenoma) shows areas of hemorrhage and focal endocrine atypia (**A**) Low power view, (**B**) high power view) Surgical pathology specimen (**C**).

5. OUTCOME AND FOLLOW-UP

The postoperative with a slight decline in calcium (9,5 mg/dL), while her parathormone (PHT) levels returned to normal limits approximately one day after surgery. She was discharged the next day, and after 2 months of follow-up, she reported no further symptoms.

6. DISCUSSION

The endocrine disease known as primary hyperparathyroidism has been defined by high PHT levels and hypercalcemia [4]. With no sex predisposition, its incidence is roughly 0.5% [5]. About 80% of PHPT cases are caused by parathyroid adenomas, which are the most common cause of PHPT. Additional factors include hyperplasia and parathyroid carcinoma, which is thought to affect 1% of patients [1].

A physical examination of the cervical region frequently reveals nothing unusual, although symptoms related to non-specific skeletal, neurological, renal, and gastrointestinal issues are linked to increased cal-

cium levels [6]. Neuromuscular weakness, exhaustion, impaired focus, and memory loss are common symptomatology. Along with peptic ulcers and muscular and joint discomfort, primary parathyroid hormone can cause nephrolithiasis and neuphrocalcinosis in patients. A uncommon illness called as hypercalcemic crisis can result from dehydration or fluid loss, which can cause an abrupt spike in serum calcium levels. Acute stomach discomfort, nausea, vomiting, and constipation are the main symptoms; cardiac or renal dysfunction may also be evident [7].

Diagnosing hyperparathyroidism (HPT) requires the study of PTH and calcium levels. may also have raised PTH and normalized calcium levels, even though elevated PHT and blood calcium levels are the hallmarks of typical primary hyperparathyroidism. It is important to differentiate this illness from normocalcemic hyperparathyroidism, a subsequent form of hyperparathyroidism [8].

Intestinal calcium malabsorption, vitamin D deficiency, and renal insufficiency are the most common causes of secondary HPT [9]. Patients with preoperatively elevated calcium levels should be closely monitored following surgery because pathological gland resection causes an abrupt drop in calcium levels, which can lead to temporary hypocalcemia. Additionally, a feedback effect causes the non-pathological parathyroid glands to stop functioning normally. [10].

With increased PTH levels of 231 pg/mL and calcium levels of 14 mg/dL, respectively, our patient was diagnosed with primary PHTP. A slightly lower calcium level of 8 was found in postoperative measurements around a day after surgery, exhibiting normal function of the three surviving parathyroid glands.

Even if clinical and laboratory criteria are employed to establish the diagnosis of PHPT, a range of imaging modalities are used for the preoperative evaluation of PHPT and localization of the diseased glands. An ultrasound scan of the neck, with an approximate sensitivity and specificity of 75% and 85%, respectively, can be used to detect the parathyroid gland prior to surgery [11].

Unfortunately, patients with somalia cannot obtain 99m Tc-MIBI parathyroid scintigraphy. It is possible to discover aberrant parathyroid tissue by identifying and using the absorption of radiotracers from hyperactive parathyroid tissue [12]. PHPT is surgically treated by excising the abnormal parathyroid tissue using either neck exploration or minimally invasive parathyroidectomy [13].

The initial strategy involved identifying each of the four parathyroid glands through a thorough thyroid examination, and then removing the most likely problematic glands according to their size. Removing a single hyperactive parathyroid gland with the least amount of intervention is the aim of minimally invasive parathyroidectomy [14]. Under local anesthetic, the MIP method involves a small cervical incision for unilateral neck exploration. Preoperative localization of the target parathyroid gland and labeling are essential to avoid needless injury to adjacent tissues. The excision of the diseased parathyroid gland can be verified by measuring intraoperative parathormone (ioPTH). The PHT returns to normal within minutes of the damaged gland being removed due to its short half-life [15]. The intraoperative PTH level recovered to normal following the excision of the adenoma.

The absence of proper healthcare facilities can be a contributing factor in late presentations and poorer outcomes in cases of primary hyperparathyroidism, such as our case, which necessitates early detection and intervention of the condition. In order to overcome the issues that are associated with late presentations of medical illnesses in underserved locations, it is essential to make efforts to promote awareness, offer training for healthcare workers, and enhance access to diagnostic equipment and treatment alternatives.

CONCLUSION

Patients who appear with vague weakness consistent with increased serum calcium levels should be suspected of having hyperparathyroidism, a common endocrine condition. Patients who exhibit symptoms related to calcium and inexplicable weakness should be suspected of having hyperparathyroidism. Clinically, primary HPT is linked to parathyroid adenoma (80–85%), hyperplasia (10–15%), and malignancy (<1–5%). Complementary cervical ultrasonography was used in conjunction with the clinical and biochemical histories to confirm the diagnosis. The recommended course of treatment is surgery. Preopera-

tive and postoperatively, we can now distinguish between single- and multi-gland parathyroid disorders because to new advancements in diagnostic imaging and intraoperative rapid PTH testing. Aside from its tiny size and delayed manifestation, our patient's adenoma was successfully treated surgically.

AUTHORS' CONTRIBUTIONS

AAO: Writing – original draft; and editing and Conceptualization. AMA: Writing original draft; investigation. IMA: writing – review and editing. ASH: Investigation; writing – review and editing. SMA: Writing – original draft. MOA: writing – original draft. MOOJ: Writing – review and editing and Conceptualization

DATA AVAILABILITY

The data is available from the corresponding author if requested.

ETHICS STATEMENT

The Ethics committee of Mogadishu Somali Turkiye Training and Research Hospital waived the ethical approval for this case report.

CONSENT FOR PUBLICATION

Oral and written informed consent were obtained from the patient to publish this case report anonymously.

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CONFLICT OF INTEREST

The author confirms that this article's content has no conflict of interest.

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CASE REPORT

Subglottic Stenosis in a 3-Year-Old Child Following Prolonged Intubation - A Case Report

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Abstract: Subglottic stenosis is a serious complication of prolonged intubation in pediatric pa- tients and Over 90% of acquired cases are iatrogenically caused and result from endotracheal intu- bation. Subglottic stenosis is an unanticipated problem that needs to be diagnosed and treated im- mediately. The majority of pediatric subglottic stenosis occurrences are mild to moderate. This case highlights the challenges and outcomes associated with this condition. Here, we present a 3-year-old child presented with high fever and scrotal pain with swelling, diagnosed as scrotal cellulitis. Laboratory results showed anemia, leukocytosis, and metabolic acidosis, and the child's condition deteriorated due to respiratory distress, requiring intubation and PICU admission. Following a scrotal abscess drainage, the child was discharged but returned with severe respiratory distress, cyanosis, and subglottic stenosis, confirmed by laryngobronchoscopy and imaging. After failed extubation attempts and further complications, a tracheostomy and endoscopic subglottic dilation were performed. The child was successfully decannulated after eight days, with near-complete recovery except for a slight change in voice tone. The case highlights the challenges in managing complex respiratory complications in pediatric patients. This case underscores the importance of monitoring for subglottic stenosis in children who have undergone prolonged intubation and demonstrates the efficacy of endoscopic dilatation in managing this complication.

Keywords: Subglottic stenosis, Children, Intensive care, Intubation, Endoscopic laryngeoscope.

1. INTRODUCTION

Tracheal subglottic stenosis is one of the two types of congenital or acquired airway obstructions that affect newborns and children. The narrowest portion of the airway in infants and children is the subglottis of the anatomical area of the trachea, which is located next to the cricoid cartilage and directly below the surface of the voice cords. This region's inflexibility makes subglottic stenosis potentially fatal because it reduces the airway's diameter in this area. Furthermore, 90% of patients with acquired subglottic stenosis undergo iatrogenic endotracheal intubation [1]. Based on either retrospective or prospective evaluations, children's subglottic stenosis prevalence varies between 0.6% and 11.38% [2, 3].

Especially in children, the most common risk factors for subglottic stenosis are extended intubation, incorrect endotracheal tube size selection, insufficient sedation and analgesia, repeated intubation, and nursing errors such as forceful suctioning. Other risk factors for subglottic stenosis include underlying respiratory illnesses, gastroesophageal reflux disease (GERD), premature birth, brain damage, congenital

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airway disorders, cerebral palsy, Down syndrome, prolonged seizures, viral infection leading to intubation, and inadequate perfusion of the airway mucosa due to hypotension, anemia, sepsis, obesity, diabetes, and shock [4-10].

Stridor during inspiration is the initial indication of subglottic stenosis. In addition, if blockage worsens, biphasic stridor ensues. The prevalence rate of stridor, a common complication in children following extubation, stands at 44%. It is particularly concerning when it is severe, late, or progressive, and requires prompt evaluation and intervention [11]. Laryngobronchoscopy is considered the most reliable method for diagnosing subglottic stenosis. Medical treatment or bronchoscopic intervention is necessary for mild to moderate cases. Furthermore, cases classified as moderate to severe require the use of open surgery and tracheostomy [4].

2. CASE PRESENTATION

A 3-year-old child presented to the emergency department with a high fever and scrotal pain accompanied by swelling, persisting for 5 days. A scrotal ultrasound was performed, revealing scrotal cellulitis, and laboratory investigations showed anemia, marked leukocytosis, and metabolic acidosis. The child's condition deteriorated due to respiratory distress, prompting transfer to the pediatric intensive care unit (PICU).

In the PICU, the child was intubated, stabilized, and pediatric surgery was consulted for drainage of a scrotal abscess. The child remained intubated for a month but was eventually extubated and discharged home after spending an additional 5 days in the pediatric hospital ward.

Seven days post-discharge, the child returned with complaints of shortness of breath and cough. On examination, he exhibited severe chest indrawing and low oxygen saturation (<90%). His vital signs included a temperature of 37°C, a respiratory rate of 50 breaths per minute indicative of tachypnea, and a pulse rate of 140 beats per minute, consistent with tachycardia. He was administered supplementary oxygen; however, 12 hours after admission, he developed worsening respiratory distress and dyspnea. While initial pharmacotherapy provided temporary relief, he soon experienced severe respiratory distress again, accompanied by cyanosis.

Upon transfer to the pediatric critical care unit, his vital signs were as follows: Glasgow Coma Scale (GCS) of 8, partial pressure of carbon dioxide (PCO2) at 75 mmHg, pulse rate of 60 beats per minute, and oxygen saturation (SpO2) of 80% despite being on high-flow oxygen therapy via a face mask. Rapid sequence intubation (RSI) was immediately performed.

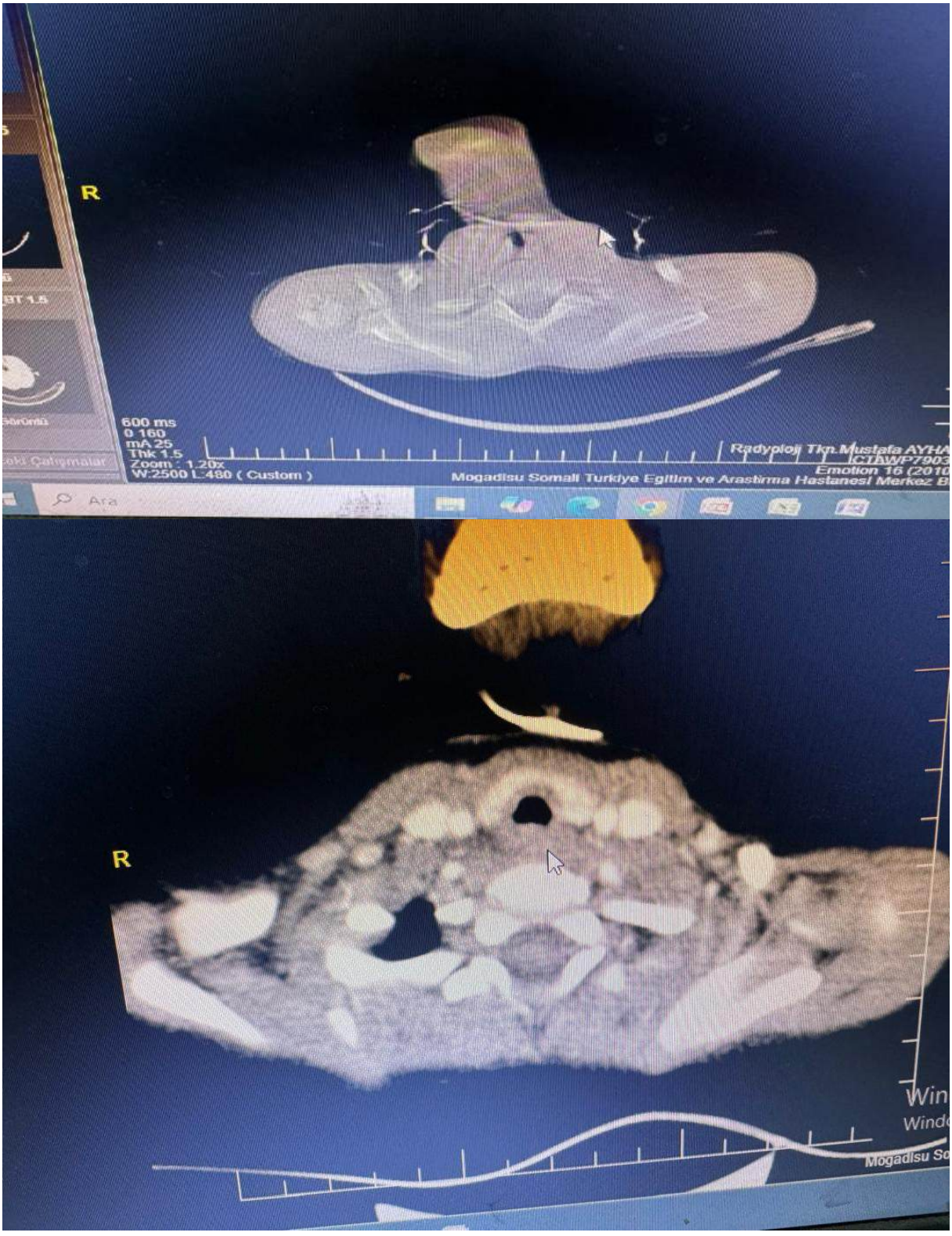
Attempts to extubate were unsuccessful due to persistent signs of obstruction, including chest indrawing, secretions, and inadequate ventilation. The child was initially intubated with a 4.0-sized endotracheal tube (ETT). Following a failed extubation attempt the next day, he required reintubation. Due to difficulty passing the previous ETT size, reintubation was achieved with a guidewire and a 3.5-sized ETT.

Subsequently, the child underwent a tracheostomy, and subglottic stenosis was diagnosed. Once his respiratory and hemodynamic status was stabilized, a diagnostic laryngobronchoscopy was performed by an otolaryngologist, which revealed severe subglottic stenosis (grade 3-4), located 2 cm below the vocal cords.

Further imaging, including CT scans of the neck and chest with intravenous contrast, confirmed the presence of subglottic stenosis and vocal cord secretions. The patient was referred to a specialized Ear, Nose, and Throat (ENT) clinic for management of tracheal stenosis.

Diagnostic laryngobronchoscopy showed near-complete tracheal stenosis (grades 3-4), located 1.5-2 cm below the vocal cords. The child underwent a lower-level retracheostomy and endoscopic subglottic dilation using dilators of 7 and 9 mm to widen the airway. A Foley catheter, inflated with 2 cc of water, was left in the dilated area for 8 days.

After eight days, the tracheostomy was removed, and the child made a near-complete recovery, with only a slight alteration in voice tone that did not cause any further breathing difficulties. He was monitored in the ICU and gradually transitioned to normal respiratory support (Figs. **1** and **2**).



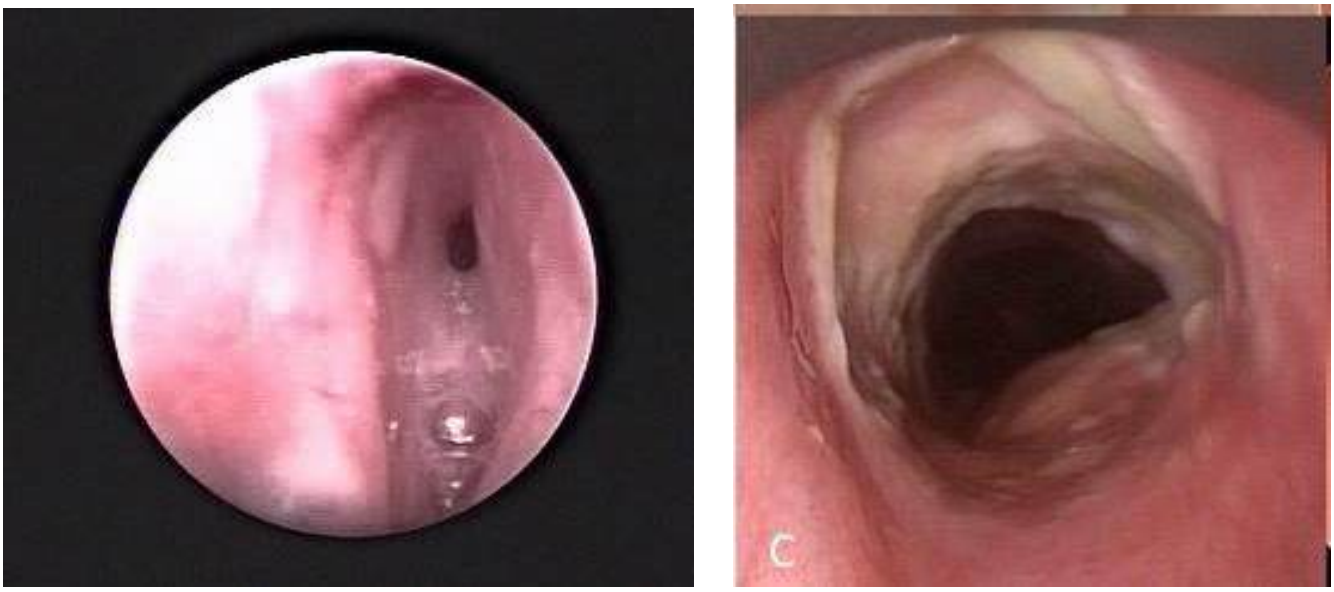
Figs. (1 and 2). Axial CT scan of the neck with intravenous contrast showing significant narrowing of the tracheal lumen, indicative of severe subglottic stenosis. The narrowing is observed approximately 2 cm below the vocal cords. Soft tissue swelling and irregularities can be noted around the stenotic segment.

2.1. Intervention

- **Procedure:** Endoscopic dilatation of the subglottic stenosis was performed. The procedure involved inserting a balloon or other dilating instruments into the narrowed area to widen the airway.
- **Post-Procedure Management:** The child was monitored in the ICU and gradually transitioned to normal respiratory support.

2.2. Outcome

- **Immediate Post-Procedure:** Significant improvement in airway patency and reduction in stridor.
- **Follow-Up:** At 6 months, the child was stable with no recurrence of stenosis and normal respiratory function. (Figs. **3** and **4**)



Figs. (3 and 4). Endoscopic view of the trachea showing severe subglottic stenosis. The image depicts significant narrowing of the airway lumen, with evident concentric fibrotic changes and thickening of the subglottic tissue, consistent with grade 3-4 stenosis. The lumen is markedly reduced, contributing to the patient's respiratory distress.

3. DISCUSSION

The most typical differential diagnosis for stridor in children is subglottic stenosis after prolonged intubation. Despite the high morbidity and mortality rates in children, additional attention is required to be made to prevent subglottic stenosis.

Patients themselves can be attributed to predisposing factors for post-intubation stenosis, including congenital airway narrowing, preterm, gastric reflux, keloid development, and systemic variables that lead to reduced blood flow in the mucosa, such as hypotension, anemia, sepsis, and shock. Extrinsic variables refer to external circumstances. These factors include the size or rigidity of the ETT (endotracheal tube), the method of intubation (traumatic, multiple attempts, or long-term intubation) [12], and the quality of nursing care (insufficient sedation, excessive tube movement, and repeated and traumatic aspirations) [13].

The main variables that lead to post-intubation subglottic stenosis (SGS) are traumatic intubation and the pressure exerted by the endotracheal tube (ETT). When the endotracheal tube (ETT) exerts pressure that exceeds the capillary perfusion requirement, ischemia develops, leading to edema, necrosis, and ulcers. Subsequently, during the repair process, the formation of granulation tissue may result in a reduction of the airway passage and cause blockage. We regard intubation lasting more than 4 weeks as elevating the risk of stenosis due to superinfection; however, damage can occur within just 48 hours [14].

Treatment for children with subglottic stenosis has advanced significantly, but managing the condition is still complicated with controversy. Some of the treatments that can be used are medication, tracheostomy, balloon endoscopic dilatation, endoscopic anterior cricoid split with balloon dilatation, endoscopic posterior cricoid split with cartilage graft, laryngotracheal reconstruction (LTR), and partial cricotracheal resection (CTR) [15]. Medication, such as systemic or inhaled corticosteroids and racemic epinephrine, is used to treat the majority of mild cases [16].

Systematic review studies have shown that endoscopic balloon dilatation has been successful in approximately two-thirds of cases with low to moderate severity. However, as the severity of stenosis and intubation period increased, the failure rate increased [17,18].

A retrospective study found that 84.5% of patients with moderate to severe post-intubation subglottic stenosis achieved decannulation with just one surgical procedure. We treated the patients using either laryngotracheal reconstruction, partial cricotracheal resection, or anterior cricoid split methods [19,20].

CONCLUSION

This case demonstrates that while subglottic stenosis grade 4-5 can be a serious complication of prolonged intubation, timely and effective management with endoscopic dilatation can lead to favorable outcomes.

RECOMMENDATIONS

Monitoring: Vigilance in monitoring for subglottic stenosis in children following prolonged intubation.

Treatment: Endoscopic dilatation as an effective treatment modality.

AUTHORS' CONTRIBUTIONS

The author confirms sole responsibility for the following: study conception and design, data collection, analysis and interpretation of results, and manuscript preparation.

CONSENT FOR PUBLICATION

We have obtained written informed consent from the patient's parent for the publication of this case report and any accompanying images. The consent form has outlined that all personal identifiers, including but not limited to names, initials, and hospital numbers, will not be disclosed in this publication to ensure the confidentiality of the patient.

CONFLICT OF INTEREST

None.

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