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Review Article

Viewpoint of COVID-19 in Africa and Latin America

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Abstract

The spread of COVID-19 across the African continent and Latin American region is of great concern due to several influencing factors. Large and densely populated areas and townships with widespread poverty and high migration are the most vulnerable populations for a pandemic of this magnitude. The latter could be complicated since known communicable diseases such as chronic obstructive pulmonary disease (COPD), diabetes, cardiovascular disorder, hypertension and lack of basic healthcare delivery systems are known risks that may enhance the degree of mortality, via the pandemic in affected regions. The aim of this review is to focus on the clinical signs, transmission, case fatalities and influencing factors that might exacerbate the pandemic in these regions.

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Introduction

Since December 31, 2019, when the outbreak began in China, and as of July 9, 2020, there are ~12M cases and over ~550,000 deaths worldwide in more than 213 countries. In Africa, those reporting most cases *(Table 1)* are from South Africa (224,665), Egypt (78,304), Nigeria (30,249), Ghana (22,822) and Algeria (17,348), whereas 5M+ cases are accounted in America comprising of the US (~3M), Brazil (1,668,589), Peru (309,278), Chile (303,083) and Mexico (268,008). The spread of COVID-19 is mainly through travellers.[1,2] Although the virus emerged from China, the mostly affected countries include the US, Brazil, the UK, Italy, Spain, France, Iran, Germany and others to name but a few.[1] COVID-19 is a broad spectrum of disease, starting from asymptomatic cases that may recover with no underlying symptoms, up to complicated

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Table 1. List of African countries with confirmed cases of COVID-19 & Fatalities (Data adopted/modified from[27]) (As of July 9, 2020)

Country	COVID-19 cases (n)	Fatalities (n)
South Africa	224,665	3,602
Nigeria	30,249	684
Ghana	22,822	129
Algeria	17,348	978
Cameroon	14,916	359
Côte d'Ivoire	11,504	78
Senegal	7,657	141
Democratic Republic of Congo	7,736	183
Guinea	5,697	34
Kenya	8,528	169
Gabon	5,871	46
Ethiopia	6,973	120
Central African Republic	4,109	52
Mauritania	5,024	135
Mali	2,358	120
South Sudan	2,106	40
Guinea Bissau	1,790	25
Madagascar	3,573	33
Zambia	1,895	42
Sierra Leone	1,584	63
Equatorial Guinea	1,043	12
Niger	1,097	68
Burkina Faso	1,003	53
Congo	1,821	47
Chad	873	74
Cabo Verde	1,542	18
Uganda	977	0
Sao Tome & Principe	404	11
Mozambique	1,071	8
Rwanda	1,194	3
Benin	1,285	23
Malawi	1,942	25
Eswatini	1,138	14
Liberia	926	41
Togo	695	15
United Republic of Tanzania	509	21
Zimbabwe	885	9
Mauritius	342	10
Comoros	313	7
Angola	396	22
Eritrea	215	0
Burundi	219	1
Botswana	314	1
Namibia	593	0
Gambia	63	3
Seychelles	94	0
Lesotho	134	1
Egypt	78,304	3,564

severe, life-threatening and even fatalities, perhaps leading to unknown non-acute effects, still to be better defined.[3]

There has been rapid response to the pandemic from public health authorities in Africa well ahead of reported cases which sounds encouraging action in fighting against it.[4] The African Centres for Disease Control and Prevention Task Force was inaugurated on February 3, 2020, for this pandemic.[4] It works in collaboration with the World Health Organisation (WHO) Regional Office for Africa on community engagement, surveillance, screening at points of entry, infection prevention and control in healthcare settings, clinical management of patients with severe COVID-19 infection, laboratory diagnosis, and risk communication.[5] Most nations in Africa have set up measures to the current COVID-19 pandemic. These efforts are not without challenges. The major ones range from lacking well-established and functional health centres up to village levels, tribal sentiments, religious and most importantly, unaccountable corrupt governments across the continent for decades. These are not bothered about using the resources at their disposal in providing basic amenities such as hospitals, education, healthcare centres, roads, electricity, water, as well as housing and improve health-related quality of life. This sort of governance is a general malaise that had engulfed the 54 nations of Africa, with the exception of Ghana, recently trying to change its trajectory prior to the pandemic. The fundamental question now is what lessons could be learnt from this pandemic? Will the leaders of the countries in Africa modify their course of governance to be accountable, prudent and use the resources to the benefit of the poor masses? Or will it continue to be business as usual in enriching themselves as has been the cases for the past decades pre-COVID-19 or a drastic change for good after this?

According to the report from the World Economic Forum 2020, Africa has the lowest capacity to provide critical and intensive care in the world.[6] Social and religious gatherings are not uncommon in Africa.[4] Many countries have banned such meetings, and this has received resistance from some people across the region thus affecting physical distancing. Family clusters, low health literacy, "infodemic" and poverty may contribute to poor response.[4] The lockdowns and stay-at-home strategy working have halted business activities, making the poorer the most vulnerable to the economic consequences, posing further difficulties to adhere to precautionary measures. Price hikes for masks and hand sanitizers have also been reported.[4]

Since the start of the outbreak, the WHO has been supporting African governments with early detection by providing thousands of COVID-19 testing kits to countries, training dozens of health workers and strengthening surveillance in communities.[4] So 44 countries in the WHO African region can now test for COVID-19.[4] At the beginning of the outbreak, only two of them could do so which is a testimony of the style they govern across the continent and lack of basic healthcare facilities available to the populace.

From February 25, 2020, when COVID-19 was confirmed for the first time in Brazil, while someone was coming from Italy, up to July 9, 2020, 3.1M+ cases with ~133,000 deaths have been reported in Latin America and Caribbean region, and this country is still leading the way with ~1.7M cases and greater than 66,000 deaths respectively.[7,8] In a complex pandemic like COVID-19, the epidemiological situation in Latin America before February 25, 2020, was already intricate, with other overlapping epidemics of varying vector-borne pathogens such as dengue and yellow fever, but also struggling from the long-term endemic consequences after 2014–2016 outbreaks of chikungunya and Zika.[3,9]

Latin America was the last significant region where COVID-19 arrived.[3] The healthcare systems in Latin America are fragile coupled with fragmentation and segmentation, which are continuing challenges facing these vulnerable systems.[10] There are multiple ongoing social and economic problems, so COVID-19 pandemic will have tremendous impact on, including the massive exodus of people from Venezuela to many countries in the region. This human migration is associated with other pathogenic diseases, such as malaria or measles.[3]

In Latin America, there is a large heterogeneity of political, social development, and economic growth capacities. For instance, in the Caribbean sub-region, countries such as Haiti have a low human development index, while in Venezuela, ongoing humanitarian crisis exists and the impact of COVID-19 will be more devastating there than those with more developed economies like Brazil

Table 2. List of Latin American countries with confirmed cases of COVID-19 & Fatalities (Data adopted/modified from[28]) (As of July 9, 2020)

Country	COVID-19 cases (n)	Fatalities (n)
Brazil	1,668,589	66,741
Peru	309,278	10,952
Mexico	268,008	32,014
Bolivia (Plurinational State of)	41,545	1,530
Chile	303,083	6,573
Argentina	83,426	1,654
Paraguay	2,554	20
Uruguay	965	29
Antigua & Barbuda	70	3
Barbados	98	7
El Salvador	8,566	235
Ecuador	63,245	4,873
Bahamas	104	11
Cayman Islands	201	1
Jamaica	745	10
Cuba	2,399	86
Suriname	635	17
Guatemala	24,787	1,004
Belize	30	2
Honduras	25,428	677
Nicaragua	2,411	91
Guyana	284	16
French Guiana	5,459	22
Martinique	249	14
Saint Vincent & The Grenadines	29	0
Trinidad & Tobago	133	8
Dominican Republic	39,588	829
Haiti	6,432	117
Venezuela (Bolivarian Republic of)	7,693	71
Aruba	105	3
Colombia	124,494	4,359
Costa Rica	5,486	23
Panama	40,291	799
Bermuda	149	9
Falkland Islands	13	0
Saint Lucia	22	0

or Mexico.[3] Incidentally, the largest Latin America country is second in ranking behind the US in terms of infected cases and corresponding fatalities with COVID-19, Jair Bolsonaro's government has been strongly criticised for the utter confusion and guidance in handling the outbreak among 210 million Brazilians *(Table 2)*. The disarray in the heart of administration is a deadly distraction at the core of a public health emergency and is also a stark indicator that Brazil's leadership has lost its moral navigation.[11]

Clinical Signs

The major symptoms associated with COVID-19 include fever, cough, fatigue, myalgia, arthralgia and dyspnea, which could eventually lead to respiratory failure.[12] They could also be preceded by non-respiratory ones such as diarrhea, abdominal pain, palpitations, dizziness and headaches. However, some of these could manifest during the period of isolation. Though the mechanism surrounding

olfactory impairment with COVID-19 is not fully understood, ageusia and anosmia might be among the first line of symptoms. COVID-19 is weird in its clinical behaviour and could be variable.

Asymptomatic individuals though do not exhibit any of COVID-19 symptoms nor aware of the infection, but have the capability of transmitting to other people from their faeces if not tested and isolated. It has been noticed that some patients who suffered from COVID-19 recovered without antibodies and it is not always those that are found after being cured.[13]

The clinical signs of COVID-19 could overlap with that of malaria or any other comorbidity and complicate diagnosis especially in the rural and suburban towns in Africa. Strangely, many millions of individuals in this region and possibly in Latin America had never received any medical attention all their lives, may even have COVID-19 and get it confused with malaria. In such localities, mass testing, contact tracing, isolation, educating people on the principle of protecting themselves as well as others will play major roles in combating the infection among such individuals. For the limited available health centres or hospitals, many inhabitants have to travel long distances to access them.

Transmission of COVID-19 in Africa & Latin America and the Caribbean

The countries in Africa, Latin America and Caribbean (LAC) share common problems where water scarcity and poor sanitation may substantially impact on the spread of COVID-19.[5] The World Bank estimates that 36 million people in LAC lack access to potable drinking water, and 110 million do not have access to improved sanitation.[5] In urban slums where there is no in-home water filtration, results in reduced usage, limited handwashing facilities, and poor family hygiene, leading to faecal contamination on a broad scale.[14] In households without clean pipe-borne water system, drinking is often from boiled and stored sources; yet such water may be contaminated through faecal means as there is no form of treatment.[14] Water shortages and delivery both in some urban and rural areas of LAC is replicated in most African countries as well. Importantly, coronaviruses can remain infectious for weeks in room temperature water.[15] If there is an increased transmission caused by faecal contamination in combination with reducing contacts, the epidemiological dynamics of COVID-19 in LAC may be fundamentally distinct from that currently noticed in the Northern Hemisphere.[16]

Despite the fact that RNA from SARS-CoV-2 has been found in blood and stool specimens and it has also been cultured from faeces of some COVID-19 patients, faecal-oral transmission has not been taken as a vital mode of infection according to a report from WHO-China.[17]

The spread could be via direct means (droplet and human-to-human transmission) or indirect contact (contaminated objects and airborne contagion). Personal protective equipment (PPE) could also be the source of airborne infections.[18] Person-to-person transmissions are mainly through respiratory droplets, when a patient coughs, sneezes, and even talks or sings. Typically, these cannot traverse more than almost two metres and remain in the air for a limited time.[18] The ones containing the virus might contaminate surfaces such as smart phones up to a period of 96 hours. The SARS-CoV-2 can be suspended in the air for up to three hours and still be intact and contagious.[19] Thus, airborne isolation precautions, room ventilation, and appropriate application of disinfectant (particularly in toilets) might minimise the aerosol spread of the virus.[20]

Asymptomatic individuals (or people within the incubation period) could transmit the virus even without any radiological symptoms.[21-23] Although each patient had at least two negative tests among four hospital staff who tested positive, as their RT-PCR results obtained from 5–13 days after being discharged.[24]

A study on semen and testicular samples of COVID-19 patients indicated that SARS-CoV-2 could not be transmitted via sexual contact.[25]

With a long incubation period for COVID-19, viral shedding in patients after recovery and presence of asymptomatic people, the rate of transmission could be controlled via education, isolation, preventive measures and treatment of infected individuals.[26]

Conclusion

The number of infected cases and fatalities

associated with COVID-19 could be higher than expected as some of the health reporting could be wildly inconsistent and possibly politically controlled. This depends on individual country preparedness, available healthcare facilities and quality deliverance. Although the pandemic seemed to have taken the world by surprise, there were indications that this outbreak will happen but remained a question of when and by how much relative to impact.

With the situation in Brazil meanwhile, beyond this pandemic, it is a lesson for any other country or political leader whether in Africa or Latin America as the case may be that will be complacent over this crisis. It is an ongoing problem and remains a potential threat to the society, way of life and healthcare system at large.

Most of the inhabitants in Africa and some in Latin America have limited or no accesses to potable water both in urban and rural areas, which will impede compliance relative to frequent hand washing. Additionally, poor sanitation plus the fact that there are in most cases no health centres within the vicinity of the populace will definitely pose a high risk of contagion and treatment. Furthermore, will this pandemic change the mind-set of some corrupt and unaccountable political leaders; this has been the case for decades while using their nations' resources to enhance qualities of lives in affected regions? What lessons can these leaders learn from COVID-19? Which way is to forward for the communities in terms of providing drinking-water quality, sanitation, healthcare, housing, electricity, education and transport network for both present and future generations to come?

Notably, there are millions of people in these regions with underlying health problems having no medical attention for years in their lives due to lack of adequate healthcare services. The health conditions of such individuals will be compounded with COVID-19 and could exacerbate the number of fatalities.

The pandemic has thrown the entire globe off balance including the developed nations. The impact is not only on healthcare along with more than half a million fatalities but is also the economic upheaval never seen before. Many businesses have gone burst and led off so many of their employees, talking less of African and Latin American regions where the hardship on people could even jump the roof. The health, economic and social impacts of COVID-19 could be minimised through appropriate lessons learnt such as running credible governance, provision of essential amenities and implementation of strategic practical measures to circumvent the crisis both today and in the future. Finally, well planned and coordinated logistical arrangements will have to be implemented from now onwards to every nook and corner of these continents to alleviate their inherent poverty and enhance their health-related quality of life.

Globally, the awareness and response to the pandemic are well known, but each country faces its strategies and scenarios in containing it based on resources and degree of preparedness.

Conflict of Interests

Authors declare that there are none.

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Original Article

Clinical Aspects of Vitamin D Deficiency in Multiple Sclerosis

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Abstract

Introduction
Multiple Sclerosis (MS) is a multifactorial, immune-mediated disorder that occurs in genetically predisposed people. Vitamin D might be an important environmental factor in the development and prevention of MS disease. We aimed to investigate the role of vitamin D in MS disease activity.

Material and Methods
The study was designed as a prospective study. Thirty-two patients and 15 healthy subjects were included. Variables were MS disease duration, number of relapses, Expanded Disability Status Scale (EDSS) scores, serum vitamin D levels, assessments through neuropsychological tests relevant to depression, cognition, anxiety and fatigue.

Results
The mean age of the subjects was 32.6±6.9 years. A significant positive correlation was found between the vitamin D level during relapse and remission. A statistically significant difference was found between the patients in relapse and controls in serum vitamin D levels (p=0.002). A statistically significant difference was found between the patients in relapse and patients in remission, in serum vitamin D concentrations (p<0.001). Statistically significant differences were found between the patients in relapse and controls in Mini-Mental State Test, Beck Depression Inventory, Benedict's Cognition Test, Fatigue Severity Scale, Paced Auditory Serial Addition Test, State-Trait Anxiety Inventory scores (p=0.01, p<0.001, p=0.01, p<0.001, p=0.007, p<0.001 and p<0.001, respectively).

Conclusions
Vitamin D in association with other therapies may prevent the progression of MS-related disabilities and the relapses in Relapsing-Remitting Multiple Sclerosis. Vitamin D levels may have effects on the symptoms (depression, anxiety, cognitive deterioration and fatigue) which are frequently seen in the course of MS.

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Introduction

Multiple Sclerosis (MS) is a multifactorial, immune-mediated disorder that occurs in genetically predisposed people. Although the reasons underlying the wide variations in its prevalence and incidence around the world have not been fully understood yet, certain genetic or environmental assumptions have been made. Data from recent observational studies have indicated that vitamin D3 [25(OH)D], synthesized upon the exposure to sunlight or ingested from diet, might be an important environmental factor in developing MS and preventing MS.[1-3] A reduced exposure to sunlight directly correlates with low serum 25(OH)D levels. Low serum 25(OH)D levels have been demonstrated to be a risk factor for developing MS and serum 25(OH)D levels have been demonstrated to be further decreased during relapses, in comparison to the levels measured during remissions.[1,2] These data suggest that vitamin D may have a possible role in autoimmune mechanisms.[4] Previous studies revealed an association between low serum 25(OH)D levels and high Expanded Disability Status Scale (EDSS) scores.[1,3,5] In patients with Relapsing Remitting Multiple Sclerosis (RRMS), the 25(OH) D levels have been found to be even lower during relapses than those in the remission periods.[1,2] Recent studies have revealed the associations between sunlight exposure, disability and 25(OH) D levels and shown that supplemental 25(OH) D given in adequate amounts have led to the proliferation of anti-inflammatory cytokines in the blood of MS patients.[1,2]

Data from recent observational studies have indicated that 25(OH)D, synthesized upon the exposure to sunlight or ingested from diet, might be an important environmental factor in developing MS and preventing MS.[1-3] Recent studies have focused on traditional parameters such as relapse activity, disability progression, and Magnetic Resonance Imaging (MRI) parameters, but should also be cautious in other MS symptoms that may be associated with low vitamin D levels, such as depressive symptoms and cognitive impairment.[6]

The aim of this study is to evaluate the serum vitamin D levels in relapse and remission periods of MS patients, and investigate the correlations with disease severity, number of relapses, disease duration, fatigue, and neuropsychological tests.

Material and Methods

The study was designed as a prospective study and 32 patients diagnosed with RRMS according to the McDonald diagnostic criteria[7], who were on the follow-up in the outpatient clinic of MS, the Department of Neurology, aged between 20 and 50 years, have not concurrent neurological disorder, graduated from primary school at least, absence of a metabolic disorder that might affect cognitive performance were included to the study. None of the patients had received vitamin D therapy 3 months before the study held, due to any reason. The control group consisted of 15 healthy individuals. Written informed consent was taken from all participants.

Patients were prospectively re-assessed 2 months after relapse, during remission periods. None of the patients leave the study during the follow up period. All of the patients were treated with steroids during the relapse period. All of the subjects in the patient and control groups received an adequate diet and exposed to the sunlight for at least 1 or 2 hours daily. None of the subjects had received vitamin D therapy by then.

Main demographic characteristics for both patient and control groups included age, gender and educational attainment. Disease associated variables were MS disease duration, number of relapses, EDSS scores, serum Vitamin D levels, assessments through neuropsychological tests relevant to depression, cognition, anxiety and fatigue.

Considering their potential impact on cognition, subjects' vitamin B12 and folic acid levels were determined. Subjects included in the study, in the event that their vitamin B12 and folic levels were within normal limits.

The tests relevant to depression, cognition, anxiety, and fatigue were administered twice to the subjects in the patient group and once to the subjects in the control group, by an expert psychologist during one-hour sessions. Patients were administered Fatigue Severity Scale (FSS), Paced Auditory Serial Addition Test (PASAT), Beck Depression Inventory (BDI), State-Trait Anxiety Inventory (STAI Form TX-1-2), Mini Mental State Examination (MMSE), Benedict's Cognitive Dysfunction test in MS.[8-15]

Regarding the metabolism of vitamin D, tests

including 25(OH)D, parathyroid hormone (PTH), thyroid stimulating hormone (TSH), calcium (Ca^{+2}), phosphorus (P), magnesium (Mg^{+2}), chlorine (Cl^{-1}), alkaline phosphatase (ALP) and creatinine were performed twice in the patient group, in the serum samples of each patient obtained during remission and relapse periods, while controls underwent testing once. Based on the kit, calibration of the measuring device, and laboratory standards used in our study, the refence range for serum 25(OH)D was determined as 11 to 43 ng/dL and values less than 11 ng/dL indicated vitamin D deficiency.

Statistical Analysis

According to the distribution of the data, the independent samples t-test or Mann-Whitney U test were used in the comparisons between two independent groups. The Wilcoxon test was used to compare two dependent groups. The Pearson's chi-square test was used to compare categorical variables. Correlations between the variables were analyzed using the Spearman's correlation analysis. Descriptive statistics included mean±standard deviation or median (minimum-maximum). A p value less than 0.05 was considered as statistically significant. An SPSS 13 statistical software package was used for statistical analyses.

Results

The mean age of the subjects was 32.634±6.89 years. Age and gender distribution of MS patients and control group were similar (31.84±7.10 vs. 34.33±6.32 years, female to male ratio: 26/6 vs. 13/2, respectively, p=0.253). Education level ratios of MS patients and control groups were not significantly different (elementary 46.9% vs. 40%, high school 28.1% vs. 13.3% and university education 25% vs. 46.6%, respectively, p=0.278).

The EDSS scores of the patients in the relapse period were higher than those in the remission period (3.5 [1.5-5] vs. 2 [0-3.5], p<0.001). Serum vitamin D levels of MS patients were significantly lower in relapse period compared with remission periods. A significant positive correlation was found between the number of relapses and the EDSS scores during relapse and remission. A negative correlation was found between the number of relapses and serum vitamin D levels in patients during the relapse and remission periods, although this correlation did not reach a statistically significant level (*Table 1*).

There was no statistically significant relationship between MS disease duration with EDSS scores and vitamin D levels in relapse and remission periods. A significant difference was observed in serum vitamin D concentrations between the patients in relapse and controls (p=0.002). No statistically significant difference was found in serum PTH concentrations (p=0.405). No statistically significant difference was found in serum vitamin D concentrations between the patients in remission and controls. However, the p value was close to the significance level (p=0.058). No statistically significant difference was found in serum PTH (p=0.690). A statistically significant difference was found in serum vitamin D

Table 1. The association between the vitamin D levels of patients during relapse and remission periods, EDSS scores and number of relapses

	VIT-D (relapse)	VIT-D (remission)	EDSS (relapse)	EDSS (remission)
VIT-D (relapse)	-	p<0.001 r=0.764	p=0.875	-
VIT-D (remission)	p<0.001 r=0.764	-	-	P=0.866
Number of relapses	p=0.491	p=0.287	**p=0.028** **r=0.389**	**p=0.016** **r=0.422**

VIT-D: vitamin D, VIT-D (relapse): serum 25(OH)D levels in patients during relapse, VIT-D (remission): serum 25(OH)D levels in patients during remission, EDSS (relapse): EDSS scores during relapse, EDSS (remission): EDSS scores during remission.

Table 2. Parathyroid hormone and vitamin D levels according to groups

	All subjects (n=47)	MS Patients in Relapse (n=32)	MS Patients in Remission (n=32)	Controls (n=15)
PTH	27(9.6-63.5)	25.3(9.6-63.5)	28.5(15.5-65.4)	33.4(11.1-53.4)
VIT-D	9.9(4-40)	8.9(4-29)	10.8(5-30)	16.2(6-40)

PTH: parathyroid hormone, VIT-D: vitamin D.

concentrations between the patients in relapse and patients in remission (p<0.001). No statistically significant difference was found in serum PTH concentrations (p=0.161) (*Table 2*).

Statistically significant differences were found between the patients in relapse and controls in MMSE, BDI, Benedict's Cognition Test, FSS, PASAT, State-Trait Anxiety Inventory scores (p=0.01, p<0.001, p=0.01, p<0.001, p=0.007, p<0.001 and p<0.001, respectively). There was no significant difference in MMSE scores between the patients in remission and controls, but the p value was close to the significance level (p=0.055). Significant differences were found in BDI, Benedict's Cognition Test, FSS, PASAT, State-Trait Anxiety Inventory scores between the patients in remission and controls (p=0.022, p=0.002, p=0.01, p=0.018, p=0.001 and p=0.001, respectively). A statistically significant difference was found in MMSE scores between the patients in relapse and patients in remission (p=0.016). Although differences were found in other neuropsychological tests between the patients in relapse and patients in remission, these differences did not reach a statistically significant level (p=0.377, p=0.482, p=0.428, p=0.082, p=0.238 and p=0.708, respectively) (*Table 3*).

The number of relapses correlated positively with PASAT scores. There were no statistically significant relationships between serum vitamin D levels and neuropsychological test scores of the patients in relapse or remission periods (*Table 4*). However, when serum vitamin D concentrations increased, BDI, Benedict, FSS and state-trait anxiety scale scores decreased while MMSE and PASAT scores increased.

Discussion

In our study we found that serum vitamin D levels of MS patients were significantly lower in relapse period compared with remission periods. A statistically significant difference was observed in serum vitamin D concentrations of the patients in relapse and controls and also between the patients in relapse and patients in remission.

One of the most frequently investigated and discussed functions of vitamin D is its effects on autoimmune diseases and particularly on the pathogenesis of MS. Unlike other vitamins, vitamin D can be synthesized in the body, and actually, it has been accepted as a hormone. The discovery of the vitamin D receptors (VDR) in numerous tissues demonstrated that vitamin D had many functions other than calcium homeostasis and bone metabolism.[16,17]

Table 3. Neuropsychological test results according to groups

	All subjects (n=47)	MS patients in relapse (n=32)	MS patients in remission (n=32)	Controls (n=15)
MMSE	28(19-30)	26.5(19-30)	27(19-30)	29(24-30)
BDI	11(0-33)	12.5(2-33)	11.5(0-41)	3(0-16)
Benedict	11(0-49)	15(0-52)	13(0-49)	0(0-24)
FSS	29(9-63)	40(13-63)	35(9-63)	17(9-63)
PASAT	44(13-60)	39.5(13-57)	43(5-59)	53(18-60)
State anxiety	41(20-70)	44(25-70)	42(20-62)	31(20-48)
Trait anxiety	44(22-67)	49(28-67)	46(24-72)	31(22-58)

MMSE: Mini Mental State Examination, BDI: Beck Depression Inventory, Benedict: Benedict's Cognitive Dysfunction test, FSS: Fatigue Severity Scale, PASAT: Paced Auditory Serial Addition Test.

Table 4. The comparisons of serum vitamin D levels, EDSS scores and neuropsychological test results of the patients in relapse and remission periods

	VIT-D (relapse)	VIT-D (remission)	Number of relapses	EDSS (relapse)	EDSS (remission)
MMSE	p=0.883	p=0.797	p=0.188	p=0.193	p=0.548
BDI	p=0.974	p=0.896	p=0.533	p=0.193	p=0.123
Benedict	p=0.257	p=0.351	p=0.191	**p=0.014**	p=0.590
FSS	p=0.508	p=0.716	p=0.318	p=0.639	p=0.066
PASAT	p=0.323	p=0.480	**p=0.015**	p=0.084	p=0.236
State Anxiety	p=0.576	p=0.560	p=0.363	p=0.440	**p=0.011**
Trait Anxiety	p=0.509	p=0.562	p=0.772	p=0.702	p=0.100

VIT-D: vitamin D, MMSE: Mini Mental State Examination, BDI: Beck Depression Inventory, Benedict: Benedict's Cognitive Dysfunction test, FSS: Fatigue Severity Scale, PASAT: Paced Auditory Serial Addition Test.

Normal serum 25(OH)D concentrations vary in a range 8 to 80 ng/mL (20-200 nmol/L). In a number of studies on serum 25(OH)D concentrations, values ranged between 0 and 20 nmol/L have been considered as severe hypovitaminosis, values ranged between 20 and 37 nmol/L have been considered as mild hypovitaminosis, while a value of 37 nmol/L has been accepted as adequate.[2,4,18] Based on the kit, calibration of the measuring device, and laboratory standards used in our study, the refence range for serum 25(OHD was determined as 11 to 43 ng/dL and values less than 11 ng/dL indicated vitamin D deficiency. In this study all of the subjects in the patient and control groups received an adequate diet. All subjects adequately exposed to the sunlight (at least 1 or 2 hours daily). None of the subjects had received vitamin D therapy.

In a study conducted in a large MS population consisting of 267 patients, an inverse correlation was found between the serum 25(OH)D concentrations and EDSS scores, while a similar correlation was not found between serum 1,25-dihydroxyvitamin D3 [1,25$(OH)_2$D] concentrations and EDSS scores. Furthermore, no difference was observed between the relapse and remission periods in serum 1,25$(OH)_2$D concentrations. This study was the first study evaluating both 1,25$(OH)_2$D and 25(OH)D concentrations in a large MS population. Results from subsequent studies have also supported these data.[1,19] Thus, in studies on this issue, serum 25(OH)D concentrations have always been the criterion to assess the effects of vitamin D. On the basis these data, we evaluated serum 25(OH)D levels and we exclude serum 1,25$(OH)_2$D levels.

Recent studies have emphasized the presence of a direct association between vitamin D and MS-related disability. These studies revealed a statistically significant negative correlation between EDSS scores and serum 25(OH)D levels in patients with MS.[11,20] Certain related studies demonstrated that the inverse correlation between serum vitamin D levels and EDSS scores was stronger in Primary Progressive Multiple Sclerosis (PPMS) and Secondary Progressive Multiple Sclerosis (SPMS) patients in comparison to Progressive Relapsing Multiple Sclerosis (PRMS) patients.[1] In line with the literature, a graphically displayable inverse correlation was observed between the serum 25(OH)D levels and EDSS scores, although it did not reach a statistically significant level.

A positive correlation was found between the number of relapses and EDSS. However, unlike previous data in the literature, in our study no statistically significant correlation was found between the number of relapses and serum 25(OH) D levels during the relapse and remission periods.

Recent studies have demonstrated an association between the relapse activity and serum 25(OH) D concentrations. In RRMS populations, serum 25(OH)D concentrations were found to be lower in relapse periods in comparison to the remission periods and higher relapse rates were associated with lower serum 25(OH)D levels.[2,4] In a study in patients who had been diagnosed with RRMS more than 5 years ago, serum 25(OH)D levels were found to be considerably lower in patients who had experienced 1 or more relapse during the last

2 years in comparison to the patients who had not experienced any relapse.[1] A large, longitudinal and prospective study in RRMS patients demonstrated that every reduction of 10 nmol/L in serum concentration levels was associated with 9 to 12% reduction in the risk of relapse.[21] In our study, the serum 25(OH)D levels in RRMS patients during remissions were found to be lower than those of control group and the difference was found to be close to the significance level. This difference was more prominent during the relapse periods. The comparisons between serum 25(OH)D levels during the relapse periods and those of controls, revealed a statistically significant difference. Similarly, a statistically significant difference was found between the serum 25(OH)D levels during the relapse and remission periods.

There are studies indicating that an adequate dose of supplemental vitamin D administered concurrently with other therapies, may reduce the disabling progression of MS and may prevent relapses.[22-26]

In line with the literature, no statistically significant differences were found in serum PTH, TSH, ALP, creatinine, Cl^{-1}, Ca^{+2}, Mg^{+2} and phosphorus levels between the patients in relapse and patients in remission, between the patients in relapse and controls and between the patients in remission and controls.[2, 27]

Vitamin D deficiency has been linked to an increased incidence of autoimmune diseases, including thyroiditis, asthma, psoriasis, type 2 diabetes, rheumatoid arthritis and type 1 diabetes and MS in particular.[28-30] Preventive effect of vitamin D on the activation of MS is an immune-mediated effect. 25(OH)D is a potent immune modulator, inhibits pro-inflammatory cells and cytokines and supports anti-inflammatory cells and cytokines. 25(OH)D receptors are found to be widely distributed in immune cells. 25(OH)D is known to play a role in the anti-inflammatory immune response and in the regulation of T-cell functions.[3,31,32] Although any quantitative analysis on the immune-modulator role of vitamin D was not carried out in our study, the presence of a concurrent autoimmune disease (including thyroiditis, asthma and diabetes) in 21.8% of our MS patients suggests the above autoimmune mechanisms.

In numerous studies common depressive symptoms and cognitive deterioration in MS patients have been linked to 25(OH)D deficiency and it has been emphasized that the inclusion of this parameter in the future studies might ensure the integrity of the knowledge.[4] A study held in our country demonstrated that neurodegeneration associated with vitamin D receptor (VDR) gene polymorphism and low serum 25(OH)D levels, might led to the Alzheimer disease and cognitive deterioration.[33] In another study, low serum 25(OH)D levels were suggested to cause cognitive dysfunction and it was emphasized that vitamin D might be a neuroprotective agent and its deficiency might be diagnostic mediator in dementia.[34] During the last decade, studies on the effects of vitamin D on brain functions revealed that vitamin D was a neuroactive steroid affecting brain development and modulation of brain functions and its deficiency might be associated with a number of neuropsychiatric disorders including schizophrenia, Parkinson, Alzheimer, depression, muscle weakness and cognitive deterioration. It was emphasized that vitamin D deficiency was associated with poor performance in neurocognitive testing.[35,36]

Strong associations were demonstrated between low serum vitamin D levels and depression or anxiety or depressive symptoms such as sleep disorders and vitamin D supplements added to antidepressant therapy were found to increase treatment success.[37-44]

Certain studies pointed out that vitamin D deficiency might cause chronic fatigue that that showed a significant improvement after vitamin D supplementation.[45-47] Another study investigated the associations between serum vitamin D levels in MS patients and fatigue and depressive symptoms and a statistically significant positive correlation between the low serum 25(OH)D levels and depressive symptoms, while no statistically significant correlation was found between the serum 25(OH)D levels and fatigue.[48]

In our study, certain neuropsychological tests were administered to the patients during attacks and remission periods and the controls, to investigate the effects of vitamin D on cognition, depression, fatigue and anxiety. There was statistically a significant differences in neuropsychological test scores between the control group and MS patients both in relapse and remission, while no statistically significant differences were found between the patients in relapse and patients in remission. No

statistically significant correlations were found between the neuropsychological test scores and serum 25(OH)D concentrations in relapse and remission. However, as the serum 25(OH)D concentration increased, Beck, Benedict, and fatigue and anxiety scales scores reduced and the increases in the MMSE and PASAT scores were shown graphically. In conclusion, low serum 25(OH)D levels in MS patients were found to have negative impacts on cognition depression, fatigue and anxiety scale scores and these impacts were more prominent during relapses, when significant reductions occurred in the serum 25(OH)D levels. The failure to attain a statistically significant level was considered to be related to the small sample size and the study population consisting of the patients with RRMS, a less disabling form compared to the progressive forms of MS.

According to the promising data from these studies, vitamin D in association with other therapies may prevent the progression of MS-related disabilities and the relapses in RRMS. Vitamin D levels may have effects on the symptoms (depression, anxiety, cognitive deterioration and fatigue) which are frequently seen in the course of MS.

Conflict of interest

The authors declared that there are no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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Original Article

Early Experience of Kidney Transplantation in a New Center

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Abstract

Introduction
Kidney transplantation is one of the most important treatments in end stage renal disease (ESRD). We aimed to share our experiences in 60 (57 deceased donors, 3 living donors) kidney transplantation cases performed in our center between July 2017 and August 2020.
Material and Methods
The demographic data of 60 patients with kidney transplantation performed in our kidney transplant center were evaluated in terms of causes and duration of renal failure human leucocyte antigen (HLA) tissue compatibility, immunosuppressive protocol used, antimicrobial agents, rejection status, graft loss, patient loss, postoperative surgical complications.
Results
Fifty-seven of our kidney transplants were made from deceased donors and 3 from living donors. The mean age of the patients was 44.66 (23-68) years. Kidney transplantation was performed in 8 patients (13.33%) in the preemptive period. The mean number of mismatches in kidney transplants was 3.95 (2-5) and the mean duration of renal replacement therapy (RRT) was 54.73 (0-270) months. While the mean follow-up period after transplantation was 18.86 (2-37) months, it was observed that the mean cold ischemia time was 742.8 (60-1080) minutes. Serum creatinine levels of 56 patients with functional grafts at the end of the first month 1.39 (0.5-4.9) mg/dL, 54 patients at the end of the sixth month, creatinine levels 1.29 (0.56-5.9) mg/dL, The creatinine levels of the 52 patients as of October 2020 were 1.37 (0.75-5.16) mg/dL. As surgical complications, hematoma developed in 5 patients (8.33%) and lymphocele in 3 patients (5%). Early graft loss developed in one patient with renal artery embolism and two patients with renal vein thrombosis, while chronic rejection developed in two patients. We performed a deceased kidney transplant again 14 months later in a patient who developed graft loss in the early period due to renal vein thrombosis. The kidney inserted later is functional in the 10th postoperative month. One of our patients died due to rhino-orbital mucor mycosis in the postoperative 2nd month, and one patient due to the development of sepsis due to infection in the hip prosthesis in the postoperative 6th month, while another patient died due to myocardial infarction in the postoperative 2nd month.
Conclusions
As a result, our kidney transplant center is in development. Our results obtained from 60 kidney transplants, almost all of which were performed from deceased donors, seem to be compatible with the literature. More detailed results can be obtained with the long-term follow-up results and the increase in the number of living donor transplants.

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Introduction

Organ transplantation is a life-saving treatment option for patients with end-stage renal disease (ESRD). Compared to the number of patients waiting for transplantation, the insufficient number of donors is the most important limiting factor of transplantation.[1,2] Organ transplantation is a condition provided by the transplantation of organs taken from living donors or deceased donors to the recipient after brain death.[3-5]

There has been a significant increase in the number and success rate of kidney transplants with the development of drugs that prevent/treat rejection and effective antimicrobial therapy. Due to these developments, there has been a decrease in the incidence of acute rejection and a remarkable increase in graft survival rates. For these reasons, kidney transplantation has become the preferred renal replacement therapy (RRT) in the treatment of ESRD, as it both prolongs the survival and increases the quality of life.[6]

The first successful kidney transplant in the world was performed in 1954. In our country, Haberal et al. performed the first successful living donor and the first deceased donor kidney transplant in1975 and 1978, respectively.[4,7]

The number of kidney transplants performed in our country has been increasing in recent years. According to the Ministry of Health data, a total of 3,861 kidney transplants were performed from 3,054 deceased donors and 807 living donors in 2019.[8] In our country, when compared to the number of patients receiving RRT due to ESRD, it is observed that the number of transplants is far below the desired.

The sharing of the first experiences of the newly established transplant centers may be beneficial in terms of raising the awareness of the physicians who will work in the new centers about the risks and possible situations related to the transplants, as well as determining the issues that will be taken into consideration by the bodies authorized to establish the center.

Kidney transplantation has become the preferred treatment option in the treatment of ESRD due to both survival advantage and high quality of life, along with developments in immunology, and the use of new immunosuppressive and antimicrobial drugs.[9,10]

Compared to dialysis, successful kidney transplantation is superior in terms of both life expectancy and quality of life.[11-13] In this study, it is aimed to share our experience with 60 kidney transplantation performed in the kidney transplant center of the University of Health Sciences, Bursa Yüksek Ihtisas Training and Research Hospital (established in July 2017), in the light of the literature.

Material and Methods

Sixty kidney transplant cases (57 from deceased donors, 3 from living donors) performed in our transplant center between July 2017 and August 2020 were evaluated retrospectively, after the local ethical committee approval (2011-KAEK-25 2019/02-05). Organs were taken from deceased donors that emerged in hospitals in 5 provinces affiliated to Bursa regional coordination unit, whose brain death was declared, and organ donations were made. The selection of all kidney transplant recipients was made by the delegation formed by the regional coordination unit under the national coordination unit in line with the organ sharing criteria.

Organ extraction from donors was done by the same team. After the potential recipients were informed about the risks of the surgery by the transplant team, their consent was obtained. Demographic data, immunosuppressive protocol, rejection status, graft or patient loss, intraoperative or postoperative surgical complications and infection status were evaluated.

Transplant surgeries were performed by the same team. Left kidneys taken from the donor were placed in the right iliac fossa, and the right kidneys were placed in the left iliac fossa. An end-to-side anastomosis was made from the renal artery to external iliac or common iliac artery, and the renal vein to the external iliac vein. Ureteroneocystostomy was performed using extravesical technique (Lich-Gregoir). A 12 cm 4.8 F double J ureter catheter was used in all cases.

Deceased donors were considered to be at high immunological risk, and polyclonal-antithymocyte globulin (ATG) were given to the recipients in a total of 9 mg/kg (peroperative 3 mg/kg/day for induction and 1.5 mg/kg/day on the following days). In maintenance treatment, triple immunosuppressive therapy consisting of prednisone (500 mg peroperative, 20 mg/day

postoperative 6th day, 5 mg/day postoperative 6th month), tacrolimus (TAC) [(0.15 mg/kg), target serum level 8-10 ng/mL for the first 3 months, then 5-7 ng/mL) and mycophenolate mofetil (MMF) (2 g/day) was preferred. In living donor transplants, those with low risk were given 1.5-2.5 mg ATG for 3 days and continued with TAC + MMF treatment. High risk patients were given ATG at the same dose for 5 days and continued with TAC + MMF treatment.

All patients received trimethoprim/sulfamethoxazole and oral nystatin for nine months and valganciclovir for three months for infection prophylaxis.

Results

The demographic characteristics of the recipients and diseases causing ESRD are given in Table 1. While the mean age of all patients was 44.66 (23-68 years), 25 (41.66%) of the patients were male and 35 (58.33%) were female. Although the mean duration of RRT was 54.73 (0-270) months, preemptive kidney transplantation was performed in 8 patients (13.33%). The average number of HLA mismatches in kidney transplants performed is 3.95 (2-5).

The average operation time was 225 (160-400) minutes and it was observed that the average duration of our last 10 operations decreased to 195 (160-225) minutes with the increased in experience. The mean follow-up time after transplantation was 18.86 (2-37) months, and the mean cold ischemia time was 742.8 (60-1080) minutes. While the mean serum creatinine levels of the patients with functional grafts in the first and sixth months were 1.39 (0.5-4.9) mg/dL and 1.29 (0.56-5.9) mg/dL, respectively, the mean creatinine levels of 52 patients with functional grafts were 1.37 (0.75-5.16) mg/dL by October 2020.

As a standard protocol, a 12 cm 4.8 F double J catheter was placed in each recipient and removed on an average of 30 days. As surgical complications, hematoma developed in five patients (8.33%), and lymphocele developed in three patients (5%). The hematoma that developed in two patients was evacuated, three wound infections were treated with incision and drainage. One of 3 lymphoceles (10.3%) was treated with percutaneous drainage and two with fenestration. Developing complications are given in Table 2.

One patient with renal artery embolism and two patients with renal vein thrombosis developed graft loss in the early period and chronic rejection was observed in two patients. We performed a deceased kidney transplant again 14 months later in our patient who developed graft loss in the early period due to renal vein thrombosis. After the

Table 1. Demographic characteristics of the recipients (n=60)

Variables	Values
Gender (males/females)	25/35
Age (years)	44.66(23-68)
RRT duration (month)	54.73(0-270)
HLA mismatch (number)	3.95(2-5)
Preemptive (n, %)	8(%13.33)
Follow-up duration (month)	18.86(2-37)
Cold ischemia duration (minutes)	742.8(60-1080)
Primary diseases	
Hypertension	23(38.33)
Diabetes Mellitus	9(15)
Polycystic kidney disease	7(11.66)
Urolithiasis	6(10)
Vesicoureteral reflux	4(6.66)
Glomerulonephritis	1(3.44)
Amyloidosis	1(1.66)
Oxalosis	1(1.66)
Systemic lupus erythematosus	1(1.66)
Sjogren syndrome	1(1.66)
Unknown	6(10)

Values are given as n (%) or mean (min-max). RRT: renal replacement therapy, HLA: human leucocyte antigen.

Table 2. Developed complications and their treatment in recipients

Complication	n (%)	Treatment
Lymphocele	3(5)	Percutaneous drainage (n=1) Fenestration (n=2)
Arterial embolus	1(1.66)	Graft nephrectomy
Hematoma	5(8.33)	Evacuation
Wound Infection	3(5)	Incision-drainage
Venous thrombosis	2(3.33)	Graft nephrectomy

second transplant, the blood creatinine level was 1.1 mg/dL in the 10th postoperative month.

A total of three recipient died after kidney transplantation. One of our patients died as a result of rhino-orbital mucormycosis in the postoperative 2nd month, a patient died of the development of sepsis from the hip prosthesis infection in the postoperative 6th month, and a patient died after myocardial infarction in the postoperative 2nd month. Kidney functions were normal in all three cases.

Discussion

The most important problem in front of organ transplantation is the inability to provide enough organ donors. In our country, as of 2020, 21,686 people are waiting in line for deceased kidney transplantation.[8] According to the Ministry of Health data, 21% of kidney transplants in our country in 2019 were performed from deceaseds.[8] While 95% of our transplants have been carried out from deceased donors since the opening of our center, in March 2019, the first living donor kidney transplant was successfully performed in our center. Until today, we have performed kidney transplantation with living donors for 3 people with the experience we have gained in transplantations with deceased donors. In living donor transplants, patients were discharged after an average of 6 days because of functioning kidney in the early postoperative period. Donors were discharged on the 4th postoperative day.

Yakupoglu et al.[7] evaluated 79 patients, 64 from living donors and 15 from deceased donors, in their study, and reported the mean serum creatinine of 76 patients with functional grafts as 1.24 mg/dL at the end of the first month. Reported lymphocele in 4 patients, venous thrombosis in 2 patients, arterial thrombosis in 2 patients, urinary leakage in 1 patient, hematoma in 2 patients, and wound infection in 6 patients. Ay et al.[14] evaluated 115 kidney transplant patients, 103 from living donors and 12 from deceased donors, and evaluated one-year graft and patient survival rates as 98.3% and 100%, respectively. Researchers also reported graft loss in 4 cases, ureteral stenosis in 1 case, and lymphocele in 5 cases. Krajewski et al.[15] evaluated postoperative urological complications in their study of 460 cases, ureteral stenosis, lymphocele, nephroureterolithiasis and urethral stenosis were detected in 38 (8.2%), 10 (2%), 5 (1%), and 5 (1%) cases, respectively. In our study, 3 patients (10.3%) developed lymphocele, one patient was treated with percutaneous drainage and the other two patients with fenestration. The hematoma that developed in five patients was drained, and three wound infections were treated with incision and drainage. The complication rates in the current study are slightly higher than the literature, which can be explained by the low rate of living donors (95% [n = 57] of our transplants were made from deceased donors).

Kidney transplants performed in the preemptive period (before dialysis treatment begins) have positive effects on both patient and graft survival and cost compared to kidney transplants performed after dialysis treatment begins. Especially, living donor kidney transplants are recommended to be performed in preemptive patients.[16] In our center, 13.33% of kidney transplants have been done to patients in preemptive period. Increasing this rate will increase our success rates.

As a result, the number of organ transplant centers is increasing day by day in our country. Most of these centers work under general surgery clinics. In fewer centers, kidney transplants are performed by urologists. It is important that urologists, who successfully perform all kidney and bladder-related surgeries, be more active in kidney transplant surgeries. The interest of more urologists in this field can be increased

by establishing transplantation training units as a sub-branch of urology in universities. The statistics of about 3 years in our relatively newly established center will become more meaningful with increased living donor transplants and longer follow-up.

Conflict of interest

The authors declared that there are no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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Ultrafiltration Through Peritoneal Dialysis in Refractory Congestive Heart Failure Patients: One Center Experience

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Abstract

Background

Hypervolemia is an important consequence of heart failure (HF) that leads poor quality of life and frequent hospitalizations. Ultrafiltration (UF) with dialysis is an option for HF patients who are resistant or inappropriate for diuretics. Peritoneal dialysis (PD) can be a long-term efficient solution for hypervolemia in appropriate HF patients.

Material and Methods

We retrospectively evaluated PD patients in our center in order to determine the ones whose indication was UF for volume control because of HF between January 2015 and January 2020.

Results

4 (2 females, 68.75±4.27 years old) HF patients who had poor volume control on diuretic based regimen were on PD for UF. PD treatment was planned as a daily single exchange with icodextrin in whom all had preserved renal function. In one patient one daily exchange with an amino acid-based PD solution was added. Exchange volume was between 1000 and 1500 mL, dwell time was 9 to 14 hours and UF was 200 to 1100 mL. During the follow-up patients lost adequate weight and none of them were hospitalized because of hypervolemia.

Conclusions

UF through PD in HF patients provides effective volume control, relief of symptoms and avoids frequent hospitalizations. A single daily exchange with icodextrin can be adequate for hypervolemic, well selected HF patients.

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Introduction

Heart failure (HF) is a clinical syndrome characterized by typical symptoms that may be accompanied by signs caused by a structural and/or functional cardiac abnormality, resulting in a reduced cardiac output and/or elevated intracardiac pressures at rest or during stress.[1] Hypervolemia is an important consequence of HF that leads poor quality of life and frequent hospitalizations. Furthermore, infection, electrolyte imbalances, and deterioration in renal function usually accompany frequent hospitalizations which are associated with morbidity and mortality risk. Salt restriction and diuretics are major components of lifestyle changings and diuretic based medical therapy for hypervolemia, respectively. In addition, ultrafiltration (UF) with dialysis is an option for HF patients who are resistant or inappropriate for diuretics. Additionally, there is a bidirectional association between renal and cardiac functions which is defined as cardiorenal syndrome. Due to this relationship, dialysis may be required in some cases beyond UF.[2]

In the cardiology guidelines, UF is recommended to be considered only for patients with refractory congestion, who failed to respond to diuretic based medical therapies.[1,3] On the other hand, in practice UF is performed more frequently for hypervolemia in congestive HF patients. UF procedure is the removal of the water and small to medium weight solutes across a semipermeable membrane with hemodialysis (HD) and peritoneal dialysis (PD). UF has several advantages in the HF patients of allowing reuse of an angiotensin converting enzyme inhibitors (ACEI) or angiotensin receptor blockers (ARB) or aldosterone antagonist which are associated with improved survival. Secondly, reducing diuretic doses prevents renal dysfunction and electrolyte imbalances. Nevertheless, compared with diuretic based treatment survival advantage of UF procedures are controversial.[2]

PD has been used for UF in the HF patients almost for 60 years.[4] UF through PD has some superiority compared with HD which are decreasing frequency of hospitalization, improvement in quality of life, decreasing in diuretic dose, comfort of home therapy, preserving residual renal function and hemodynamic stabilization. In all, the most important is slow removal of excess water which avoids hypotension in HF patients who are mostly vulnerable to unstable hemodynamics.[2] With these regards' PD seems to be a promising option for patients who are resistant to medical treatments and/or require frequent hospitalization

We aimed to present our experience of PD for UF ın patients with HF who requires frequent hospitalization for volume control.

Material and Methods

We retrospectively evaluated PD patients in our center in order to determine the ones whose indication was UF for volume control because of HF between January 2015 and January 2020. The data was obtained from electronic files. Demographic and laboratory data, hospitalizations for volume control, medical complications, and medications were recorded. At our center PD is considered for UF in diuretic resistant, frequently hospitalized (more than 4 in a year), accompanying renal dysfunction, and hypervolemic HF patients.

Statistical Analysis

Statistical analyses were performed with SPSS software (SPSS: An IBM Company, version 23.0, IBM Corporation, Armonk, NY, USA). The numerical and categorical variables were expressed as the mean ± standard deviation and ratios, respectively.

Results

76 PD patients (50% female, 53.43±15.54 years old) were retrospectively evaluated. PD modality was continuous ambulatory peritoneal dialysis (CAPD) in 36 (47.4%), automated peritoneal dialysis (APD) in 36 (47.4%) patients. In 4 (68.75±4.27 years old) patients who were diagnosed HF, PD was initiated for UF. Main reason of PD initiation was poor volume control and frequent hospitalization. 2 of 4 HF patients were female. All of 4 had poor volume control on diuretic based regimen with physical examination of tense ascites, pretibial pitting edema, and pulmonary rales. Laboratory findings revealed mean

urea of 101±42.43 mg/dL, serum creatinine of 2±0.47 mg/dL, eGFR of 36.75±13.84 mL/min, serum sodium (Na) of 133±5.2 mmol/L, serum albumin of 3.4±0.3 g/dL and hemoglobin of 10.47±1.33 g/dL. All HF patients had diuresis with a mean daily volume of 1100 mL under furosemide. A PD catheter was implanted by interventional radiologist under local anesthesia for all. PD treatment was planned as a daily single exchange with icodextrin in whom all had preserved renal function. In one patient one daily exchange with an amino acid-based peritoneal dialysis solution was added because of low serum albumin levels due to malnutrition. Exchange volume was between 1000 and 1500 mL, dwell time was 9 to 14 hours and UF was 200 to 1100 mL. During the follow-up, patients lost adequate weight and none of them were hospitalized because of hypervolemia. Peritonitis was occurred in 2 of 4 patients. 1 patient died because of sepsis due to uncontrolled peritonitis though peritoneal catheter was removed. It was learned that he went to toilet while PD exchange, and *Candida albicans* and *Acinetobacter baumannii* were isolated in the dialysate solution. A female one had poor family support for that reason they failed to perform proper PD program. Consequently, she passed away after 10 months of PD initiation due to cardiovascular reasons. 1 patient died after the mitral valve surgery because of cardiac reasons at the 8th month of PD treatment.

The 4th one is still on the PD program for 16 months who is free of peritonitis, ascites and pretibial edema. He did not require hospitalizing through this interval. His PD schedule is consisting of a 12-hour 1500 mL icodextrin and an 8-hour 1500 mL amino acid-based solution exchanges on alternate days with 900 mL and 100 mL daily UF, respectively.

Discussion

Traditionally HF treatment has 2 components of lifestyle changes and medical treatment. The lifestyle changings are salt and fluid restriction, smoking cessation and weight control. The medical treatments are consisting diuretics, ACEI or ARB, vasodilators and beta blockers. In additionally some advanced cases require more aggressive approaches such as cardiac devices, pacemakers, and mechanical circulatory support. The association between cardiac and renal functions may lead to obstacles for using ACEI/ARB, and/or diuretics. Furthermore, unresponsiveness to diuretics or inadequate dosage due to adverse outcomes of diuretics like renal function deterioration, electrolyte imbalance can provoke worsening volume control. For patients with volume overload refractory to diuretics UF can be considered through HD or PD.

In the EUPHORIA study peripheral veno-venous UF was significantly decreased length of hospital stays and readmissions in 20 HF patients with volume overload and diuretic resistance.[5] In the UNLOAD study UF strategy were stated safe and superior to diuretics in respect of volume control and rehospitalization among 200 decompensated HF patients. However, dyspnea scores, renal functions and mortality were similar among the groups.[6] Opposite to these findings in the CARRESS-HF study, UF was found inferior to a stepped pharmacologic-therapy algorithm for the preservation of renal function at 96 hours and associated with a higher rate of adverse events. Also, weight loss was similar with the two approaches.[7]

UF by PD is thought of being more advantageous compared with extracorporeal circuits. Slow removal of fluid by PD provide adequate time for allowing vascular refilling from extravascular spaces thereby avoiding hypotension in hemodynamically instable HF patients. Additionally, PD is performed at home that provides comfort for patients and improves quality of life. PD regimens for UF differ from usual dialysis PD regimens in exchange frequency.[2] Fewer exchanges can provide adequate UF with icodextrin.[8] A single daily icodextrin exchange offers better quality of life, freedom of movement, economic benefit with efficient fluid removal. Moreover, as already known PD preserves residual renal function better than HD.[9]

In our center we initiated PD for UF in 4 HF patients who had volume control problem under diuretic consisting medical treatment and required frequent hospitalizations. During the follow-ups none of the patients were hospitalized because of hypervolemia. Due the purpose of PD initiation all the patients were free of hospitalization. We did not investigate the quality of life by an item but in our outpatient clinic visits the patients and their families stated us the pleasure of being away

from hospitals. The pleasure is also a consequence of staying at home during PD. Compatible with the literature we planned the PD regimen as a single daily exchange with icodextrin. The dwell time was modified according to UF performance of changing between 9 to 14 hours. Because they did not require dialysis this program was adequate for volume control.

Intravenous diuretics provoke sympathetic nervous, renin angiotensin aldosterone, endothelin and vasopressin systems which are associated with mortality.[10] This neurohumoral activation do not occur with PD due to slow volume removal. Furthermore, preservation of residual renal function is an advantage of PD compared with diuretics in HF patients.[11] As we nephrologist know the value of every drop of urine, we effort hard to preserve residual renal function. All our HF patients had already have diuresis and during the efficient fluid removal through PD their urine volume did not decrease.

PD catheter insertion under local anesthesia should be preferred because of general anesthesia risks in HF patients. Immediate initiation also can be possible compared with laparoscopic insertion.[2] We also preferred to insert the PD catheter under local anesthesia. After the interventional radiologist implanted the catheter there were no problem associated with the catheter and we began the exchanges after approximately 3 days after implantation.

Patient selection criteria for PD essential because the success of PD mostly depends on care giver. Mental function, strength, learning skills, and ability of performing PD practice properly are the main factors for success associated with the care giver or the patient. One of our patients had visual problems and peripheral polyneuropathy due to diabetes mellitus and her daughter was educated for PD according to the family decision. But throughout the process the daughter had unwillingness of care of her mother. Even the patient's regular visits were disrupted. As a consequence, the patient died due to cardiac reasons at another center. We suggest that the clinician has to be sure about the willingness, family support, and strength of the patient and/or the caregiver before the PD decision.

Peritonitis is an important complication of PD and in the studies, it is the most reported complication associated with PD in HF patients. The rates ranged from 0.02 to 0.46 episodes which is similar to peritonitis rates among end stage renal disease PD patient.[12] In our center peritonitis rate was 0.5/patient year which is proper according to guidelines. The ISPD guidelines recommended that peritonitis rate should not be more than 0.5/patient year.[13] 2 of our patients has peritonitis episodes and in 1 patient the peritonitis caused catheter removal and death.

Mortality rate among HF patients is high. In the studies with follow-up period ≥1 year the overall mortality was 48.3% in HF patients underwent PD for UF.[12] Different of that argument in some studies that had follow-up time ≤1-year remarkable survival rates of 85% were reported.[13] In a systemic review of PD in HF patients it is stated that there are no differences in mortality between PD and extracorporeal circuits.[14] 1 of 4 patients was survived in our group for 16 months. Whereas only 1 patient died because of PD related complications. As a result, mortality risk is high in advanced HF patients and survival advantage of PD is controversial.

In conclusion PD is an advantageous option for UF in HF patients that provides effective volume control, relief of symptoms and avoids frequent hospitalizations. A single daily exchange with icodextrin can be advisable for hypervolemic, well selected HF patients.

Conflict of interest

The authors declared that there are no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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Case Report

Acute Aortic Dissection Case with Stroke Presentation

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Abstract

The correct diagnosis of acute aortic syndrome complicated by neurologic symptoms is essential. Performing thrombolytic therapy for acute-stage cerebral infarction would probably be the reason for fatal outcomes. We herein report the case of a 63-year-old man who presented with left hemiparesis and paraparesis. An acute myocardial infarction was excluded by electrocardiography and blood tests. Head computed tomography (CT) showed no remarkable findings. Although there was no chest pain, it was found in CT-angiography that he has an intramural hematoma in the ascending aorta and a severe dissection in the descending aorta. Aortic dissection may mimic acute stroke, in order to make the right decision about the treatment of acute aortic syndrome with neurologic complications, the benefits and risks should therefore be considered in individual patients.

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Keywords: *aort dissection, paraparesia, stroke, tissue plasminogen activator*

Introduction

Acute aortic syndrome (AAS) is a life-threatening medical emergency associated with high rates of morbidity and mortality. The symptoms of AAS can be variable and may mimic those of more common conditions such as myocardial infarction, stroke, shock, and paraplegia, which could cause difficulty to diagnose early and treat in clinical settings.[1] We herein report a patient with an AAS presenting with signs of acute stroke as left hemiparesis and paraparesis of lower extremities.

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Case Report

A 63-year-old man admitted to emergency department with the complaints of acute onset of left upper extremity hemiparesis and asymmetric paraparesis with hypoesthesia for two hours. It was suspected that he may have an acute ischemic stroke and thrombolytic treatment was planned. So far he was a healthy man without any cardiovascular risk factors. Upon further questioning, the patient denied any kind of trauma, and skip a dose of medications. On physical exam, he was anxious and had a heart rate of 110 beats per minute. An acute myocardial infarction was excluded by electrocardiography and blood tests. A transthoracic echocardiography showed no definite abnormalities in the ascending aorta, valve, regional wall motion, and global left ventricular function in conventional echocardiographic views (data not shown). Head computed tomography (CT) and magnetic resonance imaging (MRI) showed no remarkable findings (Figure 1). In the clinical evaluation it was revealed that he has a pulse deficit in the left-sided extremities and 40 mmHg blood pressure difference was observed between the upper extremities. Although there was no chest pain, CT angiography revealed an aortic dissection which extended to the descending aorta (Stanford type A, Figure 2). We therefore carried out the strict control of the patient's blood pressure and gave up the decision of thrombolytic treatment aside. He underwent emergency allograft replacement, but he died during the operation.

It is extremely difficult to diagnose painless acute aortic dissection (AAD) that presents with neurologic symptoms solely. It is important to exclude AAD in patients with acute neurological symptoms that needs to receive tissue plasminogen activator (tPA), due to their fatal course.

Discussion

AAS complicated by neurologic symptoms or neurologic complications is not rare. This clinical scenario may lead to inappropriate thrombolytic or anticoagulant therapy, resulting in hemorrhagic complications and mortality.[2,3] Aortic CT-angiography should have been made for correct diagnosis. In our case, operative examination confirmed the intramural hematoma

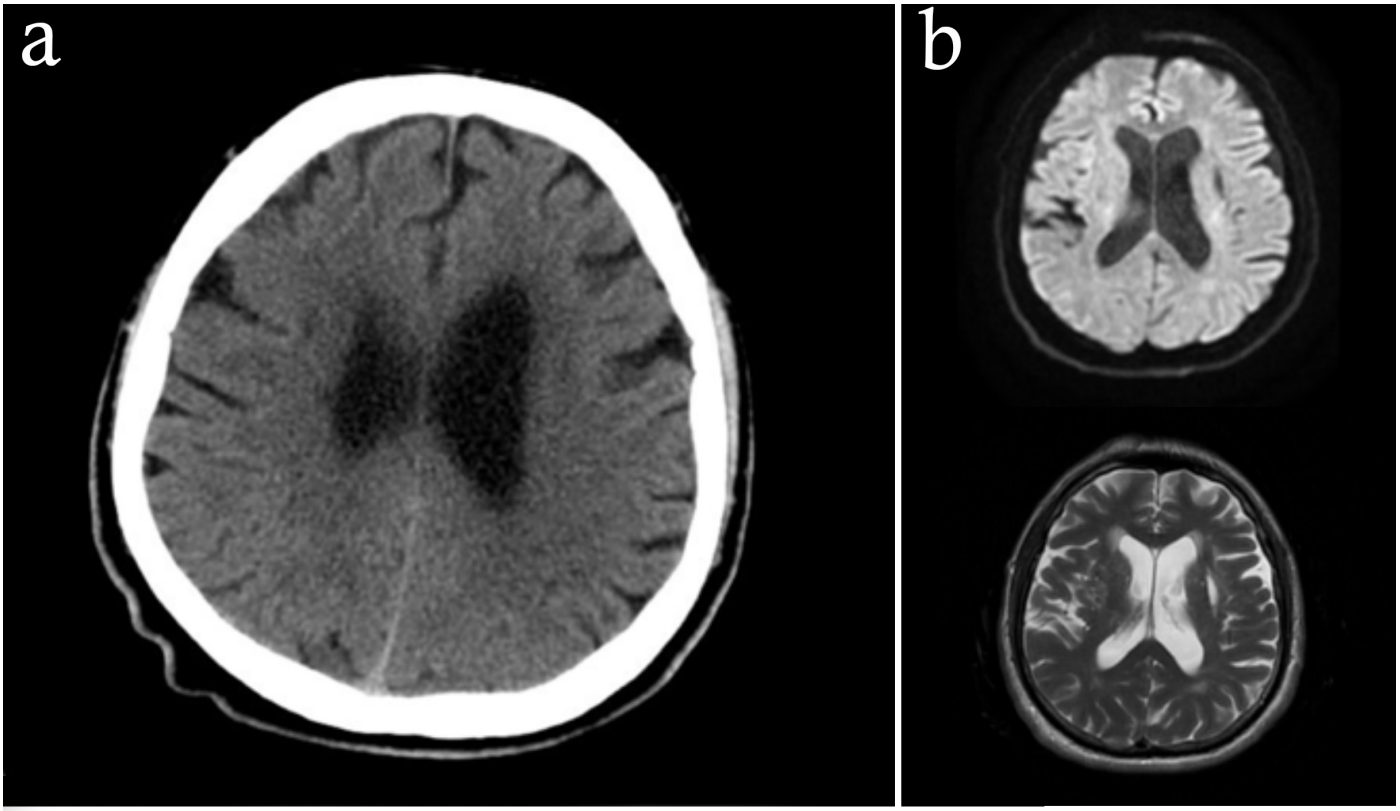

Figure 1: *Head computed tomography (CT) (a) and magnetic resonance imaging (MRI-T2 and Diffusion MRI) (b) showed no remarkable findings*

of the ascending aorta, which extends retrograde from the subclavian tearing site to the descending aorta. Although we did not find an intimal flap by echocardiography, long intramural hematoma along the whole length of the lesion was suspected to be a complication of AAS. In this case, paraparesis as a result of the spinal ischemia could have occurred secondary to the compression or occlusion of the spinal artery or intercostal arteries by the hematoma. Different neurophysiological characteristics have been described according to the anatomical position of the spinal infarction: anterior spinal artery syndrome is the most clinically frequent. Its severity depends on the transversal extension of the infarction. At most the anterior two-thirds of the spinal cord are involved, with massive motor deficit below the lesion, constant vesical-sphincter disorders, and reduced sensitivity to pain and temperature below the wound. Longitudinal extension of the infarction is determined by the quality of the anastomoses of the anterior spinal artery.[4,5]

Paraplegia or paraparesis after AAS is a rare manifestation. If a patient complains of neurologic symptoms after AAS, clinicians should thus consider many conditions in the differential diagnosis, such as embolism of the spinal artery, acute stroke and spinal infarction due to AAS complicated with myocardial infarction. One study including 44 patients with spinal ischemia or infarction reported that AAS occurred in two patients (4.4%), which was not extremely rare.[6] When the dissection was spiral it was more probably responsible for avulsion of the intercostal arteries, which represented a factor of poor perfusion.[7] Therefore, evaluation for the cause of non-traumatic paraplegia or paraparesis must be included in aortic imaging studies such as CT. Also, only an imaging study can find AAS as a cause of paraplegia or paraparesis, especially in patients with painless aortic dissection with paraplegia.[8] In humans, embolic disease can occur secondary to chronic aortic dissection with resultant hypercoagulability or from thrombi formed at the site of the aneurysm.[9] ''Blue toe'' syndrome in humans is the result of those showered emboli causing distal limb ischemia.[9,10] Thrombi theoretically form secondary to weakening of the intimal layer of the aortic aneurysm, which allows endothelial activation of coagulation factors.[9]Although aortic dissection can cause paraparesis secondary to deranged spinal blood

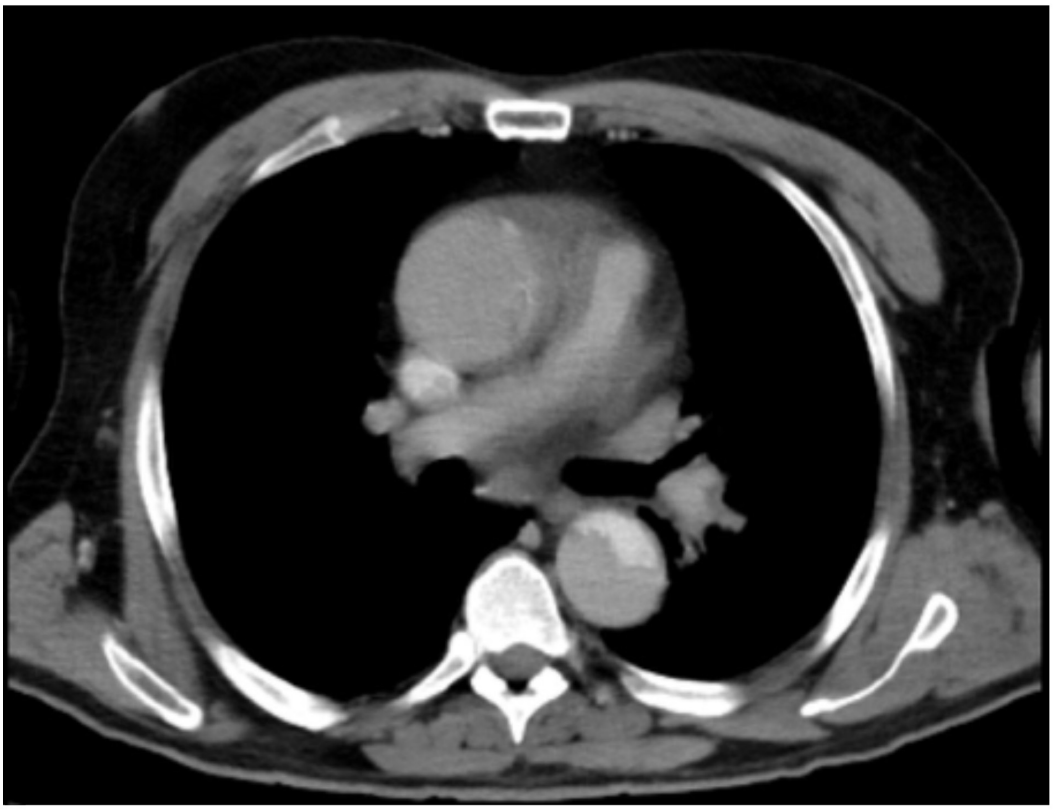

Figure 2: *A dissection detected in the ascending aorta, which may be retrograde extended from the subclavian tearing site to the descending aorta complicated with neurologic complaints was observed.*

flow or femoral arterial emboli; given the existence of unilateral arterial pulse deficit and bilateral neurologic complaints, the latter was thought to be a less important factor in this case.

In conclusion, the correct diagnosis of AAS has many potential pitfalls because AAS may mimic myocardial ischemia, stroke, heart failure and shock. In this case, balancing treatment for aortic dissection versus arterial thromboembolism was a clinical challenge. Acute aortic dissection is a clear contraindication for the use of antithrombotic and thrombolytic, such as heparin or tPA, given the inhibition of clotting mechanisms that potentially could stem further dissection. Overall prognosis for aortic dissection is assumed to be poor without surgical intervention. This case also highlights the importance of serial physical examination. Careful interpretation of the imaging results and a high index of suspicion in patients with neurologic complaints are therefore critical. To make the right decision about the treatment of AAS with neurologic complications, the benefits and risks should therefore be considered in individual patients.

Conflict of Interests

Authors declare that there are none.

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Case Report

Gastric Diverticulum in Computed Tomography

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Abstract

Gastric diverticula are the outpouchings of the stomach wall. They are the least common diverticula of the gastrointestinal system. They are usually asymptomatic and are diagnosed accidentally by upper gastrointestinal contrast radiographic studies or upper gastrointestinal endoscopy. Identification is important as they can cause serious complications such as upper gastrointestinal bleeding or perforation. We herein present a case of asymptomatic congenital gastric diverticulum.

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Keywords: *gastric diverticulum, stomach diverticulum, diverticula, endoscopy*

Introduction

Gastric diverticula (GD) are very rare anomalies seen in upper gastrointestinal system (GIS) contrast radiographic studies (0.04%), in upper GIS endoscopy examinations (0.01-0.11%) and in autopsy series (0.02%).[1-3] They are similar structures with small intestine and colon diverticula and seen equally in men and women between the ages of 50-70.[4] Although they are generally asymptomatic, sometimes cause symptoms such as epigastric pain, discomfort, nausea, vomiting, halitosis, bloating, early satiety, anorexia and dysphagia.[3] GD greater than 4 cm in diameter are more susceptible to complications and are less likely to respond favorably to medical management.[3]

Since the symptoms are uncertain and have no distinctive findings from other GIS diseases, the most important step to diagnose the disease is to keep this pathology in mind and in the list of possible diagnoses. Follow-up or palliative treatment options such as proton pump inhibitors and antacid treatments are preferred in asymptomatic patients, surgical treatment is required if serious complications such as ulceration, malignant transformation or perforation occur in the gastric diverticulum.

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Case Report

Our patient is a 30-year-old woman. When she applied to the Internal Diseases outpatient clinic with a complaint of dyspnea, thorax computerized tomography (CT) study was performed. CT scan showed an incidental stomach diverticulum with 3x2 cm size in the gastric fundus posterior wall (*Figure 1a and 1b*). Although it was very close to the left adrenal gland, the continuity of diverticulum with the stomach lumen, air density (*Figure 2*) in it and the fat line between the lateral adrenal crus could be seen (*Figure 3*). After CT study, upper GIS endoscopy was performed and wide-mouthed diverticulum was observed in the fundus (*Figure 4*).

Since our patient was asymptomatic and pathologies such as ectopic mucosa, ulcer or malignancy were not found in the gastric diverticulum, clinical monitoring without treatment advised. Informed consent was taken before all procedures.

Discussion

GD can be classified as congenital or true diverticulum and acquired or false diverticulum. True or congenital diverticula are mostly located on the posterior wall of the gastric fundus, contain all the layers of the gastric wall and are thought to be associated with the defect in the fusion of the dorsal and ventral mesentery in the embryonic period.[5] Seventy-five percent of them are located in fundus, 2 cm below the gastroesophageal junction on the posterior wall, 3 cm from the small curvature, and their diameter ranges from 3 cm to 11 cm.[2,6,7]

The false diverticula do not contain layers of muscularis or serosa and tend to form more often in the antrum. It is possible to classify as pulsation and traction diverticulum according to the formation mechanisms. Conditions such as obesity or chronic cough cause chronic increase in intragastric pressure, trigger pulsion diverticulum; where conditions associated with inflammatory processes such as surrounding peptic ulcer, malignant disease, pancreatitis, gastric outlet obstruction and patients who undergo to a bypass with Roux-Y gastric can develop traction gastric diverticulum.[5,6,8]

Gastric diverticulum patients are generally asymptomatic or have ambiguous symptoms seen in other diseases of GIS, such as peptic ulcer or gastritis, so it is necessary to doubt this pathology for differential diagnosis. GD may not be visualized in upper GIS contrast radiographic studies and during endoscopy, especially when they are narrow-necked. In a large review, Palmer[9] reported that 5% of GD are missed during upper gastrointestinal investigation.

The upper GIS endoscopy has the highest diagnostic value since it can directly see the high morbidity conditions such as ectopic mucosa, ulceration and malignancy in the diverticulum, and has the possibility of simultaneous biopsy.[10,11] The upper GIS radiographs with barium, which have been used more frequently in the radiology routine in the past, can show gastric diverticulum with high accuracy when obtained with appropriate position and technique. It has been shown that during contrast radiographic series,

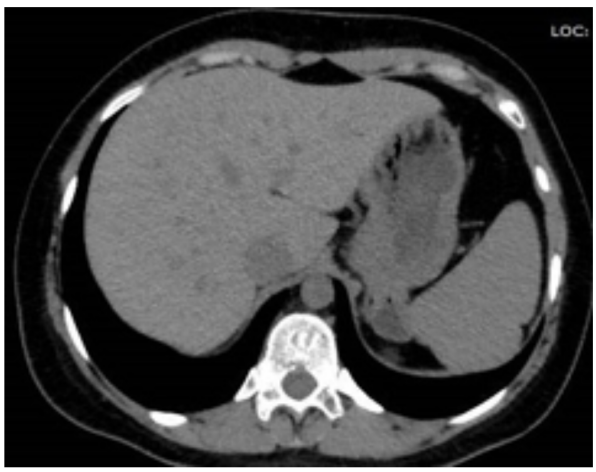

Figure 1a: *CT-scan-axial sections, GD continuous with stomach lumen*

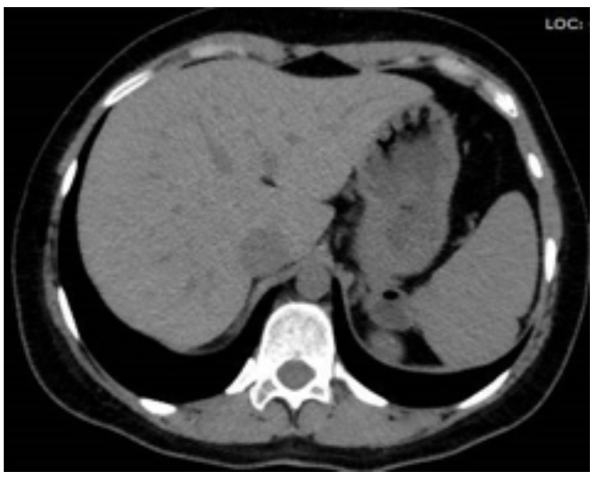

Figure 1b: *CT-scan-axial sections, GD containing air*

the GD is best recognized with the use of a right, anterior oblique angle while the individual is in a trendelenburg and slightly left lateral decubitus position.[12,13]

Since CT scans are not able to show real time gastrointestinal tract movement, the peristaltic activity occurring in the stomach wall at the time of the examination causes false images and therefore diagnostic errors in daily practice. Sometimes radiologists misunderstand this normal gastric wall appearance. In order to diagnose gastric diverticulum with CT, it is necessary to observe the continuity with gastric lumen and/or to observe the air density, if possible, to fill the diverticular lumen with given oral contrast agent. As most GD take part along the posterior wall of the stomach, it has been suggested that CT scans obtained in the prone position may facilitate air movement to the top and form an air-fluid level.[14]

However, CT scans are reported to mistake diverticula for adrenal masses[15], we think, this usually depends on the experience of the radiologist. The fat line between the lateral adrenal crus can be seen with attention and also coronal or sagittal images are very helpful to distinguish between GD and left adrenal mass. The CT study is non-invasive and has much less radiation dose with advanced multislice 3D reformat technology. Major advantages of CT are the ability to show perigastric space, accompanying epigastric inflammation, abscess and perforation. Life threatening complications accompanying the diverticulum can be investigated and definitely reported with CT examination.

However, the methods used to detect GD occasionally fail, combined radiological and endoscopic diagnostic approach should be used.[16]

Conclusion

GD are one of the rarest anomalies of the GIS and are generally asymptomatic or cause vague symptoms, such as pain, discomfort, and dyspepsia. Although not very often, their diagnosis and follow-up are important because of potential risk for life threatening complications. First of all, suspicion of this pathology is required for the diagnosis, followed by combined use of radiological and endoscopic studies.

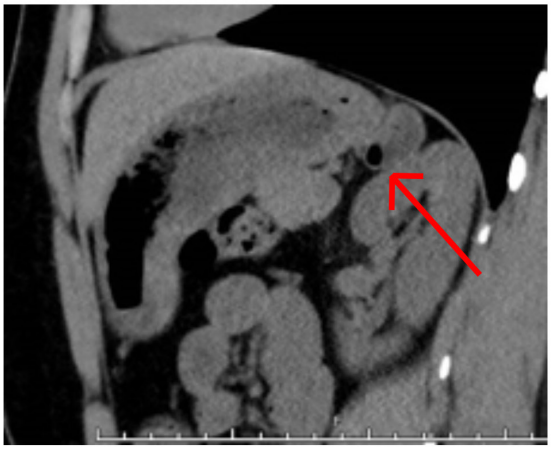

Figure 2: *CT-scan-sagittal section observing diverticulum on the posterior wall of the stomach containing air (Arrow)*

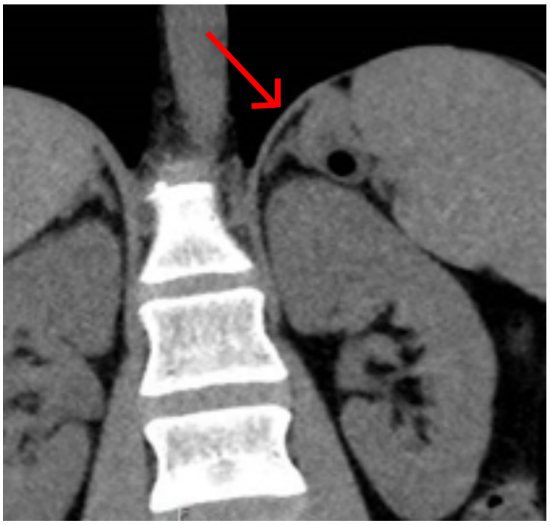

Figure 3: *CT-scan-coronal section where saccular image is observed with air density inside. Thin fat line (Arrow) can be seen between the GD and left adrenal gland.*

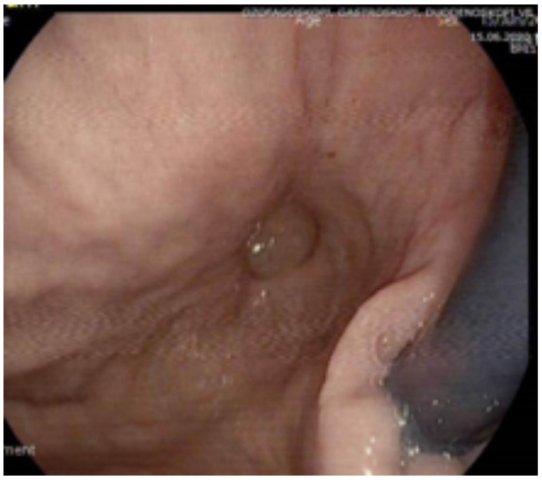

Figure 4: *Endoscopic view of the gastric diverticulum located in the fundus of the stomach*

Conflict of Interests

The authors declared that there are no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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