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From the Editor

Ahmad Husari *(Chief Editor)*
Email: editor@me-jim.com

This is the first issue this year of the journal that has a number of interesting papers dealing with various subjects of interest. There are three papers that dealt with Sickle Cell Disease.

Mustafa et al., looked at improving the outcome of Sickle Cell disease patients in a resource limited setting Sudan Sickle Cell Anemia Center (SSCAC). They stressed that it is a promising and developing experience. In 2010, the percentage of newborns with SCD in sub-Saharan Africa was79%, and this proportion is expected to increase to 88% by 2050. Africa has high mortality rates ranging from 50 to 90% for those aged less than 5 years. This high mortality is due to the lack of several facilities like prenatal diagnostic services, systematic follow-up, and life-saving measures such as penicillin prophylaxis, vaccination for common bacterial diseases, and the provision of disease-modifying treatment with Hydroxyurea, and Poor access to hematopoietic stem cell transplantation. Infectious diseases like malaria may also play a role in increasing the severity and mortality. The prevalence rate of sickle cell anemia in Sudan ranging from 2 to 30.4%. The highest prevalence of SCA in the Sudanese population is found in Western Sudan residents. Because of this increased prevalence of SCD in west Sudan, it is of high importance to improve the quality of care for sickle cell disease patients in this area. The authors present their experience at SSCAC.

Helvaci*, et al., tried to understand the underlying mechanism of pulmonary hypertension (PHT) in the sickle cell diseases (SCD). All patients with the SCD were included. The study included 434 patients (212 females) with similar mean ages in males and females (30.8 versus 30.3 years, respectively, $p>0.05$). Smoking (23.8% versus 6.1%, $p<0.001$) and alcohol (4.9% versus 0.4%, $p<0.001$) were higher in males, significantly. Transfused units of red blood cells (RBC) in their lives (48.1 versus 28.5, $p=0.000$), disseminated teeth losses (<20 teeth present) (5.4% versus 1.4%, $p<0.001$), chronic obstructive pulmonary disease (COPD) (25.2% versus 7.0%, $p<0.001$), ileus (7.2% versus 1.4%, $p<0.001$), cirrhosis (8.1% versus 1.8%, $p<0.001$), leg ulcers (19.8% versus 7.0%, $p<0.001$), digital clubbing (14.8% versus 6.6%, $p<0.001$), coronary heart disease (CHD) (18.0% versus 13.2%, $p<0.05$), chronic renal disease (CRD) (9.9% versus 6.1%, $p<0.05$), and stroke (12.1% versus 7.5%, $p<0.05$) were all higher but not PHT (12.6% versus 11.7%, $p>0.05$) in males, significantly. The authors concluded that SCD are severe inflammatory processes on vascular endothelium, particularly particularly at the capillary level since the capillary system is the main distributor of hardened RBC into the tissues. Although the higher smoking, alcohol, and disseminated teeth losses, COPD, ileus, cirrhosis, leg ulcers, digital clubbing, CHD, CRD, and stroke-like atherosclerotic consequences in male sex, PHT was not higher in them in the present study. In another definition, PHT may not have an atherosclerotic background in the SCD. Instead, the hardened RBC-induced capillary endothelial damage, inflammation, edema, and fibrosis around the alveoli may be the major underlying cause.

Helvaci*, et al., tried to understand prevalence of chronic obstructive pulmonary disease (COPD) in both genders in sickle cell diseases (SCD).All cases with the SCD in the absence of smoking and alcohol were included. The study included 368 patients (168 males). Mean ages were similar in males and females (29.4 versus 30.2 years, respectively, $p>0.05$). Mean values of body mass index (BMI) were similar in males and females, too (21.7 versus 21.6 kg/m2, respectively, $p>0.05$). Interestingly, total bilirubin value of the plasma (5.2 versus 4.0 mg/dL, $p=0.011$), transfused units of red blood cells (RBC) in their lives (46.8 versus 29.2, $p=0.002$), COPD (20.8% versus 6.0%, $p<0.001$), and digital clubbing (13.0% versus 5.5%, $p<0.001$) were all higher in males. Whereas painful crises per year (5.0 versus 5.0), pulmonary hypertension (10.1% versus 12.5%), acute chest syndrome (2.3% versus 3.5%), mortality (8.3% versus 6.5%), and mean age of mortality (29.0 versus 32.5 years) were similar in males and females, respectively ($p>0.05$ for all). The authors concluded that SCD are severe inflammatory processes on vascular endothelium particularly at the capillary level, since capillary system is the main distributor of hardened RBC into tissues. The capillary endothelial damage, inflammation, edema, and fibrosis induced hypoxia may be the underlying cause of COPD in the SCD. Although the similar BMI and absence of smoking and alcohol, the much higher prevalence of COPD may be explained by the dominant role of male sex in life according to the physical power that may accelerate systemic atherosclerotic process in whole body.

Abyad & Hammami in the first of a series on Frailty discusses frailty. They stressed Life expectancy continues to rise globally. However, the additional years of life do not always correspond to years of healthy life, which may result in an increase in frailty. Given the rapid aging of the population, the association between frailty and age, and the impact of frailty on adverse outcomes for older adults, frailty is increasingly recognized as a significant public health concern. Early detection of the condition is critical for assisting older adults in regaining function and avoiding the negative consequences associated with the syndrome. Despite the critical nature of frailty diagnosis, there is no conclusive evidence or consensus regarding whether routine screening should be implemented. A variety of screening and assessment instruments have been developed from a biopsychosocial perspective, with frailty defined as a dynamic state caused by deficits in any of the physical, psychological, or social domains associated with health. All of these aspects of frailty should be identified and addressed through the use of a comprehensive and integrated approach to care. To accomplish this goal, public health and primary health care (PHC) must serve as the fulcrum around which care is delivered, not just to the elderly and frail, but to all individuals, by emphasizing a life-course and patient-centered approach centered on integrated, community-based care.

Questioning and prying into botulinum toxin after aesthetic treatment Dr. Elghblawi reported a case of an allergy to Botox toxin A. that had arisen shortly after the injection, to be added to the existing literature. A 41-year-old Philippino lady experienced a severe localised reaction, with redness and nodular swelling on her face, after her second Botox injection. The lady did not have any prior medical illness. This case can help in assessment and appraisal of anticipated Botox allergies and raise awareness of the rare infrequent incident.

Improving the outcome of Sickle Cell disease patients in a resource limited setting Sudan Sickle Cell Anemia Center (SSCAC): a promising and developing experience

Alam Eldin Musa Mustafa (1.2)
Osman Abelgadir Osman (3)
Niemat Mohammed Tahir (1)

(1) Assistant Professor of Pediatrics, Department of Child Health, College of Medicine, King Khalid University, Abha, Saudi Arabia
(2) Associate Professor of Pediatrics, Department of Pediatrics, Faculty of Medicine and Health Sciences, Kordofan University, Sudan
(3) Lecturer, Faculty of Medical Laboratory Sciences, University of Kordofan, Sudan

Corresponding author:
Dr. Alam Eldin Musa Mustafa
Department of Child Health,
College of Medicine,
King Khalid University,
Abha, Saudi Arabia
Email: alameldinmustafa641@gmail.com

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ABSTRACT

This is a descriptive health service research and quantitative study, based on a population of 1400 patients with sickle cell disease, pediatric and adult population. Their age, gender, and frequency of follow-up and hospitalization are recorded from the statistical records and analyzed. And the description of the health facility and the services provided by it was compiled from observations and interviewing the staff.

Specific clinics for children and adults with sickle cell disease are available in several African countries but only a few countries have newborn screening programs [17]. Sudan Sickle Cell Anemia Centre (SSCAC) is the only specialized center for SCD in Sudan for children and adults. Its location in Al Obeid in the West is Justified by the highest percentage of patients in Sudan being in the West region[6].

During the six years of its work, the number of registered patients increased from 112 to 1400 patients with the age range of 3 months to 34 years. The percentage of male patients is 56%. More than half of the registered patients were of the under 5 age groups. This is in concordance with a previous study done in Al-Obeid where the under five years age group was dominating[11].

It is recommended that:
-The World Health Organization is recommended to provide technical and financial support to SSCAC in framing policies and strategies for the prevention and management of sickle-cell disease.
-The collaboration of the Sudan Ministry of Health, the WHO, and the non-governmental organizations with the center is needed to support constructing buildings, providing ambulance, the diagnostic equipment including Genetic screening, needed treatment facilities, transportation methods for patients from areas of Kordofan and Darfur to the center, and help funding research on sickle-cell disease to increase life expectancy and improve patient's quality of life.
-Funding resources for sickle-cell disease prevention and control, including training of staff to offer genetic counseling and health education, in addition to the introduction of newborn screening services in the center.
-Establishing similar specialized centers in Khartoum and different states of Sudan to provide easier access to services for most of the patients.

Key words: **Sickle Cell disease, Sudan Sickle Cell Anemia Centre (SSCAC)**

Introduction

Sickle cell disease is an autosomal recessive disorder that consists of a group of disorders that are characterized by the presence of sickle hemoglobin (Hb S). In Sickle cell disorders, hemoglobin S is formed as a result of the substitution of valine to glutamic acid in position number six in the Beta globin chain [1]. There are more than 700 structural hemoglobin variants but the commonest in Africa are Hb S and Hb C. [2]. When the red blood cells are exposed to hypoxia, their membrane is distorted producing the characteristic sickle-shaped cell which occludes small capillaries and venules and causes tissue ischemia, acute pain, and gradual end-organ damage [3][4].

In 2010, the percentage of newborns with SCD in sub-Saharan Africa was 79%, and this proportion is expected to increase to 88% by 2050[5].

Africa has high mortality rates ranging from 50 to 90% for those aged less than 5 years. This high mortality is due to the lack of several facilities like prenatal diagnostic services, systematic follow-up, and life-saving measures such as penicillin prophylaxis, vaccination for common bacterial diseases, and the provision of disease-modifying treatment with Hydroxyurea, and poor access to hematopoietic stem cell transplantation [4]. Infectious diseases like malaria may also play a role in increasing the severity and mortality[5].

The prevalence rate of sickle cell anemia in Sudan ranges from 2 to 30.4%. The highest prevalence of SCA in the Sudanese population is found in Western Sudan residents[6]. Studies performed in different cities in Sudan relating SCA to Sudanese tribes also concluded that most of the cases were from tribes belonging to the western area in Sudan and those migrating from Western Africa and Sudan, for example, a study done in Gedarif state in Eastern Sudan showed a high rate of sickle cell gene among the population that migrated from the west[7][8][9][10]. The Misseriya tribe in Kordofan and Darfur showed the highest rate of sickle cell disease in Sudan. This is related to the increased consanguinity rates and the rate of first-cousin marriages in Sudan[9]. In El Obeid, high frequencies of sickle cell disease were found among Falatah and Jawama, 80% of children's parents were relatives or from the same tribe[11].

Because of this increased prevalence of SCD in west Sudan, it is of high importance to improve the quality of care for sickle cell disease patients in this area. According to the WHO definition quality of care is defined as the extent to which health care services provided to individuals and patient populations improve desired health outcomes. To achieve this, health care must be safe, effective, timely, efficient, equitable, and people-centered [12].

These points are described by WHO as being safe; meaning delivering health care that minimizes risks and harm, effective service based on scientific knowledge and evidence-based guidelines, reducing delays in providing and receiving health care, efficient service that maximizes resource use and avoids waste, and equal service for all people from different genders, race, ethnicity, geographical location or socioeconomic status and providing care that takes into account the preferences and aspirations of individual service users and the culture of their community[13].

Providing health care for SCD patients requires trained professionals and a social support system so that their physical, emotional, psychological, and financial needs are fulfilled. Unfortunately, SCD patients in most sub-Saharan countries have limited access to clinical, health educational, social and psychological care[14].

The Specialized sickle cell centers are important in improving quality of life, reducing health care costs, and reducing health care utilization rates among patients with SCD[15]. Several strategies have been proposed to improve the quality of care for patients with SCD. System approaches include comprehensive sickle cell centers, hub and spoke models, satellite clinics, and telemedicine [13].

Sudan Sickle Cell Anemia Centre (SSCAC) is a voluntary, national, non-governmental organization accredited by the Federal Humanitarian Aid Commission. It was established in 2012 in El Obeid, North Kordofan State. As the city formerly acted as the capital for the whole Kordofan region, establishing SSCAC in El Obeid is justifiable. It was started as a sickle cell clinic and patients were observed by a senior pediatrician then evolved gradually when laboratory investigations, genetic counseling, and training packages were added. From 2015 onward, SSCAC spread in the form of sickle cell clinics in different states of Sudan; South Kordofan, West Kordofan, and South Darfur. The core mission of SSCAC is to improve the quality of all services dealing with Sickle Cell Disorders, thereby improve the quality of life for people with Sickle Cell Disorder.

Methodology and description

This is a descriptive health service research and quantitative study, based on a population of 1400 patients with sickle cell disease, pediatric and adult population. Their age, gender, and frequency of follow-up and hospitalization are recorded from the statistical records and analyzed. And the description of the health facility and the services provided by it was compiled from observations and interviewing the staff.

SSCAC interventions in El Obeid – the headquarters that is located in El Obeid Specialized Pediatric Hospital include; medical care for those presentingt with sickle cell crises at the emergency department of the hospital and sickle cell clinic for regular follow up for both pediatric and adult patients. The follow-up services are made up of clinical examination, growth assessment and routine laboratory tests. Basic laboratory investigations to establish the diagnosis and to continuously assess the patient status are available. Regularly patients, especially at age 6 – 16 years, undergo Transcranial Doppler assessment as an effective measure for CVA prevention. Echocardiography is an emerging service for selected cases.

Health promotion activities are carried out in the form of genetic counseling sessions for parents and some patients, as well as families. Raising awareness of the public is conducted through talks in schools, hospitals, universities and people gatherings,

radio programs, and television shows. As a part of prevention measures, pneumococcal vaccine is available for patients especially under-fives.

As building capacity will guarantee good performance in medical care and counseling, several training activities were conducted.

Research in sickle cell disorders is inconsistent in different aspects of the disease; SCD mapping, the natural history of the disease, accessibility, and sustainability of medical care, effectiveness and impact of dedicated centers and clinics, etc. Many kinds of research that touch on viable issues regarding sickle cell disease are conducted. The research ranges from KAP studies to molecular studies on the disease haplotypes and correlations between phenotypes and single nucleotides polymorphism (SNPs).

Ethical consideration

Informed consent was obtained from the managers of El-Obied specialized pediatrics Hospital to which the center belongs and is part of that hospital. They accepted to provide us, as authors, the free use of all the data and statistics of the SSCAC.

Findings

Six years have passed since the foundation of SSCAC in El Obeid. The number of registered patients increased from 112 to 1400 patients with an age range of 3 months to 34 years. Among patients, two thirds (63%) are from North Kordofan State, 52% are under five years, males are 56%.

Up to date, about 3400 patients have ben provided with the benefit of the sickle cell clinic for both pediatric and adult patients, with only 15 – 25% of total registered patients visiting the clinic regularly and the percentage of patients presenting with crises and the need to be hospitalized is only 10 – 20% of total registered patients. The number of patients who visit the pediatric clinic is around 100 – 160, while adults´ clinic is about 20 – 30 per month.

The training was started earlier; courses and workshops were organized for doctors, nurses, medical assistants. Limited activities were carried out due to a shortage of resources and lack of funding. Here are some events;

	Course / workshop	Target group	Number trained
1	Nursing sickle cell patients; basic skills	Nurses	20
2	Basic skill in TCD (Transcranial Doppler)	Doctors, Nurses	16
3	Genetic counseling course	Health workers	15

Research works performed at SSCAC till the year (2018)

SSCAC studies				
No	Title	Year	Level	Publication
1	Sickle Cell Anemia among Children in El Obeid Hospitals, Sudan: A clinical and hematological study	2013	Study	IJMRHS • International Journal of Medical Research &Health Sciences, 2018, 7(11): 66-71
2	Knowledge and attitude of health professionalstowards sickle cell disorders in El Obeid Teaching Hospital, Sudan	2014	Undergraduate	
3	University students in Sudan: knowledge, attitude toward sickle cell disease and pre-marital genetic counseling	2014	Undergraduate	
4	KAP study among families of patients with sickle cell disease in El Obeid, Sudan in 2013.	2014	Undergraduate	
5	Prevalence of alloimmunization in multiple blood transfusion sickers in El Obeid, 2015.	2015	MSc	
6	Management of sickle cell crises in El Obeid Hospitals, 2014	2015	Undergrad	
7	C - reactive Protein Level and WBC Count as Biomarkers for vaso-occlusive crisis among patients with Sickle Cell Disease	2015	MSc	American Journal of Medicine and Medical Sciences2015; 5(6): 283 – 286.
8	Relationship between Painful Crisis and Serum Zinc level in Children's with Sickle Cell Anemia	2016	MSc	
9	Association of Endothelial Nitric Oxide Synthase Gene T-786C polymorphism with Complication of Sickle Cell Anemia among Children in Khartoum 2017	2017	MSc	
10	Assessment of Microalbuminuria and Lactate Dehydrogenase as Early Indicators of Renal Impairment among Sudanese Children with Sickle Cell Anemia in North Kordofan State	2016	MSc	

11	Determination of Selected Trace Elements among Children with Sickle Cell Anemia in Elobied City - North Kordofan State	2017	Undergrad	European Journal of Pharmaceutical Sciences 2017, 4(10) 855-857.
12	Estimation of potential patients for stroke risk in children with sickle cell anemia using ultrasound in Jaffer ibn Aouf Pediatric hospital 2015	2018	PhD	
13	Prevalence of Sickle Cell hemoglobin in Shikan locality, North Kordofan State, 2017	2017	Undergrad	
14	Impact of Sickle Cell Disease in Renal Arteries Blood Flow Indices Using Ultrasonography	2017	PhD	International Journal of Medical Imaging 2017; 5(2): 9-13.
15	*Evaluation of Transcranial Doppler Abnormalities in Children with Sickle Cell Disease in Elobied Specialized Children`s Hospital in the Time Period from December 2016 to February 2017.*	2017	MD	
16	Frequency of HbS Gene Among Population of Northern Korodofan Area; Hematological and Molecular Analysis	2017	PhD	
17	Pregnancy and birth outcome and essential nutrient status of Sudanese pregnant women with sickle cell disease	2017	PhD	
18	Role of trans-cranial Doppler ultra-sound in Sickler patients as a screening tool, in EL-Obied North Kordofan State in Kuwaiti Hospital, within the period from November 2017 – January 2018	2017	MD	

Discussion

Specialized SCD centers are important and must fulfill three goals; affording direct and quick access to the health service, presence of a multidisciplinary team providing the best quality medical care, and cost-effectiveness because of their proximity to and location in an area with significant SCD populations[16]. Specific clinics for children and adults with sickle cell disease are available in several African countries but only a few countries have newborn screening programs [17]. Sudan Sickle Cell Anemia Centre (SSCAC) is the only specialized center for SCD in Sudan for children and adults. Its location in Al Obeid in the West is Justified by the highest percentage of patients in Sudan being in the West region[6].

During the six years of its work, the number of registered patients increased from 112 to 1400 patients with the age range of 3 months to 34 years. The percentage of male patients is 56%. More than half of the registered patients were of the under 5 age groups. This is in concordance with a previous study done in Al-Obeid where the under five years age group was dominating[11].
It is observed that the percentage of patients visiting the clinic regularly and that of patients who present with crises and need to be hospitalized is very low compared to the total registered number. This can be attributed to the distance from the center, low socioeconomic status, or underreporting [18]. The center is treating both pediatric and adult patients but the number of patients visiting the pediatric clinic is around 100 – 160, while adults´ clinic is only about 20 – 30 per month. This is in agreement with the results of the recent review of cross-sectional population surveys and cohort studies of SCD in Africa, which estimated that between 50 and 90% of SCA children died before age 5 years [17]. In the late 1970s, studies in Africa reported a childhood survival of less than 2% in sickle cell disease [18]. With improvements in healthcare, this has increased to nearly 50% [19].

The WHO Regional Office for Africa has recommended the need for developing national SCD control programs that include advocacy, prevention and counseling, early detection, treatment, surveillance, research, and community education and partnerships [20]. SSCAC has conducted some training activities; courses and workshops were organized for doctors, nurses, and medical assistants. Limited activities were carried out due to a shortage of resources and lack of funding.

More efforts and funds are needed in training and education. Some studies recommend the training of community health workers to improve the outcome of SCD, especially with urban or rural populations. [21] In our Sudanese society, if they get the required training, they will be of great help in education, early referral for treatment, and reducing the load from medical staff. Although results are not yet available, the high rate of patient acceptance of community health workers is an early indicator that their interventions can be feasible [22].

Another important point in education is educating the patients and their families by using educational manuals or by interactive learning environment in a friendly atmosphere that might be an efficient way to present disease education to patients, families, and the community [23]. All these need extra funds so that it will be achieved acceptably and continuously.

The capacity for doing clinical research is an important feature of the specialized health facility. This will help in testing the possibility of implementation of SCD guidelines and assess their impact on patient outcomes[24].

Eighteen research studies are done in the center by postgraduates and medical students in different aspects of the disease. The research ranges from KAP studies to molecular studies on the disease haplotypes and correlations between phenotypes and single nucleotides polymorphism (SNPs).

Establishing a quality improvement process in resource-limited settings faces lots of challenges. Stepping forward for improved quality care requires critical self-assessment, the willingness to change, and determined commitment and contributions from staff, management, patients, community and government.

Recommendations

Sudan Sickle Cell Anemia Center is unique in Sudan in form of services provided to patients with SCD.

-The World Health Organization is recommended to provide technical and financial support to SSCAC in framing policies and strategies for the prevention and management of sickle-cell disease.

-The collaboration of the Sudan Ministry of Health, the WHO, and the non-governmental organizations with the center is needed to support constructing buildings, providing ambulance, the diagnostic equipment including Genetic screening, needed treatment facilities, transportation methods for patients from areas of Kordofan and Darfur to the center, and help funding research on sickle-cell disease to increase life expectancy and improve patient's quality of life.

-Funding resources for sickle-cell disease prevention and control, including training of staff to offer genetic counseling and health education, in addition to the introduction of newborn screening services in the center.

-Establishing similar specialized centers in Khartoum and different states of Sudan to provide easier access to services for most of the patients.

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A much higher prevalence of chronic obstructive pulmonary disease in males with sickle cell diseases even in the absence of smoking and alcohol

Mehmet Rami Helvaci (1)
Emin Maden (2)
Atilla Yalcin (1)
Orhan Ekrem Muftuoglu (1)
Abdulrazak Abyad (3)
Lesley Pocock (4)

(1) Specialist of Internal Medicine, MD
(2) Specialist of Pulmonary Medicine, MD
(3) Middle-East Academy for Medicine of Aging, MD
(4) medi-WORLD International

Corresponding author:
Prof Dr Mehmet Rami Helvaci,
07400, ALANYA, Turkey
Phone: 00-90-506-4708759
Email: mramihelvaci@hotmail.com

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ABSTRACT

Background: We tried to understand prevalence of chronic obstructive pulmonary disease (COPD) in both genders in sickle cell diseases (SCD).

Methods: All cases with the SCD in the absence of smoking and alcohol were included.

Results: The study included 368 patients (168 males). Mean ages were similar in males and females (29.4 versus 30.2 years, respectively, p>0.05). Mean values of body mass index (BMI) were similar in males and females, too (21.7 versus 21.6 kg/m2, respectively, p>0.05). Interestingly, total bilirubin value of the plasma (5.2 versus 4.0 mg/dL, p=0.011), transfused units of red blood cells (RBC) in their lives (46.8 versus 29.2, p=0.002), COPD (20.8% versus 6.0%, p<0.001), and digital clubbing (13.0% versus 5.5%, p<0.001) were all higher in males. Whereas painful crises per year (5.0 versus 5.0), pulmonary hypertension (10.1% versus 12.5%), acute chest syndrome (2.3% versus 3.5%), mortality (8.3% versus 6.5%), and mean age of mortality (29.0 versus 32.5 years) were similar in males and females, respectively (p>0.05 for all).

Conclusion: SCD are severe inflammatory processes on vascular endothelium particularly at the capillary level, since capillary system is the main distributor of hardened RBC into tissues. The capillary endothelial damage, inflammation, edema, and fibrosis induced hypoxia may be the underlying cause of COPD in the SCD. Although the similar BMI and absence of smoking and alcohol, the much higher prevalence of COPD may be explained by the dominant role of male sex in life according to the physical power that may accelerate systemic atherosclerotic process in whole body.

Key words: Sickle cell diseases, chronic obstructive pulmonary disease, male sex, chronic endothelial damage, atherosclerosis, metabolic syndrome, aging

Introduction

Chronic endothelial damage may be the leading cause of aging and death by causing disseminated tissue hypoxia all over the body. Probably whole afferent vasculature including capillaries are mainly involved in the process since much higher blood pressure (BP) of the afferent vasculature may be the major underlying cause by inducing recurrent endothelial injuries. Thus the term of venosclerosis is not as famous as atherosclerosis in the literature. Secondary to the chronic endothelial damage, inflammation, edema, and fibrosis, vascular walls become thickened, their lumens are narrowed, and they lose their elastic nature that reduces blood flow and increases systolic BP further. Some of the well-known accelerators of the systemic atherosclerotic process are physical inactivity, excess weight, smoking, alcohol, prolonged infections such as tuberculosis, and chronic inflammatory processes including sickle cell diseases (SCD), rheumatologic disorders, and cancers for the development of terminal endpoints including obesity, hypertension (HT), diabetes mellitus (DM), peripheric artery disease (PAD), chronic obstructive pulmonary disease (COPD), pulmonary hypertension (PHT), chronic renal disease (CRD), coronary heart disease (CHD), cirrhosis, mesenteric ischemia, osteoporosis, and stroke, all of which terminate with early aging and premature death. They were researched under the title of metabolic syndrome in the literature, extensively (1, 2). Although early withdrawal of the causative factors may delay terminal endpoints, the endothelial changes cannot be reversed completely after the development of obesity, HT, DM, PAD, COPD, PHT, CRD, CHD, or stroke due to their fibrotic nature (3, 4). Similarly, SCD are severe inflammatory processes on vascular endothelium, particularly at the capillary level terminating with an accelerated atherosclerosis induced end-organ failure in early years of life. We tried to understand prevalence of COPD in both genders in the SCD.

Material and Methods

The study was performed in the Medical Faculty of the Mustafa Kemal University between March 2007 and June 2016. All patients with the SCD in the absence of smoking and alcohol were included into the study. The SCD are diagnosed with the hemoglobin electrophoresis performed via high performance liquid chromatography (HPLC). Medical histories of the patients including painful crises per year and transfused units of red blood cells (RBC) in their lives were learnt. Due to the cumulative atherosclerotic effects of smoking and alcohol together with the SCD, current and/or previous smokers or drinkers at least for a period of one year were excluded from the study. A complete physical examination was performed by the same internist. Body mass index (BMI) of each case was calculated by the measurements of the same internist instead of the verbal expressions. Weight in kilogram is divided by height in meter squared (5). Cases with acute painful crisis or any other inflammatory event were treated at first, and the laboratory tests and clinical measurements were performed on the silent phase. Check up procedures including serum iron, iron binding capacity, ferritin, total bilirubin, a posterior-anterior chest x-ray film, and a Doppler echocardiogram to measure systolic BP of pulmonary artery were performed. Systolic BP of the pulmonary artery which is 40 mmHg or higher is accepted as PHT (6). Associated thalassemia minors were detected with serum iron, iron binding capacity, ferritin, and hemoglobin electrophoresis performed via HPLC. The criterion for diagnosis of COPD is post-bronchodilator forced expiratory volume in one second/forced vital capacity of less than 70% (7). Acute chest syndrome (ACS) is diagnosed clinically with the presence of new infiltrates on chest x-ray film, fever, cough, sputum production, dyspnea, or hypoxia (8). Digital clubbing is diagnosed with the ratio of distal phalangeal diameter to interphalangeal diameter which is greater than 1.0, and with the presence of Schamroth's sign (9, 10). Eventually, the mean age, associated thalassemia minors, BMI, painful crises per year, total bilirubin value of the plasma, transfused units of RBC in their lives, COPD, digital clubbing, PHT, ACS, overall mortality, and mean age of mortality were detected in both genders, and compared in between. Mann-Whitney U test, Independent-Samples t test, and comparison of proportions were used as the methods of statistical analyses.

Results

The study included 368 patients with the SCD (168 males and 200 females). Smoking and alcohol restrictions were the cause of female predominancy in the study cases since both of them are much higher in males. Mean ages of the patients were similar in males and females (29.4 versus 30.2 years, respectively, $p>0.05$). Prevalence of associated thalassemia minor was also similar in both genders (72.0% versus 69.0%, respectively, $p>0.05$). Mean values of BMI were similar in males and females, too (21.7 versus 21.6 kg/m2, respectively, $p>0.05$) (Table 1). Interestingly, total bilirubin value of the plasma (5.2 versus 4.0 mg/dL, $p=0.011$), transfused units of RBC in their lives (46.8 versus 29.2, $p=0.002$), COPD (20.8% versus 6.0%, $p<0.001$), and digital clubbing (13.0% versus 5.5%, $p<0.001$) were all higher in males, significantly. On the other hand, painful crises per year (5.0 versus 5.0, $p>0.05$), PHT (10.1% versus 12.5%, $p>0.05$), and ACS (2.3% versus 3.5%, $p>0.05$) were similar in both genders. Although the overall mortality during the ten-year follow up period was higher in males (8.3% versus 6.5%, $p>0.05$), the difference was nonsignificant probably due to the small sample size of the mortality cases. Similarly, although the mean age of mortality was lower in males, the difference was nonsignificant (29.0 versus 32.5 years, $p>0.05$), probably due to the small sample size of the mortality cases again (Table 2).

Table 1: Characteristics of the study cases

Variables	Males with the SCD*	*p*-value	Females with the SCD
Prevalence	45.6% (168)		54.3% (200)
Mean age (year)	29.4 ± 9.9 (5-58)	Ns†	30.2 ± 9.9 (8-59)
Associated thalassemia minors	72.0% (121)	Ns	69.0% (138)
BMI‡ (kg/m²)	21.7 ± 3.5 (14.3-32.5)	Ns	21.6 ± 3.7 (14.5-46.4)

*Sickle cell diseases †Nonsignificant (p>0.05) ‡Body mass index

Table 2: Gender differences in associated pathologies of the study cases

Variables	Males with the SCD*	*p*-value	Females with the SCD
Painful crises per year	5.0 ± 7.0 (0-36)	Ns†	5.0 ± 8.7 (0-52)
Total bilirubin (mg/dL)	*5.2 ± 4.9 (0.6-29.0)*	*0.011*	*4.0 ± 3.4 (0.6-22.9)*
Transfused units of RBC‡	*46.8 ± 61.0 (0-434)*	*0.002*	*29.2 ± 36.5 (0-206)*
COPD§	*20.8% (35)*	*<0.001*	*6.0% (12)*
Digital clubbing	*13.0% (22)*	*<0.001*	*5.5% (11)*
PHT¶	10.1% (17)	Ns	12.5% (25)
ACS**	2.3% (4)	Ns	3.5% (7)
Mortality	8.3% (14)	Ns	6.5% (13)
Mean age of mortality (year)	29.0 ± 6.9 (19-42)	Ns	32.5 ± 9.0 (19-47)

*Sickle cell diseases †Nonsignificant (p>0.05) ‡Red blood cells §Chronic obstructive pulmonary disease ¶Pulmonary hypertension **Acute chest syndrome

Discussion

SCD are chronic inflammatory processes on vascular endothelium terminating with an accelerated atherosclerosis induced end-organ failure and a shortened survival in both genders (11, 12). Hemoglobin S (HbS) causes loss of elastic and biconcave disc shaped bodies of RBC. Probably loss of elasticity instead of shape is the major pathology since sickling is rare in peripheric blood samples of the SCD patients with associated thalassemia minors, and human survival is not affected in hereditary spherocytosis or elliptocytosis. Loss of elasticity is present during the whole lifespan but it is exaggerated with inflammations, infections, and various stresses of the body. The abnormally hardened RBC induced chronic endothelial damage, inflammation, edema, and fibrosis terminate with disseminated tissue hypoxia all over the body (13, 14). The SCD may keep vascular endothelium particularly at the capillary level (15), since the capillary system is the main distributor of the abnormally hardened RBC into the tissues. The hardened RBC induced chronic endothelial damage builds up an advanced atherosclerosis in much younger ages of the patients. As a result, mean lifespans of the patients were 42 and 48 years in males and females in the literature, respectively (16), whereas they were 29.0 versus 32.5 years in the present study. The great differences may be secondary to delayed diagnosis, delayed initiation of hydroxyurea therapy, and inadequate RBC supports during emergencies in Turkey (17). Actually, RBC supports must be given immediately during all medical or surgical events in which there is evidence of clinical deterioration in the SCD (8). RBC supports decrease sickle cell concentration in circulation and suppress bone marrow for the production of abnormal RBC. So it decreases sickling-induced endothelial damage, inflammation, and edema all over the body.

COPD is the third leading cause of death with various causes in the world (18). It is an inflammatory disorder that mainly affects the pulmonary vasculature. Aging, smoking, and excess weight may be the major underlying causes of COPD. Regular alcohol consumption may also be important in the inflammatory process of COPD. For example, COPD was one of the most frequent diagnoses in patients with alcohol dependence (19). Furthermore, 30-day readmission rates were higher in the COPD patients with alcoholism (20). Probably an accelerated atherosclerotic process is the major structural background of

functional changes seen in the COPD. The inflammatory process on vascular endothelium is enhanced by release of various chemicals by inflammatory cells, and it terminates with an advanced atherosclerosis, fibrosis, and pulmonary losses. Although the COPD may mainly be an accelerated atherosclerotic process of the pulmonary vasculature, there are several reports about coexistence of associated endothelial inflammation all over the body (21, 22). For example, there may be close relationships between COPD, CHD, PAD, and stroke (23). Furthermore, two-thirds of mortality cases were caused by cardiovascular diseases and lung cancers in the COPD, and the CHD was the most common cause in a multi-center study of 5.887 smokers (24). When the hospitalizations were researched, the most common causes were the cardiovascular diseases again (24). In another study, 27% of all mortality cases were due to the cardiovascular diseases in the moderate and severe COPD patients (25). Similarly, COPD may just be one of the terminal endpoints including priapism, leg ulcers, digital clubbing, CHD, CRD, and stroke in the SCD (26).

Smoking may have a major role in systemic atherosclerotic processes such as COPD, digital clubbing, cirrhosis, CRD, PAD, CHD, stroke, and cancers (27). Its atherosclerotic effects are the most obvious in the Buerger's disease and COPD. Buerger's disease is an inflammatory process terminating with obliterative changes in small and medium-sized vessels, and it has never been reported in the absence of smoking in the literature. Smoking induced endothelial damage probably affects pulmonary vasculature much more than the other organs due to the higher concentration of its products in the respiratory system. But it may even cause cirrhosis, CRD, PAD, CHD, stroke, and cancers with the transport of its products by means of the blood. COPD may also be accepted as a localized Buerger's disease of the lungs. Although its strong atherosclerotic effects, smoking in human beings and nicotine administration in animals may be associated with some weight loss (28). There may be an increased energy expenditure during smoking (29), and nicotine may decrease caloric intake in a dose-related manner (30). Nicotine may lengthen intermeal time, and decrease amount of meal eaten (31). BMI seems to be the highest in former, the lowest in current, and medium in never smokers (32). Similarly, smoking may also show the weakness of volition to control eating, and prevalences of HT, DM, and smoking were the highest in the highest triglyceride having group as a significant parameter of the metabolic syndrome (33). On the other hand, smoking-induced endothelial damage may increase plasma triglycerides (34), since triglycerides may behave as acute phase reactants whose plasma values may not be negatively affected by pathologic weight loss (35, 36). Additionally, although CHD were detected with similar prevalences in both sexes, smoking and COPD were higher in males against the higher prevalences of BMI and its consequences including dyslipidemia, HT, and DM in females (27). Probably tobacco smoke induced acute inflammation on vascular endothelium all over the body is the major cause of loss of appetite, since the body doesn't want to eat during fighting. On the other hand, when we thought of some antidepressant properties of smoking and alcohol, the higher prevalences of them may also show some additional stresses on the male sex in life and a shorthened survival.

Probably alcohol consumption also causes a vascular endothelial inflammation all over the body (37). Similar to the tobacco smoke, alcohol leads to an increased proinflammatory cytokine secretion and reactive oxygen species (ROS) production by tissue macrophages that damage organs via oxidative stresses, and these effects lie far beyond lungs and liver. Against the harmful effects of the ROS, there are various enzymatic and non-enzymatic antioxidants in the body. Enzymatic ones include catalase, superoxide dismutase, glutathione reductase, and glutathione peroxidase, and non-enzymatic ones include glutathione, carotene, bilirubin, tocopherol, uric acid, and metal ions (38). Both tobacco smoke and ethyl alcohol resulted in a change of glutathione levels in serum and tissues in rats (38), and tobacco smoke had the strongest effect on protein nitrozylation in the brain (38). Ethyl alcohol affected glutathione levels in serum, kidney, and brain and superoxide dismutase activity in the brain (38). Vascular endothelial effects of alcohol may even be seen in the absence of a significant liver disease. For example, erectile dysfunction was higher among aborigines with alcohol dependence (39). There was a significant increase in leukocyte adhesion after chronic alcohol exposition in pancreas, and histological changes and cytokine levels correlated with the duration of exposition in rats (40). Probably, cirrhosis also shows a capillary endothelial inflammation terminating with disseminated hepatic destruction, and it may even be accepted as a localized Buerger's disease of the liver caused by alcohol. Stromal cells including hepatic stellate and endothelial cells were proposed to control the balance between hepatic fibrosis and regeneration, but chronic damage eventually leads to progressive substitution of hepatic parenchyma by scar tissue in cirrhosis (41). Although the atherosclerotic effect of alcohol is the most obviously seen in the liver due to the highest concentrations of its products via the portal blood flow there (37), alcohol may even cause COPD, clubbing, CRD, PAD, CHD, stroke, and cancers-like other atherosclerotic endpoints by the transport of its products in the blood.

Digital clubbing is characterized by increase of the normal angle of 165° between nailbed and fold, increased convexity of the nail fold, and thickening of the whole distal finger (42). The exact cause and significance is unknown but chronic tissue hypoxia is highly suspected (43). In the previous study, only 40% of clubbing cases turned out to have significant underlying diseases while 60% remained well over the subsequent years (10). But according to our experiences, digital clubbing is frequently associated with smoking and pulmonary, cardiac, renal, or hepatic disorders those are characterized by chronic tissue hypoxia (3). As an explanation for that hypothesis, lungs, heart, kidneys, and liver are closely related organs those affect their functions in a short period of time. On the other hand, digital clubbing is also common in patients with the SCD and its prevalence was 10.8% in the previous study (44). It probably shows chronic tissue hypoxia caused by disseminated endothelial damage, inflammation, edema, and fibrosis at the capillary level in the SCD. Beside the effects of SCD, smoking, alcohol, cirrhosis, CRD, CHD, and COPD, the higher prevalence of clubbing in males in the present study (13.0% versus 5.5%, $p<0.001$) may also show some additional role of male sex on clubbing.

PHT may also be found among atherosclerotic endpoints of the SCD. PHT is defined as the increased BP in the pulmonary artery, vein, or capillaries. It is observed in 60% of systemic sclerosis, 40% of the SCD, 14% of systemic lupus erythematosus, 21% of rheumatoid arthritis, 5% of portal hypertension, and 0.5% of HIV patients (45). Whereas we detected PHT just in 11.4% (42 cases) of the SCD patients in the present study. Younger mean ages of our study cases (29.4 and 30.2 years of males and females, respectively) may be the cause of the lower prevalence. PHT and COPD may actually have similar atherosclerotic background but PHT may be a more advanced disease since its mean age is higher (34.0 versus 33.6 years), prevalence is lower (12.2% versus 16.3%), and it is nearly equally seen in both genders than the COPD (52.8% versus 78.8% in males) (44). On the other hand, venous PHT is the most commonly seen type in society (46). In venous PHT, left heart fails to pump blood efficiently, leading to pooling of blood in the lungs. This causes pulmonary edema and pleural effusions. In chronic thromboembolic PHT, blood vessels are blocked or narrowed with clots that lead to a similar pathophysiology with arterial PHT (47). In hypoxic PHT, hypoxia is thought to cause vasoconstriction or tightening of pulmonary arteries. This pathophysiology may also be the major underlying mechanism in the SCD due to the inflammated and edematous capillary endothelium secondary to the damage of abnormally hardened RBC in the lungs (48). Whatever the initial cause, PHT involves vasoconstriction or tightening of blood vessels connected to and within lungs. This further increases BP within lungs and impairs their blood flow. Eventually, increased workload of heart causes thickening and enlargement of right ventricle, right heart failure, and cor pulmonale. As blood flowing through lungs decreases, left heart receives less blood. This blood may also carry less oxygen than normal in the SCD due to the capillary endothelial inflammation and edema. Thus it becomes harder and harder for the left heart to pump sufficient oxygen to the rest of body, particularly during physical activity

ACS is responsible for considerable mortality in the SCDs (49). It usually occurs as a single episode, and a past history of an ACS is associated with an early mortality. It is usually seen between the ages of 2 to 4 years, and the risk decreases with age (50). The decreased incidence with age may be due to the excess mortality of the ACS and fewer viral and bacterial episodes in the older age groups due to acquired immunities. The incidence of ACS is more common in sickle cell anemia (Hb SS) cases, and a higher white blood cells (WBC) count is associated with a higher incidence (49, 50). Probably ACS is a sudden onset event without a chronic inflammatory background in the SCD (51). It has a complex nature, and one of the major clinical problems lies in distinguishing between infections, infarctions, and fat embolism in the ACS. For example, ACS did not show an infectious etiology in 66% of episodes (49, 50). Similarly, 12 of 27 episodes of ACS had evidence of fat embolism as the cause (52). But according to our experiences, the increased basal metabolic rate during systemic infections may terminate with the ACS, and the ACS may be characterized by disseminated endothelial damage, fat embolism, and infarctions at the capillary level all over the lungs. A preliminary result from the Multi-Institutional Study of Hydroxyurea indicated a significant reduction of ACS with hydroxyurea in the SCD (53). Hydroxyurea interferes with cell division by blocking the formation of deoxyribonucleotides via inhibition of ribonucleotide reductase (54). The deoxyribonucleotides are the building blocks of DNA. Hydroxyurea mainly affects hyper-proliferating cells. The main action of hydroxyurea is the suppression of leukocytosis and thrombocytosis via blocking the DNA synthesis in the SCD (54). In this way, the continuous inflammatory process of the SCD that initiated at birth on the vascular endothelium is suppressed to some extent. Due to the same action, hydroxyurea is also used in moderate and severe psoriasis to suppress hyper-proliferating skin cells. Similar to the viral hepatitis cases, although presence of a continuous damage of sickle cells on the capillary endothelium, the severity of the destructive process is probably exaggerated by the patients' own immune system, particularly by the actions of WBC and platelets (PLT). So suppression of excessive proliferation of WBC and PLT probably limits the endothelial damage-induced tissue ischemia and infarctions all over the body. Some authors suggested that antibiotics do not shorten the clinical course (8, 55), and RBC transfusions must be given whenever there is evidence of clinical deterioration in the ACS (56). RBC transfusions decrease sickle cell concentration in the circulation and suppress the bone marrow production of abnormal RBC. In this way, they prevent further sickling-induced damage to the lungs or other organs. RBC transfusions should be performed early in the course since they have prophylactic benefit rather than late, when the patient is clearly comatose. According to our ten-year experiences on the SCD, simple and repeated RBC transfusions are superior to exchange. First of all, preparation of one or two units of RBC suspensions at each time rather than preparation of six units or more provides time for clinicians to prepare more units by preventing sudden death of such patients. Secondly, transfusions of one or two units of RBC suspensions at each time decreases the severity of pain, and relaxes anxiety of the patients and surroundings in a short period of time. Thirdly, transfusions of lesser units of RBC suspensions at each time by means of simple transfusions will decrease transfusion-related complications including infections, iron overload, and cross-matching problems in the future. Fourthly, transfusion of RBC suspensions in secondary health centers may prevent some deaths developed during transport to tertiary centers for the exchange.

As a conclusion, SCD are severe inflammatory processes on vascular endothelium, particularly at the capillary level since the capillary system is the main distributor of the hardened RBC into the tissues. The capillary endothelial damage, inflammation, edema, and fibrosis induced hypoxia may be the major underlying cause of COPD in the SCD. Despite the similar BMI and absence of smoking and alcohol, the much higher prevalence of COPD in males may be explained by the dominant role of male sex in life according to the physical power that may accelerate systemic atherosclerotic process all over the body.

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Pulmonary hypertension may not have an atherosclerotic background in sickle cell diseases

Mehmet Rami Helvaci (1)
Zeki Arslanoglu (2)
Atilla Yalcin (1)
Orhan Ekrem Muftuoglu (1)
Abdulrazak Abyad (3)
Lesley Pocock (4)

(1) Specialist of Internal Medicine, MD
(2) Specialist of Dentistrby, PhD
(3) Middle-East Academy for Medicine of Aging, MD
(4) medi-WORLD International

Corresponding author:
Prof Dr Mehmet Rami Helvaci,
07400, ALANYA, Turkey
Phone: 00-90-506-4708759
Email: mramihelvaci@hotmail.com

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ABSTRACT

Background: **We tried to understand the underlying mechanism of pulmonary hypertension (PHT) in the sickle cell diseases (SCD).**

Methods: **All patients with the SCD were included.**

Results: **The study included 434 patients (212 females) with similar mean ages in males and females (30.8 versus 30.3 years, respectively, p>0.05). Smoking (23.8% versus 6.1%, p<0.001) and alcohol (4.9% versus 0.4%, p<0.001) were higher in males, significantly. Transfused units of red blood cells (RBC) in their lives (48.1 versus 28.5, p=0.000), disseminated teeth losses (<20 teeth present) (5.4% versus 1.4%, p<0.001), chronic obstructive pulmonary disease (COPD) (25.2% versus 7.0%, p<0.001), ileus (7.2% versus 1.4%, p<0.001), cirrhosis (8.1% versus 1.8%, p<0.001), leg ulcers (19.8% versus 7.0%, p<0.001), digital clubbing (14.8% versus 6.6%, p<0.001), coronary heart disease (CHD) (18.0% versus 13.2%, p<0.05), chronic renal disease (CRD) (9.9% versus 6.1%, p<0.05), and stroke (12.1% versus 7.5%, p<0.05) were all higher but not PHT (12.6% versus 11.7%, p>0.05) in males, significantly.**

Conclusion: **SCD are severe inflammatory processes on vascular endothelium, particularly at the capillary level since the capillary system is the main distributor of hardened RBC into the tissues. Although the higher smoking, alcohol, and disseminated teeth losses, COPD, ileus, cirrhosis, leg ulcers, digital clubbing, CHD, CRD, and stroke-like atherosclerotic consequences in male sex, PHT was not higher in them in the present study. In another definition, PHT may not have an atherosclerotic background in the SCD. Instead, the hardened RBC-induced capillary endothelial damage, inflammation, edema, and fibrosis around the alveoli may be the major underlying cause.**

Key words: **Sickle cell diseases, chronic endothelial damage, pulmonary hypertension, atherosclerosis, male sex, smoking, alcohol**

Introduction

Chronic endothelial damage may be the leading cause of aging and death by causing persistent tissue hypoxia all over the body. Probably whole afferent vasculature including capillaries are mainly involved in the process since much higher blood pressure (BP) of the afferent vasculature may be the major underlying cause by inducing recurrent endothelial injuries. Therefore the term of venosclerosis is not as famous as atherosclerosis in the literature. Secondary to the chronic endothelial damage, inflammation, edema, and fibrosis, arterial walls become thickened, their lumens are narrowed, and they lose their elastic nature, which reduces blood flow and increases systolic BP further. Some of the well-known accelerators of the life-threatening atherosclerotic process are male sex, physical inactivity, excess weight, smoking, alcohol, and chronic inflammatory and infectious processes including sickle cell diseases (SCD), rheumatologic disorders, tuberculosis, and cancers, for the development of terminal consequences including obesity, hypertension (HT), diabetes mellitus (DM), peripheric artery disease (PAD), chronic obstructive pulmonary disease (COPD), chronic renal disease (CRD), coronary heart disease (CHD), cirrhosis, mesenteric ischemia, osteoporosis, and stroke, all of which terminate with early aging and premature death. They were researched under the title of metabolic syndrome in the literature, extensively (1-3). Although early withdrawal of the causative factors may delay terminal consequences, the endothelial changes cannot be reversed completely after the development of obesity, HT, DM, PAD, COPD, CRD, CHD, or stroke due to their fibrotic nature (4, 5). Similarly, SCD are severe inflammatory processes on vascular endothelium mainly at the capillary level, terminating with an accelerated atherosclerosis induced end-organ failures in early years of life. We tried to understand the underlying mechanism of pulmonary hypertension (PHT) in the SCD.

Material and Methods

The study was performed in the Medical Faculty of the Mustafa Kemal University between March 2007 and June 2016. All patients with the SCD were included into the study. The SCD are diagnosed with the hemoglobin electrophoresis performed via high performance liquid chromatography (HPLC). Medical histories including smoking, alcohol, painful crises per year, transfused units of red blood cells (RBC) in their lives, leg ulcers, stroke, surgical operations, deep venous thrombosis (DVT), epilepsy, priapism, and symptoms of benign prostatic hyperplasia (BPH) including urgency, weak stream, incomplete emptying, and nocturia were learnt. Patients with a history of one pack-year were accepted as smokers, and one drink-year were accepted as drinkers. A complete physical examination was performed by the Same Internist, and patients with disseminated teeth losses (<20 teeth present) were detected. Cases with acute painful crisis or any other inflammatory event were treated at first, and the laboratory tests and clinical measurements were performed on the silent phase. Check up procedures including serum iron, iron binding capacity, ferritin, creatinine, liver function tests, markers of hepatitis viruses A, B, C and human immunodeficiency virus (HIV), a posterior-anterior chest x-ray film, an electrocardiogram, a Doppler echocardiogram both to evaluate cardiac walls and valves and to measure systolic BP of pulmonary artery, an abdominal ultrasonography, a venous Doppler ultrasonography of the lower limbs, a computed tomography (CT) of brain, and a magnetic resonance imaging (MRI) of hips were performed. Other bones for avascular necrosis were scanned according to the patients' complaints. So avascular necrosis of bones was diagnosed via MRI (6). Associated thalassemia minors were detected with serum iron, iron binding capacity, ferritin, and hemoglobin electrophoresis performed via HPLC since the SCD with associated thalassemia minors show a milder clinic than the sickle cell anemia (SCA) alone (7). Systolic BP of the pulmonary artery of 40 mmHg or higher is accepted as PHT (8). The criterion for diagnosis of COPD is post-bronchodilator forced expiratory volume in one second/forced vital capacity of less than 70% (9). Acute chest syndrome is diagnosed clinically with the presence of new infiltrates on chest x-ray film, fever, cough, sputum production, dyspnea, or hypoxia (10). An x-ray film of abdomen in upright position was taken just in patients with abdominal distention or discomfort, vomiting, obstipation, or lack of bowel movement, and ileus is diagnosed with gaseous distention of isolated segments of bowel, vomiting, obstipation, cramps, and with the absence of peristaltic activity on the abdomen. CRD is diagnosed with a persistent serum creatinine level of 1.3 mg/dL or higher in males and 1.2 mg/dL or higher in females. Cirrhosis is diagnosed with physical examination findings, laboratory parameters, and ultrasonographic evaluation. Digital clubbing is diagnosed with the ratio of distal phalangeal diameter to interphalangeal diameter which is greater than 1.0, and with the presence of Schamroth's sign (11, 12). An exercise electrocardiogram is performed in cases with an abnormal electrocardiogram and/or angina pectoris. Coronary angiography is taken for the exercise electrocardiogram positive cases. So CHD was diagnosed either angiographically or with the Doppler echocardiographic findings as the movement disorders in the cardiac walls. Rheumatic heart disease is diagnosed with the echocardiographic findings, too. Stroke is diagnosed by the CT of brain. Sickle cell retinopathy is diagnosed with ophthalmologic examination in patients with visual complaints. Eventually, the mean age, associated thalassemia minors, smoking, alcohol, painful crises per year, transfused units of RBC in their lives, and consequences of the SCD were detected in both genders, and compared in between. Additionally, mean ages of the consequences were calculated. Mann-Whitney U test, Independent-Samples t test, and comparison of proportions were used as the methods of statistical analyses.

Results

The study included 434 patients with the SCD (222 males and 212 females). Mean ages of the patients were similar in males and females (30.8 versus 30.3 years, respectively, $p>0.05$). Prevalence of associated thalassemia minors were similar in both genders, too (72.5% versus 67.9%, respectively, $p>0.05$). Smoking (23.8% versus 6.1%) and alcohol (4.9% versus 0.4%) were higher in males, significantly ($p<0.001$ for both) (Table 1).

Similarly, transfused units of RBC in their lives (48.1 versus 28.5, $p=0.000$), disseminated teeth loss (<20 teeth present) (5.4% versus 1.4%, $p<0.001$), COPD (25.2% versus 7.0%, $p<0.001$), ileus (7.2% versus 1.4%, $p<0.001$), cirrhosis (8.1% versus 1.8%,

p<0.001), leg ulcers (19.8% versus 7.0%, p<0.001), digital clubbing (14.8% versus 6.6%, p<0.001), CHD (18.0% versus 13.2%, p<0.05), CRD (9.9% versus 6.1%, p<0.05), and stroke (12.1% versus 7.5%, p<0.05) were all higher in male sex, significantly. There were 11 males (4.9%) with symptoms of BPH with a mean age of 41.5 ± 10.6 (27-58) years. Additionally, there were 23 males (10.3%) with priapism with a mean age of 33.4 ± 7.9 (18-51) years. There were 31 mortality cases (17 males and 14 females) during the ten-year follow up period. The mean ages of mortality were 30.2 ± 8.4 (19-50) in males and 33.3 ± 9.2 (19-47) years in females (p>0.05) (Table 2). On the other hand, when we look at the mean ages of the consequences, PHT (34.0 years), leg ulcers (35.3 years), digital clubbing (35.4 years), CHD (35.7 years), DVT and/or varices and/or telangiectasias (37.0 years), cirrhosis (37.0 years), CRD (39.4 years), and BPH (41.5 years) may indicate advanced diseases in such patients due to the significantly shortened survival of the SCD in both genders (Table 3).

Table 1: Characteristic features of the study cases

Variables	Male patients with SCD*	*p*-value	Female patients with SCD
Prevalence	51.1% (222)	Ns†	48.8% (212)
Mean age (year)	30.8 ± 10.0 (5-58)	Ns	30.3 ± 9.9 (8-59)
Associated thalassemia minors	72.5% (161)	Ns	67.9% (144)
Smoking	***23.8% (53)***	*<0.001*	***6.1% (13)***
Alcoholism	***4.9% (11)***	*<0.001*	***0.4% (1)***

*Sickle cell diseases †Nonsignificant (p>0.05)

Table 2: Associated pathologies of the study cases

Variables	Male patients with SCD*	*p*-value	Female patients with SCD
Painful crises per year	5.0 ± 7.1 (0-36)	Ns†	4.9 ± 8.6 (0-52)
Transfused units of RBC‡	***48.1 ± 61.8 (0-434)***	*0.000*	***28.5 ± 35.8 (0-206)***
Disseminated teeth losses (<20 teeth present)	***5.4% (12)***	*<0.001*	***1.4% (3)***
COPD§	***25.2% (56)***	*<0.001*	***7.0% (15)***
Ileus	***7.2% (16)***	*<0.001*	***1.4% (3)***
Cirrhosis	***8.1% (18)***	*<0.001*	***1.8% (4)***
Leg ulcers	***19.8% (44)***	*<0.001*	***7.0% (15)***
Digital clubbing	***14.8% (33)***	*<0.001*	***6.6% (14)***
CHD¶	***18.0% (40)***	*<0.05*	***13.2% (28)***
*CRD***	***9.9% (22)***	*<0.05*	***6.1% (13)***
Stroke	***12.1% (27)***	*<0.05*	***7.5% (16)***
PHT***	12.6% (28)	Ns	11.7% (25)
Autosplenectomy	50.4% (112)	Ns	53.3% (113)
DVT**** and/or varices and/or telangiectasias	9.0% (20)	Ns	6.6% (14)
Rheumatic heart disease	6.7% (15)	Ns	5.6% (12)
Avascular necrosis of bones	24.3% (54)	Ns	25.4% (54)
Sickle cell retinopathy	0.9% (2)	Ns	0.9% (2)
Epilepsy	2.7% (6)	Ns	2.3% (5)
Acute chest syndrome	2.7% (6)	Ns	3.7% (8)
Mortality	7.6% (17)	Ns	6.6% (14)
Mean age of mortality (year)	30.2 ± 8.4 (19-50)	Ns	33.3 ± 9.2 (19-47)

*Sickle cell diseases †Nonsignificant (p>0.05) ‡Red blood cells §Chronic obstructive pulmonary disease ¶Coronary heart disease **Chronic renal disease ***Pulmonary hypertension ****Deep venous thrombosis

Table 3: Mean ages of the consequences of the sickle cell diseases

Variables	Mean age (year)
Ileus	29.8 ± 9.8 (18-53)
Hepatomegaly	30.2 ± 9.5 (5-59)
Acute chest syndrome	30.3 ± 10.0 (5-59)
Sickle cell retinopathy	31.5 ± 10.8 (21-46)
Rheumatic heart disease	31.9 ± 8.4 (20-49)
Autosplenectomy	32.5 ± 9.5 (15-59)
Disseminated teeth losses (<20 teeth present)	32.6 ± 12.7 (11-58)
Avascular necrosis of bones	32.8 ± 9.8 (13-58)
Epilepsy	33.2 ± 11.6 (18-54)
Priapism	33.4 ± 7.9 (18-51)
Left lobe hypertrophy of the liver	33.4 ± 10.7 (19-56)
Stroke	33.5 ± 11.9 (9-58)
COPD*	33.6 ± 9.2 (13-58)
PHT†	*34.0 ± 10.0 (18-56)*
Leg ulcers	*35.3 ± 8.8 (17-58)*
Digital clubbing	*35.4 ± 10.7 (18-56)*
CHD‡	*35.7 ± 10.8 (17-59)*
DVT§ and/or varices and/or telangiectasias	*37.0 ± 8.4 (17-50)*
Cirrhosis	*37.0 ± 11.5 (19-56)*
CRD¶	*39.4 ± 9.7 (19-59)*
*BPH***	*41.5 ± 10.6 (27-58)*

*Chronic obstructive pulmonary disease †Pulmonary hypertension ‡Coronary heart disease §Deep venous thrombosis ¶Chronic renal disease **Benign prostatic hyperplasia

Discussion

SCD are chronic inflammatory processes on vascular endothelium terminating with accelerated atherosclerosis induced end-organ failures and a shortened survival in both genders (13, 14). Hemoglobin S causes loss of elastic and biconcave disc shaped structures of RBC. Probably loss of elasticity instead of shape is the main pathology since sickling is rare in peripheric blood samples of the SCD patients with associated thalassemia minors, and human survival is not affected in hereditary spherocytosis or elliptocytosis. Loss of elasticity is present during the whole lifespan, but exaggerated with inflammation, infection, or various stresses of the body. The abnormally hardened RBC induced chronic endothelial damage, inflammation, edema, and fibrosis terminate with disseminated tissue hypoxia all over the body (15, 16). As a difference from other causes of chronic endothelial damage, the SCD may keep vascular endothelium particularly at the capillary level (17), since the capillary system is the main distributor of the abnormally hardened RBC into the tissues. The hardened cells induced chronic endothelial damage builds up an advanced atherosclerosis in much younger ages of the patients. As a result, the mean lifespans of the patients were 42 and 48 years in males and females in the literature, respectively (18), whereas they were 30.2 and 33.3 years in the present study. The great differences may be secondary to delayed diagnosis, delayed initiation of hydroxyurea therapy, and inadequate RBC supports during emergencies in Turkey (19). Actually, RBC supports must be given immediately during all medical or surgical events in which there is evidence of clinical deterioration in the SCD (10). RBC supports decrease sickle cell concentration in circulation and suppress bone marrow for the production of abnormal RBC. So it decreases sickling-induced endothelial damage, inflammation, edema, and tissue hypoxia all over the body.

PHT is found among the terminal consequences of the SCD (20). PHT is defined as the increased BP in pulmonary artery, vein, or capillaries. It is seen in 60% of systemic sclerosis, 40% of the SCD, 14% of systemic lupus erythematosus, 21% of rheumatoid arthritis, 5% of portal HT, and 0.5% of HIV patients (21). Whereas we detected PHT just in 12.2% of the SCD patients in the present study. The relatively younger mean ages of our patients (30.8 years of males versus 30.3 years of females) may be a cause of the lower prevalence. Although the highly atherosclerotic background of the COPD, PHT may actually have a different underlying mechanism in the SCD since its mean age is higher (34.0 versus 33.6 years), prevalence is lower (12.2% versus 16.3%), and it is equally seen in both genders than the COPD (52.8% versus 78.8% in males) in the present study. Additionally, although the higher prevalences of smoking, alcohol, and disseminated teeth losses, ileus, cirrhosis, leg ulcers, digital clubbing, CHD, CRD, and stroke-like other atherosclerotic consequences in male sex, the prevalence

of PHT was not higher in males with the SCD, significantly (12.6% versus 11.7%, respectively, p>0.05). On the other hand, venous PHT is the most common cause of PHT in the society (22). In venous PHT, left heart fails to pump blood efficiently, leading to the pooling of blood in the lungs. This causes pulmonary edema and pleural effusions. In chronic thromboembolic PHT, blood vessels are blocked or narrowed with clots, which leads to a similar pathophysiology with arterial PHT (23). In hypoxic PHT, hypoxia is thought to cause vasoconstriction of the pulmonary arteries. This pathophysiology may also be the major underlying mechanism in the SCD due to the inflammated and edematous capillary endothelium around the alveoli secondary to the damage of abnormally hardened RBC (24). Whatever the initial cause, PHT involves vasoconstriction of blood vessels connected to and within lungs. This further increases BP within lungs and impairs their blood flow. Eventually, increased workload of the heart causes thickening and enlargement of the right ventricle, right heart failure, and cor pulmonale. As blood flowing through lungs decreases, left heart receives less blood. This blood may also carry less oxygen than normal as in the SCD due to the capillary endothelial inflammation and edema around the alveoli. Thus it becomes harder and harder for the left heart to pump sufficient oxygen to the rest of body, particularly during physical activity. Although the possible arterial and venous involvement mechanisms, capillary endothelial damage, inflammation, edema, and fibrosis around the alveoli may be the main cause of PHT in the SCD since the capillary system is the main distributor of the abnormally hardened RBC into the lungs.

COPD is the third leading cause of death with various causes and pathophysiologic mechanisms in the world (25). It is an inflammatory disease that mainly affects the pulmonary vasculature. Aging, smoking, and excess weight may be the major underlying causes. As also observed in the present study, regular alcohol consumption may also be important in the inflammatory process. For example, COPD was one of the most common diagnoses in patients with alcohol dependence (26). Furthermore, 30-day readmission rates were higher in the COPD patients with alcoholism (27). Probably an accelerated atherosclerotic process is the main structural background of functional changes, characteristics of the COPD. The inflammatory process of vascular endothelium is enhanced by release of various chemicals by inflammatory cells, and it terminates with an advanced atherosclerosis, fibrosis, and pulmonary losses. Although the COPD may mainly be an accelerated atherosclerotic process of the pulmonary vasculature, there are several reports about coexistence of associated endothelial inflammation all over the body (28, 29). For example, there may be close relationships between COPD, CHD, PAD, and stroke (30). Furthermore, two-thirds of mortality cases were caused by cardiovascular diseases and lung cancers in the COPD, and the CHD was the most common cause in a multi-center study of 5,887 smokers (31). When the hospitalizations were researched, the most common causes were the cardiovascular diseases again (31). In another study, 27% of mortality cases were due to the cardiovascular diseases in the moderate and severe COPD cases (32). As a result, COPD is one of the terminal consequences of the SCD due to the higher prevalences of priapism, leg ulcers, digital clubbing, CHD, CRD, and stroke in the SCD patients with COPD (33).

Digital clubbing is characterized by increase of the normal angle of 165° between nailbed and fold, increased convexity of the nail fold, and thickening of the whole distal finger (34). The exact cause and significance is unknown but chronic tissue hypoxia is highly suspected (35). In the previous study, only 40% of clubbing cases turned out to have significant underlying diseases while 60% remained well over the subsequent years (12). But according to our experiences, digital clubbing is frequently associated with smoking alone and with pulmonary, cardiac, renal, or hepatic disorders that are characterized with chronic tissue hypoxia (4). As an explanation for that hypothesis, lungs, heart, kidneys, and liver are closely related organs that affect their functions in a short period of time. On the other hand, digital clubbing is also common in patients with the SCD and its prevalence was 10.8% in the present study. It probably shows chronic tissue hypoxia caused by disseminated endothelial damage, inflammation, edema, and fibrosis at the capillary level in the SCD. Beside the effects of SCD, smoking, alcohol, cirrhosis, CRD, CHD, and COPD, the higher prevalence of digital clubbing in males (14.8% versus 6.6%, p<0.001) may also show some additional role of male sex on clubbing.

Leg ulcers are seen in 10-20% of patients with the SCD (36), and the ratio was 13.5% in the present study. Its incidence increases with age, male sex, and SCA (37). Similarly, its ratio was higher in males (19.8% versus 7.0%, p<0.001), and mean age of the patients with leg ulcers was significantly higher than the others (35.3 versus 29.8 years, p<0.000) in the present study. The leg ulcers have an intractable nature, and around 97% of healed ulcers relapse in a period of one year (36). As evidence of their atherosclerotic nature, the leg ulcers occur in distal areas with less collateral blood flow in the body (36). The abnormally hardened RBC induced chronic endothelial damage, inflammation, edema, and fibrosis at the capillary level may be the major underlying cause in the SCD (37). Prolonged exposure to the hardened bodies due to the pooling of blood in the lower extremities may also explain the leg but not arm ulcers in the SCD. The hardened RBC induced venous insufficiencies may also accelerate the process by pooling of causative hardened bodies in the legs, and vice versa. Pooling of blood may also have some effects on development of venous ulcers, diabetic ulcers, Buerger's disease, digital clubbing, and onychomycosis in the lower extremities. Furthermore, probably pooling of blood is the cause of delayed wound and fracture healings in the lower extremities. Beside the hardened bodies, smoking and alcohol may also have some additional effects on the leg ulcers since both of them are much more common in males. Hydroxyurea is the only drug that was approved by Food and Drug Administration for the treatment of SCD (17). It is an orally-administered, cheap, safe, and effective drug that blocks cell division by suppressing formation of deoxyribonucleotides which are the building blocks of DNA (19). Its main action may be the suppression of hyperproliferative white blood cells (WBC) and platelets (PLT) in the SCD (38). Although presence of a continuous damage of hardened RBC on vascular endothelium, severity of the destructive process is probably exaggerated by the patient's own immune system. Similarly, lower WBC counts were associated with lower crises rates, and if a tissue infarct occurs, lower WBC counts may decrease severity of pain and tissue damage (39). According to our ten-year experience, prolonged resolution of leg ulcers with

hydroxyurea therapy may also suggest that the leg ulcers may be secondary to the increased WBC and PLT counts induced prolonged endothelial damage, inflammation, and edema at the capillary level in the SCD.

Both frequency and complications of cirrhosis are increasing in the world, and it was the 10th leading cause of death for men and the 12th for women in the United States in 2001 (5). Although the improvements of health services worldwide, the increased morbidity and mortality of cirrhosis may be explained by prolonged survival of the human being and increased prevalence of excess weight all over the world. For example, nonalcoholic fatty liver disease (NAFLD) affects up to one third of the world population, and it has become the most common cause of chronic liver disease even at childhood at the moment (40). NAFLD is a marker of pathological fat deposition combined with a low-grade chronic inflammation, which results with hypercoagulability, endothelial dysfunction, and an accelerated atherosclerosis (40). Beside terminating with cirrhosis, NAFLD is associated with higher overall mortality rates as well as increased prevalence of cardiovascular diseases (41). Authors reported independent associations between NAFLD and impaired flow-mediated vasodilation and increased mean carotid artery intima-media thickness (CIMT) (42). NAFLD may be considered as the hepatic consequences of the metabolic syndrome and SCD (13, 43). Probably smoking also takes a role in the endothelial inflammatory process of the liver, since the systemic inflammatory effects of smoking on endothelial cells is well-known with Buerger's disease and COPD (44). Increased oxidative stresses, inactivation of antiproteases, and release of proinflammatory mediators may terminate with a systemic atherosclerosis in smokers. The atherosclerotic effects of alcohol is much more prominent in hepatic endothelium probably due to the highest concentrations of its metabolites in the liver. Chronic infectious and inflammatory processes may also terminate with an accelerated atherosclerosis all over the body (45). For example, chronic hepatitis C virus (HCV) infection raised CIMT, and normalization of hepatic function with HCV clearance may be secondary to reversal of favourable lipids observed with the chronic infection (45, 46). As a result, beside COPD, ileus, leg ulcers, digital clubbing, CHD, CRD, and stroke, cirrhosis may also be found among the atherosclerotic consequences of the metabolic syndrome and SCD.

Both frequency and complications of CRD are increasing all over the world, too (47). The increased frequency and complications of CRD may be explained by aging of the societies and increased prevalence of excess weight all over the world, since CRD may also be found among the atherosclerotic consequences of the metabolic syndrome (48). Aging, physical inactivity, excess weight, smoking, alcohol, and inflammatory and infectious processes may be the major underlying causes of the endothelial inflammation in the kidneys. The inflammatory process is enhanced by release of various chemicals by lymphocytes to repair the damaged renal tissues, especially endothelial cells of the renal arteriols. Due to the continuous irritation of the endothelial cells in the above pathologies, prominent changes develop in the architecture of the renal tissues with advanced atherosclerosis, fibrosis, and tissue hypoxia and infarcts. Excess weight induced metabolic abnormalities such as hyperglycemia, dyslipidemia, elevated BP, and insulin resistance may cause various cellular stresses during acceleration of tissue inflammation and immune cell activation (49). For example, age ($p= 0.04$), high-sensitivity C-reactive protein ($p= 0.01$), mean arterial BP ($p= 0.003$), and DM ($p= 0.02$) had significant correlations with the CIMT (48). Increased renal tubular sodium reabsorption, impaired pressure natriuresis, volume expansion due to the activations of sympathetic nervous system and renin-angiotensin system, and physical compression of kidneys by visceral fat tissue may be some mechanisms of the increased BP with excess weight (50). Excess weight also causes renal vasodilation and glomerular hyperfiltration that initially serve as compensatory mechanisms to maintain sodium balance due to the increased tubular reabsorption (50). However, along with the increased BP, these changes cause a hemodynamic burden on the kidneys in the long term that causes chronic endothelial damage (51). With prolonged weight excess, there are increased urinary protein excretion, loss of nephron function, and exacerbated HT. With the development of dyslipidemia and DM in the overweight and obese individuals, CRD progresses much more easily (50). On the other hand, the systemic inflammatory effects of smoking on endothelial cells may also be important in the etiology of CRD (52). The inflammatory and atherosclerotic effects of smoking are much more prominent in the respiratory endothelium due to the highest concentrations of its metabolites there. Although some authors reported that alcohol was not related with the CRD (52), it is not logical since various metabolites of alcohol circulate even in the blood vessels of the kidneys and give harm to the renal vascular endothelium. Chronic inflammatory and infectious disorders may also terminate with the accelerated atherosclerosis on the renal endothelium (45). Although CRD is mainly an advanced atherosclerotic process of the renal vasculature, there are close relationships between CRD and other consequences of the metabolic syndrome including CHD, COPD, PAD, cirrhosis, and stroke (53). For example, the most common cause of death in the CRD is cardiovascular diseases rather than the renal failure again (54). In another definition, CRD may also be found among the atherosclerotic consequences of the metabolic syndrome and SCD, again (55).

Stroke is an important cause of death, and thromboembolism in the background of atherosclerosis is the most common cause of it. Aging, male sex, smoking, increased serum glucose and lipids, elevated arterial BP, and excess weight may be the major accelerator factors of it. Stroke is also a common complication of the SCD (56, 57). Similar to the leg ulcers, stroke is higher in SCA cases (58). Additionally, a higher WBC count is associated with a greater incidence of stroke (38). Sickling induced endothelial damage, activations of WBC, PLT, and coagulation system, and hemolysis may terminate with chronic endothelial inflammation, edema, remodeling, and fibrosis (59). Probably, stroke is a complex and terminal event in the SCD, and it may not have a macrovascular origin, instead disseminated capillary inflammation induced endothelial edema may be much more important. Infections and other stressful conditions may precipitate stroke, since increased metabolic rate during such episodes may accelerate sickling. A significant reduction of stroke with hydroxyurea may also suggest that a significant proportion of strokes is secondary to the increased WBC and PLT counts induced disseminated capillary inflammation and edema (60).

Although the presence of an accelerated atherosclerotic process, the venous endothelium is also involved in the SCD (61). For example, varices are abnormally dilated veins with tortuous courses, and they usually occur in the lower extremities. Related factors include aging, obesity, menopause, pregnancy, and heredity. Normally, leg muscles pump veins to return blood against the gravity, and the veins have pairs of leaflets of valves to prevent blood from flowing backwards. When the leaflets are damaged, varices and/or telangiectasias develop. DVT may also cause varicose veins. Varicose veins are the most common in superficial veins of the legs, which are subject to higher pressure when standing up, thus patient's physical examination must be performed in upright position. Although the relatively younger mean ages of the patients in the present study (30.8 and 30.3 years in males and females, respectively) and significantly lower body mass index of the SCD cases in the literature (16), DVT and/or varices and/or telangiectasias of the lower limbs were higher in the study cases (9.0% versus 6.6% in males and females, respectively, $p>0.05$) indicating an additional venous endothelial involvement in the SCD (61). Similarly, priapism is the painful erection of penis that cannot return to its flaccid state within four hours in the absence of any stimulation (62). It is an emergency since damage to the blood vessels may terminate with a long-lasting fibrosis of the corpus cavernosa, a consecutive erectile dysfunction, and eventually a shortened, indurated, and non-erectile penis (62). It is seen with hematological and neurologic disorders including SCD, leukemia, thalassemia, Fabry's disease, spinal cord lesions (hanging victims), and glucose-6-phosphate dehydrogenase deficiency (63, 64). Ischemic (veno-occlusive and low flow), stuttering (recurrent ischemic), and nonischemic priapisms (arterial and high flow) are the three types of priapism (65). Ninety-five percent of clinically presented priapisms are the ischemic or low-flow disorders in which blood cannot return adequately from the penis into the body as in the SCD, and they are very painful (62, 65). The other 5% are nonischemic high-flow type usually caused by a blunt perineal trauma in which there is a short circuit of the vascular system of the penis (62). Treatment of high-flow type is not as urgent as the low-flow type due to the absence of risk of ischemia (62). RBC support is the treatment of choice in acute phase in the SCD (66). Whereas in the chronic phase, hydroxyurea should be the treatment of choice of the priapism in the SCD. According to our ten-year experiences, hydroxyurea is an effective drug for prevention of attacks and consequences of priapism if iniatiated in early years of life, but it may be difficult due to the excessive fibrosis around the capillary walls if initiated later in life.

As a conclusion, SCD are severe inflammatory processes on vascular endothelium, particularly at the capillary level since the capillary system is the main distributor of hardened RBC into the tissues. Although the higher smoking, alcohol, and disseminated teeth losses, COPD, ileus, cirrhosis, leg ulcers, digital clubbing, CHD, CRD, and stroke-like atherosclerotic consequences in male sex, PHT was not higher in them in the present study. In another definition, PHT may not have an atherosclerotic background in the SCD. Instead, the hardened RBC-induced capillary endothelial damage, inflammation, edema, and fibrosis around the alveoli may be the major underlying cause.

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Frailty : Update on Diagnosis Evaluation and Management Part 1

Abdulrazak Abyad (1)
Sonia Ouali Hammami (2)

(1) CEO, Abyad Medical Center, Lebanon.
Chairman, Middle-East Academy for Medicine of Aging,. President, Middle East & North Africa Association on Aging & Alzheimer's, Coordinator, Middle-East Primary Care Research Network Coordinator, Middle-East Network on Aging,
(2) Internal Medicine Department-Endocrinology, Geriatric Unit, CHU F Bourguiba Monastir, Research Lab : Human Nutrition & metabolic disorder, University of Monastir, Tunisia

Corresponding author:
Dr Abdulrazak Abyad,
Email: aabyad@cyberia.net.lb; amcmeli@gmail.com

Corresonding author:
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ABSTRACT

Life expectancy continues to rise globally. However, the additional years of life do not always correspond to years of healthy life, which may result in an increase in frailty. Given the rapid aging of the population, the association between frailty and age, and the impact of frailty on adverse outcomes for older adults, frailty is increasingly recognized as a significant public health concern. Early detection of the condition is critical for assisting older adults in regaining function and avoiding the negative consequences associated with the syndrome. Despite the critical nature of frailty diagnosis, there is no conclusive evidence or consensus regarding whether routine screening should be implemented. A variety of screening and assessment instruments have been developed from a biopsychosocial perspective, with frailty defined as a dynamic state caused by deficits in any of the physical, psychological, or social domains associated with health. All of these aspects of frailty should be identified and addressed through the use of a comprehensive and integrated approach to care. To accomplish this goal, public health and primary health care (PHC) must serve as the fulcrum around which care is delivered, not just to the elderly and frail, but to all individuals, by emphasizing a life-course and patient-centered approach centered on integrated, community-based care. Personnel in public health should be trained to address frailty not just clinically, but also in a societal context. Interventions should take place in the context of the individuals' environment and social networks. Additionally, public health professionals should contribute to community-based frailty education and training, promoting community-based interventions that assist older adults and their caregivers in preventing and managing frailty. The purpose of this paper is to provide an overview of frailty for a public health audience in order to increase awareness of the multidimensional nature of frailty and how it should be addressed through an integrated and holistic approach to care.

Key words: **Frailty, diagnosis, evaluation, management**

Introduction

• There is currently no consensus on a definition or clinical tool for frailty, and there is insufficient evidence to guide primary care frailty case finding and management.

• While studies have demonstrated that frailty increases the likelihood of medical complications, disability, institutionalization, or even death, evidence regarding how well frailty predicts adverse outcomes at the individual patient level is lacking.

• Screening for frailty in primary care will be justified only after sufficient evidence of interventions that improve clinical and patient-centered outcomes becomes available.

One of the century's major achievements is the continued increase in life expectancy.

The world is aging at a breakneck pace. There are currently 703 million people aged 65, according to the United Nations Department of Economic and Social Affairs' "World Population Aging 2019" report. By 2050, this figure is expected to reach 1.5 billion, or one in every six people, up from one in every 11 in 2019 (1). Similarly, the number of people over the age of 80 is expected to triple in the next 30 years, while life expectancy after 65 is expected to increase by 19 years (1). However, the additional years of life do not always correspond to years of healthy life. According to Eurostat's most recent figures for 2020, the proportion of healthy life years in the European Union (EU) accounts for approximately 76.7 and 81.4 percent of total life expectancy for women and men, respectively (2). The decline in healthy life years is accompanied by an increase in frailty, multimorbidity, and disability (3), all of which contribute to older adults' frequent use of healthcare services (4). All of the conditions listed above have the potential to impair multiple domains of health (physical, psychological, cognitive, and social), necessitating holistic care for complex needs resulting from multiple determinants of health.

The aging of the population is bringing about changes and challenges that necessitate a comprehensive public health response. The challenge is to ensure that people can live longer while also remaining healthy, active, and self-sufficient. The challenge is to establish sustainable and efficient health and care systems capable of dealing with the prospect of an increase in chronic diseases, cognitive decline, or dependency, as well as the associated consequences.

The frailty of the elderly is a distinguishing feature (5). Frailty has long been a part of the everyday lexicon. 'How easily a frail tree is overturned by the wind,' Buddha reflected some 2500 years ago (6). This historical ubiquity has resulted in an inherited proclivity for recognizing frailty. Frailty, on the other hand, has only recently been brought into focus for more rigorous medical definition as a result of a shift in emphasis away from single-system conditions and toward unifying constructs for holistic patient care.

Frailty is a physiological state of vulnerability caused by dysregulation in multiple physiological systems. It results in a decrease in an individual's functional capacity and resilience to external stressors, resulting in increased rates of illness, disability, and death (3), (7), (8).

Frailty can occur at any age and is frequently triggered by specific circumstances such as malnutrition or chronic disease states such as diabetes, chronic obstructive pulmonary disease,[9] chronic heart failure,[10], or HIV infection (11–13). While it is tempting to view frailty as an inevitable consequence of aging, associated with an increased risk of poor health outcomes,[14] a distinction must be made between an individual's chronological and biological ages, as some individuals may remain robust and disability-free well into their advanced years. Individual-level factors such as resilience (physical and mental), external supports, and other forms of intrinsic capacity[18] can help moderate frailty, and these must also be considered when examining clinical practice-based pathways to alleviate frailty [20].

Frailty is increasing in prevalence. Around 10% of people over the age of 65 and 25%–50% of those over the age of 85 are frail (20). Age-related frailty, disability, and suffering are major priorities for our society and health and care systems. Care delivery in an efficient manner that is tailored to individual needs and social circumstances is an unavoidable responsibility for policymakers and management teams. The critical mass of experiences and knowledge generated by already-implemented interventions, contributes to paving the way toward that goal.

Frailty has compelled a number of countries to make fundamental changes to their national health policies. For example, since 2017, England's new General Medical Services (GMS) contract requires all primary care practices to use an appropriate tool to identify patients aged 65 with moderate or severe frailty. Due to the complexity of frailty, healthcare professionals face difficulties in identifying and managing this condition (HCPs). To meet these challenges, countries must develop a health workforce equipped with the appropriate skill mix. A goal-oriented education and training of health care professionals is critical for the effective and efficient delivery of health care to the world's aging population (21).

Thus, screening and monitoring for changes in older people's individual resilience is critical for early intervention in order to avoid a loss of functional and cognitive reserve and to maintain self-capacity for this growing population of older citizens (22).

Frailty - What is it?

Frailty is a multifaceted age-related syndrome that lacks a widely accepted definition (23,24). It is caused by a decline in multiple physiological systems, resulting in an increased susceptibility to stressor events and an impaired ability to maintain homeostasis (25). These triggers can include a chronic condition deteriorating (26), environmental factors (27), a change in therapy (3), or adverse life events (28). Frailty is characterized by a progressive decline in physiological reserve in older adults (29). Frailty is also associated with an increased risk of adverse outcomes (30), including falls (31), fractures (32), disability (31), delirium (33), depression (34), cognitive impairment (35), hospitalizations (36, 37), need for long-term care (31), poor

quality of life (38), shortened life expectancy, and premature death (39). While research into frailty is ongoing, certain tenets of the condition have been established: it is an age-related condition (40), though it is not a necessary consequence of the aging process (41). It is multidimensional, affecting multiple domains of health, including the physical, psychological, cognitive, social, emotional, spiritual, economic, and nutritional domains (41, 42, 43). It is a dynamic and reversible state, at least in its early stages (44), in which individuals can fluctuate between states of robustness and frailty until their physiological reserve is depleted and recovery to their baseline status is impossible (45). Additionally, reversing frailty is more common than transitioning to more severe levels of frailty. Given that frailty reflects biological rather than chronological age (46, 47), it is critical to identify biomarkers for this condition. However, biomarkers that more accurately reflect biological age than chronological age are currently unavailable (48). These may also aid in objectively identifying frailty and contributing to a better understanding of its pathophysiology.

Transition to Frailty

Because frailty transitions should ideally indicate changes in physiological reserve and function, accurately characterizing them may eventually provide a means of detecting and delineating these underlying changes. Although various transitions between frailty states were observed, the most frequently observed transition was a worsening of frailty, as previously discovered (49). Pre-frailty was found to be extremely prevalent (46%) and was associated with a higher risk of adverse outcomes than being non-frail (0.12 odds of death vs 0.05 in non-frail), as well as an increased risk of becoming frail (0.17 odds of frailty vs 0.03 in non-frail). This information, combined with the finding that frail individuals are more likely to die (0.28 vs. 0.16), suggests that pre-frail individuals are the optimal target for frailty intervention and prevention, but pre-frail individuals are not always easily identifiable in the clinical setting. As a result, although screening for frailty in the clinical setting is not routine clinical practice, it is becoming increasingly recognized as critical for identifying vulnerable older adults (50).

While the association between COPD and frailty may seem intuitive given the well-characterized clinical manifestations of pulmonary cachexia syndrome, obesity, insulin resistance, and diabetes mellitus are emerging risk factors for sarcopenia and frailty (51). Given the high prevalence of diabetes mellitus and prediabetes among older adults, frailty screening may be especially beneficial in identifying those at greatest risk of decline. Additionally, the study's finding that increased leg power was associated with improved frailty suggests that exercise, a critical component of lifestyle modification in individuals with prediabetes or diabetes mellitus, may help prevent frailty in older adults (52).

As noted in a recent review(53), measurement precision for phenotypic frailty measures such as those used by Pollack and colleagues has received scant attention (54). Gill and colleagues evaluated interrater test–retest agreement in a study of frailty transitions and hospitalization; they reported a kappa statistic of 0.78 for frailty measurements taken three days apart—an impressive overall agreement of roughly 90% at the study's observed 26% frailty prevalence. Apart from agreement, the accuracy with which observed criteria measure an underlying trait or state of frailty is also critical. In the Study of Health, Ageing, and Retirement in Europe, Theou and colleagues reported a Cronbach alpha of 0.47 for frailty phenotype measurements, indicating only moderate trait measurement reliability. Using latent class analyses (LCAs) of data from the Women's Health and Aging Study, Xue and colleagues (55) estimated the positive predictive value of a phenotype measurement for detecting frailty to be 53%. (56). These LCAs indicated a significant over-representation of prefrail assessment in frail and robust states. As such, we found it intriguing that Pollack and colleagues discovered near equality in the rates of improvement from frail to prefrail status, prefrail to robust status, and progression from prefrailty to frailty between Visits 1 and 2 (range 15.0–17.4 percent). We believe that additional research is necessary to distinguish between phenotypic transitions that represent meaningful frailty change and those that are spurious or indicative of non-frailty related change. Additionally, we acknowledge that, in addition to the phenotypic method, there are a variety of other approaches to frailty assessment (57) that complicate measurement.

Models of Frailty

The physical frailty and deficit accumulation models of frailty are the two most frequently used approaches for classifying frailty. The Frailty Physical Phenotype was first proposed by Fried et al. (58), who used the Cardiovascular Health Study to define the "frailty phenotype" by identifying five physical components: exhaustion (self-reported), low physical activity, weakness (low grip strength), slow gait speed, and shrinking (unintentional weight loss of 5% in the preceding year), the presence of which in number 3 indicates frailty. When only one or two criteria are met, individuals are classified as pre-frail, whereas when no components are present, individuals are classified as robust. Rockwood and Mitnitski (59) and Mitnitski et al. (60) validated the cumulative deficit model using data from the Canadian Study of Health and Aging to develop a Frailty Index, which initially included a total of 70 deficits, including signs, symptoms, disabilities, diseases, and laboratory investigations (61). The total number of disorders present in an individual is divided by the total number of items examined: the more deficits present, the greater the likelihood that the individual is frail (62). The frailty index may contain a variety of items, including activities of daily living, diseases, and impairments, because not all deficits must be considered, and a subset may be used (63). While these two operational models are the most frequently used frailty constructs, they are distinct and should be viewed as complements rather than substitutes (63). It is worth noting that neither measure encompasses all facets of frailty; the frailty phenotype almost exclusively measures physical frailty, whereas the frailty index measures multimorbidity but does not clearly distinguish frailty from disability (63). Frailty is more than the presence of multiple deficits, limitations in daily living activities, or physical deficits on their own. Additionally, it incorporates elements pertaining to the individual's functional reserve, psychology, and social environment. Recently, a variety of screening and assessment instruments, such as the Comprehensive Frailty

Assessment Instrument (64) and the Tilburg Frailty Index (65) with a more biopsychosocial orientation have been developed (66). This definition defines frailty as a dynamic state caused by deficiencies in any of the physical, psychological, or social domains associated with health. Along with the physical and deficit accumulation models of frailty, this conceptual model lacks a specific operational definition.

Frailty and Sarcopenia

Numerous pathophysiological changes associated with frailty remain unknown (32). Rosenberg coined the term sarcopenia in the late 1980s to refer to the progressive loss of lean body mass associated with aging (67). One of the earliest theories linking frailty and sarcopenia dates all the way back to 1994, when Fiatarone et al. hypothesized a link between frailty and muscle mass decline, implying that increasing muscle mass may be beneficial for frailty sufferers (68). While a link has been established between sarcopenia and frailty, the pathophysiology of frailty appears to be more complicated than the effect of sarcopenia alone (69–71). For instance, it is still unclear whether sarcopenia causes frailty or is a symptom of it. Sarcopenia, like frailty, is more prevalent in older adults, is associated with adverse outcomes, and may be reversible (72). Both conditions have the potential to result in functional decline and disability; thus, early detection is recommended for both (72). To further investigate this connection, Calvani et al's ongoing study "BIOmarkers associated with Sarcopenia and PHysical frailty in Elderly People" (BIOSPHERE) proposes to identify biological markers for sarcopenia and physical frailty through blood sample analysis, which may shed some light on the relationship between frailty and sarcopenia (72). A better understanding of the two disorders and their relationship may aid in their prevention and management.

Multimorbidity and Frailty

The epidemiological shift has resulted in an increase in life expectancy. As a result, chronic rather than acute conditions have surpassed acute conditions as the leading cause of morbidity and mortality (73). As a result, as they age, older adults are increasingly confronted with multimorbidity and chronic diseases such as diabetes, hypertension, and dementia (74). The presence of two or more chronic diseases is referred to as multimorbidity (75, 76). Its effect on health status is contingent upon the interaction of the specific illnesses that affect the individual concurrently (77), which is greater than the sum of the effects expected from each disease individually (78). Frailty and multimorbidity are two distinct but overlapping conditions (19, 58, 69) that require distinct management and prevention strategies (79, 80). While having multiple chronic conditions is associated with the development of frailty, frailty is not always a result of chronic disease. Frailty can exist in the absence of chronic conditions, implying that it develops via a variety of different pathways (81). The evidence demonstrating how multimorbidity can result in frailty is still lacking (82, 83), and additional research is required. Both conditions become more prevalent as people age, even if they do not affect only the elderly (84). Multimorbidity, on the other hand, is more prevalent than frailty, with up to three out of four people aged 75 years meeting the criteria for multimorbidity (85–87). Additionally, chronic diseases and frailty are associated with adverse outcomes and a poor prognosis when both are present (88).

Due to the fact that frailty is a more reliable predictor of adverse outcomes than multimorbidity (89), the National Institute for Health and Care Excellence and the British Geriatric Society emphasize the critical nature of recognizing frailty in older adults with multimorbidity, as these individuals are at a higher risk of adverse outcomes (90, 91). This could aid in the targeting and rationalization of appropriate multimorbidity treatment, given that evidence suggests that intensive or excessive treatment of chronic diseases may worsen health outcomes in frail people (92). Additionally, when caring for individuals who are frail and have multiple diagnoses, it is critical to keep in mind that frailty may impair adherence to both pharmacological and physical therapies (93).

Frailty and cognition

Within the biopsychosocial model of frailty, research into the cognitive and psychological aspects of the syndrome has revealed a link between physical frailty and cognitive impairment, resulting in the conceptualization and operationalization of cognitive frailty (94). The International Academy of Nutrition and Aging reached consensus on a definition of cognitive frailty, defining it as a state that requires the presence of physical pre-frailty or frailty [according to the Frailty Phenotype], as well as mild cognitive impairment (MCI), defined as questionable dementia on the Clinical Dementia Rating (CDR) (score 0.5), a state similar to MCI (95). Recently, two distinct subtypes of cognitive frailty have been proposed based on these criteria: reversible cognitive frailty (i.e., pre-MCI, CDR score = 0) and potentially reversible cognitive frailty (i.e., MCI, CDR score = 0.5) (96–98). Both subtypes require the coexistence of physical pre/frailty, and studies have revealed that gait speed or grip strength is the most frequently associated physical characteristic with cognitive frailty (99). Other than the CDR, a variety of instruments have been used to detect cognitive impairment (100), resulting in a variety of operational definitions of cognitive frailty (98). As with general frailty, additional research is required to develop a commonly accepted operational definition. In comparison to physical frailty, cognitive frailty can be delayed and reversed, at least in its early stages, and the condition can result in an increased risk of adverse health outcomes , including disability (101), decreased quality of life (102), hospitalization, and mortality (103). Thus, public health professionals advocate for a life-course approach that includes early intervention with preventative strategies such as physical activity and dietary modification, such as the Mediterranean diet (98). These interventions may help prevent or delay the onset of cognitive frailty, as well as sarcopenia and physical frailty (104), though additional research is necessary to confirm these findings.

Frailty and health-related social determinants

In a broader sense, health is influenced by a variety of factors other than medical ones, including social, economic, political, and environmental factors; individuals are impacted by a variety of environmental and social factors that have an effect on their health (105), and contribute to social vulnerability (106). Additionally, social determinants of health, such as education,

housing, employment, nutrition, and environmental protection (107), can impair an individual's intrinsic and extrinsic capacity, resulting in frailty. The capacity of the individual and their social and caregiver network to manage frailty has a greater impact on the risk of a wide variety of adverse outcomes, including institutionalization and death, than their medical conditions or ability to perform daily activities do (108). Thus, because frailty manifests itself not only in the physical and psychological realms, but also in the social realm, it is critical to investigate the social consequences of frailty. While patient-centered care is becoming more prevalent in health management, additional research into the relationship between frailty and social vulnerability is necessary to ensure that an individual's social environment, perspective, and desires are not overlooked. The work of Azzopardi et al. demonstrates how, even within the biopsychosocial model of frailty, health and social care professionals fail to adequately consider the social aspects of the individual, particularly the environmental and personal factors (e.g., relationships) (106). A recent scoping review determined that the loss of social activities and self-management abilities are critical components of social frailty (i.e., insufficient social resources to meet an individual's social needs) and must be supported to minimize adverse outcomes (109). Because public health professionals have a broader perspective on health determinants than clinicians do, they are uniquely positioned to address people's social needs and intervene in their home environment.

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Questioning and prying into botulinum toxin after aesthetic treatment

Ebtisam Elghblawi

Dermatologist

Correspondence:
Dr Ebtisam Elghblawi
Email: ebtisamya@yahoo.com

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ABSTRACT

To the author's best knowledge, this is another reported case of an allergy to Botox toxin A. that had arisen shortly after the injection, to be added to the existing literature. A 41-year-old Philippino lady experienced a severe localised reaction, with redness and nodular swelling on her face, after her second Botox injection. The lady did not have any prior medical illness. This case can help in assessment and appraisal of anticipated Botox allergies and raise awareness of the rare infrequent incident.

Key words: botulinum, botulinum toxin A, lump, bump.

Introduction

Botulinum toxin type A (BTA) (also called as Onabotulinumtoxin A, Abobotulinumtoxin A, and Incobtulinumtoxin A) injection is extensively applied in cosmetic dermatology, to give a youthful appearance with minimal downtime (Levy and Emer, 2012, Moon et al, 2017). It works by inducing muscle paralysis at the neuromuscular junction through inhibiting the release of acetylcholine.

It has been noticed that over the last decade, many Botox (BTA) brands have emerged strongly in the aesthetic industry, predominantly from the Republic of Korea (Pickett, 2018). Some are on-label and some are off-label. Notably, all are meant to serve one function; to improve the facial outlook by minimising wrinkles and boosting confidence and stamina. To name some, Nabota/Jeuveau, Meditoxin/Neuronox and Botulax all contain nontoxic accessory proteins and excipients (Park JY, Sunga O, 2020).

The injected brand was Botulax. Botox is a Botulinum A, and Botulax is another Botulinum A; botulinum toxin serotype A (BoNT/A). Botulax is made in Korea, by the manufacturer Hugel. Its active ingredient is Clostridium Botulinum Toxin A type, and it is not FDA approved for use but in some places, it is applied illegitimately. The only FDA approved are Botox, Dysport and Xeomin. However, Botulax is extensively used in Asia, and certain countries including Libya, and is well known and has no problems attached with it.

In the West and America, Onabotulinum toxin A, also recognised as Botox Cosmetic, is one of the commonest injectable constituents to improve and rectify facial wrinkles appearance and is manufactured by the bacterium Clostridium botulinum. BTX is considered safe but it has been reported in rare cases to cause a fulminate anaphylactoid reaction.

My reported case represented a localised allergic reaction to Botulax and shall serve as an admonitory observation for similar reactions should they arise.

Case Report

A healthy 41-year-old Philippino lady sought my medical attention after experiencing severe swelling after 8 hours of receiving her second Botulax injection, with localised bumps and lumps on her face that lasted for more than 48 hours. She was completely healthy and has no other medical conditions. She had one encounter of the same brand injection a year previously and did not elicit any reaction at that time as it was a completely uneventful incident. She did not have any concomitant filler injection. The Botulax preparation and the number of units received were unknown, however, she received the Botulax injection on her glabella, forehead, and the 'crow line'. The total treatments the patient received were two, with a year apart.

On examining her sent photos, there were multiple, tender, firm, well-defined, non-itchy red swellings at all sites of injections, namely cheek, 'crows feet', and the forehead. There were no generalised skin reactions, no headache, no difficulty in breathing, no diplopia or trouble swallowing and no eye, tongue, lips or throat swelling either.

The expected momentarily common self-limiting reactions are pain, itching, erythema and bruising. In this lady, the swelling had receded, without any scars, by itself after 72 hours. She did not take any over-the-counter (OTC) medications. She only received intravenous (IV) drip for whitening her complexion which is a common practice in certain nations.

Skin bumps and lumps are seldomly and unexpectedly seen as consequences of botulinum toxin injection, where no guided consensus is existing to rectify it; but when it happens, it can be notoriously distressing to both the patients and the injecting clinicians.

There was no confusion or disorientation encountered in this lady. There was no facial or scalp complaint. The total duration of the reaction lasted for more than 72 hours and after that the bumps and lumps self-resolve. She was requested to have an assessment for her IgE, C1-esterase inhibitor, prick and patch test; a regular allergy testing, with the same type of Botulax used but the patient opted not to and declined as she had recovered.

Figure 3 and 4 shows complete self-resolution after 3 days.

A communication was initiated with the manufacturer online, but to no avail. Reviewing the existing literature did not yield any similar encounter, which will be disturbing and distressing to both the clinicians and the patients.

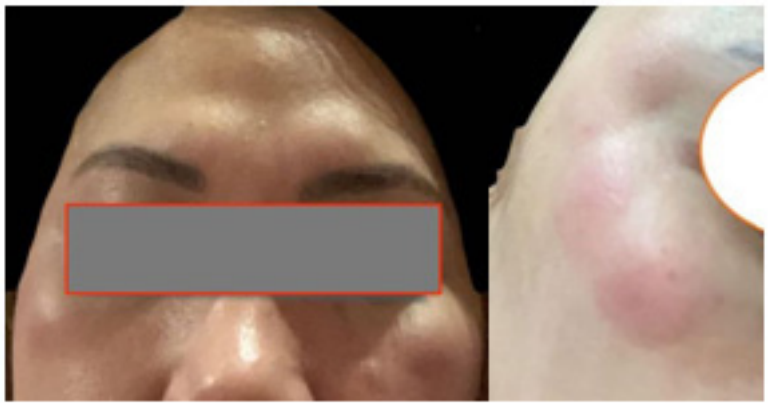

Figure 1

Figure 2

Figure 3

Figure 4

Discussion

With the incremental daily uses of Botox injections, it is projected to see and confront some rare unknown side effects.

Botox has immunogenic potential which is attributed to some factors, namely, the assembly of its biochemical material, which involves denaturation by oxidation, the storage and packing, impurities, dose and frequency with sites of injections, and the genetic makeup of each individual (Brüggemann et al, 2009, Namazi, et al, 2016). Both BOTOX® and DYSPORT® encompass a crystalline composite of purified toxin and a binding protein, known as haemagglutinin. However, DYSPORT® unify human serum albumin and lactose, which is capable of triggering an allergic reaction, but the lactose role remains conjectural (Namazi, et al, 2016).

According to Anabtawi et al's 2020 review, five cases were reported with nodular outbursts after various brands of Botox administration respectively (Dysport ®, Germany, Botox ®, Allergan, and Neuronox ®, South Korea, and Botulax ®, Korea), all of which were females between 42 and 57 years old, of whom, two had sarcoidosis, one was hypertensive and two were completely fit and well. Presentation varied between a few weeks to six years and biopsies results varied between granuloma formation, to foreign body formation.

One postulation could be the protein (human serum albumin or gelatin) component of Botox-A product which could cause a foreign body reaction and initiate immune reactions. Also, the skin reactions after Botox injection can be attributed merely to sensitized, pseudosensitized and intolerance responses.

The concern about BoNT/A-induced immunogenicity is significantly disputed, as they are loaded with higher amounts of inactive total neurotoxin that renders patients to potential immunogenic reactions. Additionally, multiple reports of treatment failures necessitate repeated injections, due to BoNT/A-induced neutralizing antibodies, and thus cumulative exposure to potential immunogens (Park JY, Sunga O, 2020).

Hypersensitivity and allergic body reactions are classified under the main four well-known groups. The first, type I, is the immediate body reaction after exposure to an antigen, which can be anaphylaxis or anaphylactoid, where the mast cell will determine the reaction type by either IgE or non-IgE-mediated factors.

While in type II reaction, it comprises a dependent antibody reaction by stimulating the complement system (natural killer cells or macrophage) within the initial 12 hours. In type III hypersensitivity, it involves the formation of the immune complex (IC) within hours after repeated triggering to the complement system. The delayed reaction, IV, is characterised by sensitisation of the cytotoxic T-cells, where symptoms prevail between 2-3 days. However, in pseudosenstisation, the symptoms develop due to histamine release directly and are dose related, whereas, intolerance reaction occurs due to imbalance in both the histamine release and degrading systems (Brüggemann et al, 2009).

Careta et al, 2015, reported a case with known allergy, developed post Botox immediate urticarial plaques reaction, minutes after, and it has been documented after a Chinese Botulinum toxin (CBTX-A) injection to correct dynamic wrinkles. Whereas, Namazi et al, 2016, documented a case of vasculitis with panniculitis post Chinese Botulinum toxin injection.

In this case, the time course had been in keeping with either type II, type IV hypersensitivity pathway or an intolerance response. It is not clear as biopsy was not examined. The explanations for these reported case skin reactions currently remain unidentified but speculative. As there are scarcely any reported cases in the existing literature, it is quite challenging to establish the tangible cause. Grounded on the existing information, no firm conclusion can be arrived at regarding the risk of skin reactions between different preparations of Botox. However, it would be wise to be wary, when applying Botox for the possibility of any peculiar skin allergic reactions, or bumps and lumps post Botox injections.

To my knowledge this is another case reported to be added to the existing literature.

With current COVID times in mind, it would be presumed that the providing clinic in the Philippines had followed the utmost standard etiquette in Botulax® formulation and reconstitution, as per the standard technique advised by the Korean producer; Hugel. The freeze-dried botulax100 U, prior to injection, is reconstituted with 0.9% preservative-free, sterile saline to make 100 U/2.5 mL (4 U/0.1 mL), which should be administrated within four hours after dilution technique, as per their web page instruction. This was discussed with the patient who affirmed that protocol was exercised.

For the regular allergy testing, if it was a positive verdict, then advice should be given to avoid the used brand in future, however, if the test results were negative, then it would be possible that the used brand can be safely given in the future (Rosenfield et al, 2014). After all, appropriate precautions should be exercised and taken seriously with strict cautions in such cases, to avoid any misfortune.

As the ingredient was not tested, then the argument would not be complete and valid. There are many possible explanations for this allergic reaction encountered as explained. The strong claim is that botulax allergy seems to have happened in this case and thus injecting physicians should be conscious of the possibility of this brand reaction.

Conclusion

Botox generally speaking, is well-known to be a safe, well-tolerated and an effectual treatment for cosmetic wrinkles improvement without down time, or serious drawbacks.

I report a lady patient who developed extraordinary, localised skin bumps and lumps 8 hours post Botulax injection (BoNT/A), which can be added to the existing literature to learn and share knowledge.

This case showed that Botulax can cause a severe localised skin reaction on the face and this report can serve as a blueprint and a proposal to assess and evaluate cases of Botulax allergies. Thus, patients with a confirmed allergy to Botulax should refrain from receiving further treatment with this product. The patient agreed to keep me updated once having her next Botulax injection.

Additional appraisal and research assessment are needed to reach a consensus on management. However, due to the scarcity of reported cases, this can be hard to achieve.

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