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From the Editor

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

In this issue a number of paper reviewed issues of interest to the medical field including CPR , sickle cell, frailty and surgical review.

Bshabshe et al., did a retrospective descriptive study conducted in the Southern Region of Saudi arabia and enrolled 1185 subjects. After attaining a formal consent , a pre-formulated questionnaire formulated on themes from the literature review was given to the subjects which addressed some basic questions about their opinions regarding family presence during cardiopulmonary resuscitation. After attaining a formal consent , a pre-formulated questionnaire formulated on themes from the literature review was given to the subjects which addressed some basic questions about their opinions regarding family presence during cardiopulmonary resuscitation. Out of the 1185 respondents, 174 (14.6%) had witnessed the CPR of their relatives while 85.3% had never done so. This study demonstrated that more than half of the family members (58.9%) expressed a desire to be with their loved ones during resuscitation. The authors concluded that most of the family members wish to be present with their relatives at the time of CPR. However, more than 50% subjects we interviewed were concerned that it may have a negative effect on them in the long term. Thus , all family members must be allowed an option to witness the efforts of the medical team during CPR and their wishes must be respected and it is the duty of the hospital to facilitate this process by all means necessary.

Helvaci et al., tried to understand whether or not there is a significant relationship between acute chest syndrome (ACS) and atherosclerosis in sickle cell diseases (SCD). All patients with the SCD were included. The study included 434 patients (222 males) with similar mean ages in male and female genders (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. The authors concluded that 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 and alcohol-like strong atherosclerotic risk factors and disseminated teeth losses, COPD ileus, cirrhosis, leg ulcers, digital clubbing, CHD, CRD, and stroke-like obvious atherosclerotic consequences in male gender, ACS was not higher in them, significantly. In another definition, ACS may not have an atherosclerotic background in the SCD.

In the second paper Helvaci et al.,tried to understand prevalence and clinical severity of sickle cell anemia (SCA) alone or sickle cell diseases (SCD) with associated alpha- or beta-thalassemias in adults. All adults with the SCA or SCD were studied. The study included 441 patients (215 females). The prevalence of SCA was significantly lower than the SCD in adults (29.0% versus 70.9%, $p<0.001$). The mean age and female ratio were similar in the SCA and SCD groups (31.2 versus 30.5 years and 52.3% versus 47.2%, $p>0.05$ for both, respectively). The mean body mass index was similar in both groups, too (21.5 versus 21.7 kg/m2, $p>0.05$, respectively). On the other hand, the total bilirubin value of the plasma was higher in the SCA, significantly (5.7 versus 4.4 mg/dL, $p= 0.000$). Whereas the total number of transfused units of red blood cells in their lives was similar in the SCA and SCD groups (43.6 versus 37.1 units, $p>0.05$, respectively). The authors concluded that the SCA alone and SCD are severe inflammatory processes on vascular endothelium particularly at the capillary level, and terminate with an accelerated atherosclerosis and end-organ failures in early years of life. The relatively suppressed hemoglobin S synthesis in the SCD secondary to the associated thalassemias may decrease sickle cell-induced chronic endothelial damage, inflammation, edema, fibrosis, and end-organ failures. The lower prevalence of the SCA in adults and the higher total bilirubin value of the plasma in them may indicate the relative severity of hemolytic process, vascular endothelial inflammation, and hepatic involvement in the SCA.

Abyad & Hammami reviewed evaluation of frailty. They stressed that 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.

Family opinion regarding their presence with the physicians during active cardio-pulmonary resuscitation of their relatives

Ali Al Bshabshe (1)
Mir Nadeem (2)
Mohammed A. Bahis (3)
Javed Iqbal Wani (2)
Shahid Aziz (2)
Zia ul Sabah (2)
Tabinda Ayub shah (4)

(1) Department of Medicine/Critical Care, College of Medicine, King Khalid University, Abha, Kingdom of Saudi Arabia
(2) Department of medicine College of Medicine, King Khalid University, Abha, Saudi Arabia
(3) Department of adult critical care, Asir central hospital, Abha, Saudi Arabia
(4) Govt. Medical college Srinagar

Corresponding author:
Ali Al Bshabshe
Department of Medicine/Critical Care, College of Medicine, King Khalid University, Abha, Kingdom of Saudi Arabia
Email: Albshabshe@yahoo.com

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ABSTRACT

Background: Family presence during resuscitation has been a controversial topic ever since it was first introduced. Despite claims that it may exaggerate the burden on health care workers, this practice is widely gaining attention and a lot of evidence refutes these claims. In fact, a number of international organizations have supported this practice as being useful and with a positive impact on family members. There is not a lot of research in this area in Saudi Arabia and we conducted this research with this aim.

Methods: This was a cross-sectional study conducted in the Southern Region of Saudi Arabia and 1185 subjects were enrolled. After attaining formal consent, a pre-formulated questionnaire, formulated on themes from the literature review, was given to the subjects which addressed some basic questions about their opinions regarding family presence during cardiopulmonary resuscitation.

Results: Out of the 1,185 respondents, 174 (14.6%) had witnessed Cardiopulmonary Resuscitation (CPR) of their relatives while 85.3% had never done so. This study demonstrated that more than half of the family members (58.9%) expressed a desire to be with their loved ones during resuscitation. While 587 (49.5%) people were concerned their presence in the treatment room may interfere in the medical help being provided to their relative, a slight majority i.e. 598 (50.3%) did not agree with this statement. When asked about the psychological impact of witnessing the CPR of their relative, 54.6% (650) people said it might affect them negatively in the long run while 45% (535) did not feel the same. Moreover, 609 (51.4%) did not feel their presence in the Emergency Room (ER) would help the patient in any way while 48.6% agreed that it may indeed do so. 69.8 % of attendants disagreed that they would interfere with the medical process if they were allowed to be present.

Conclusion: This study supports that FPDR has shown promising benefits . Therefore, family members must be offered an option to witness the efforts of the medical team and their wishes must be respected and it is the duty of the health care institutions to facilitate this process .

Key words: FPDR, family presence, Cardiopulmonary resuscitation, CPR

Introduction

Cardiopulmonary resuscitation or CPR is a lifesaving maneuver employed all over the world in hospital emergency rooms (and sometimes general wards) to maintain cerebral blood flow in case a patient develops a cardiac arrest. It is a difficult and distressing time both for the family and the health care providers. A lot of discussion has ensued about whether family members should be allowed to stay in the resuscitation room during CPR. This controversial topic first made its formal appearance in literature in the early 1980s at the Foote Hospital in America where several family members requested permission to be present in the resuscitation room (1). Consequently, Doyle et al conducted a study in the emergency department at the Foote Hospital in 1985 amongst the attendees and the health care workers (2). Ever since, this subject has gained a lot of attention and the pros and cons of allowing relatives in the treatment room have been argued.

Family presence during resuscitation (FPDR) has been defined as "the presence of family in the patient care area, in a location that affords visual or physical contact with the patient during resuscitation events" (3). Some authors like Helmer et al argue that witnessing the CPR may put an additional emotional and physical burden on the relatives and thus, impair the coping process and may also interfere with the quality of medical care decisions (4). FPDR may also result in increased levels of stress amongst the health care team and sometimes, even disrupt the communication necessary during resuscitation (5,6). One study demonstrated that the presence of a disruptive family member led to a delay in delivering the first shock and fewer total shocks delivered (5). However, proponents of this practice believe that being present during cardiopulmonary resuscitation (CPR) may help the family member understand that everything possible to bring the patient back to life has been done. Moreover, the relative's presence in the ER may offer the opportunity for a last goodbye and help that person grasp the reality of the patient's imminent death, in addition to quashing suspicion about what happened behind closed doors (7,8,). Some also suggest that it may eventually help them cope with the grief and the bereavement will not be prolonged along with a decreased incidence of PTSD (post traumatic stress disorder) (9,10). For instance, in a trial in UK families that were randomized to be present during resuscitation and who were followed up it was found that they had lower bereavement scores, using the Texas Inventory of Grief at both 3 and 9 months after the resuscitation event. This was considered strong evidence in favour of FPDR so the trial was stopped and the practice adopted (11). However, there is a need for analyzing further the potential benefits to family members against the stress induced in health care providers as well as the risk of legal claims. Despite these debates about benefits and harms, major international guidelines for CPR state that there is evidence based positive aspects of family-witnessed resuscitation, and this action is considered reasonable and generally useful (12). Furthermore, it has been adopted as a standard by the Emergency Nurses Association (13) the American Academy of Pediatrics (14), and the American Heart Association (15).

Keeping in view that the social and moral values differ among different parts of the world, we formulated this cross sectional study to assess the psychological effects of family attendance in the resuscitation room. In our study, our principal aim was to determine the response of family members to their presence in the resuscitation room and how likely it was to affect their ability to cope with their loss. We also assessed the effect of family presence on medical efforts at resuscitation, the well-being of the health care workers and their response to a witnessed CPR.

Aims and Objectives

To study, assess and form evidence based conclusions on the practice of allowing family members to be present at the time of resuscitation.

Materials and Methods

This was a cross-sectional study conducted in the southern region of Saudi Arabia and 1185 subjects were enrolled. After attaining formal consent, a pre-formulated questionnaire, formulated on themes from the literature review, was given to the subjects, which addressed some basic questiona about their opinions regarding family presence during cardiopulmonary resuscitation.

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Study Participants

Inclusion Criteria:

Regular Community members

Visitors to Aseer Central Hospital (ACH)

Attendants of Inpatients at ACH

ER Visitors.

Exclusion Criteria:

1- Physicians

2-Nurses and nurses' assistants

3-Respiratory therapists.

Ethical clearance was obtained from the Human Research Ethics Committee of the King Khalid University (KKU), and permission was obtained from the administration of the hospital. The total study group canvassed, comprised 1,185 respondents.

After attaining formal consent, a pre-formulated questionnaire formulated on themes from the literature review was given to the subjects which addressed some basic questions about their opinions regarding family presence during cardiopulmonary resuscitation. The questionnaire was divided into 2 sections comprising a total of 13 questions. Section 1 consisted of four demographic queries. Section 2 consisted of 9 survey questions relating to the attitude, desires and any concerns regarding family presence in the resuscitation room. These questions were formulated after careful and detailed literature review and keeping in view the religious and ethical sentiments of people.

This was then collected and the data assessed by standard statistical analysis.

Statistical Analysis:

Qualitative and quantitative data were analyzed using IBM SPSS ver. 22. Responses were tabulated and compared. Data analysis was conducted using descriptive statistics

Results

Of the 1,185 subjects, the maximum (52%) were aged between 21 – 32 years, 23% were 32- 42 years, 15% were aged less than 20 years and 0.34% were above 53 years (Figure 1). The occupation of the respondents is given in Figure 2.

The response of family members to each query is given in Table 1.

Out of the 1,185 respondents, 174 (14.6%) had witnessed the CPR of their relatives while 85.3% had never done so. When asked , 91.4% (1,083) attendants were not allowed by the attending physicians to witness the CPR. 698 (58.9 %) subjects wished to be present with the medical team as they performed CPR. However, 487 (40.7%) attendants did not wish to do so. While 587 (49.5%) people were concerned their presence in the treatment room may interfere in the medical help being provided to their relative, a slight majority i.e. 598 (50.3%) did not agree with this statement. When asked, in general terms, about the psychological impact of witnessing the CPR of their relative, 54.6% (650) people said it might affect them negatively in the long run while 45% (535) did not feel the same. Moreover, 609 (51.4%) did not feel their presence in the ER would help the patient in any way while 48.6% agreed that it may indeed do so. 69.8 % attendants disagreed that they would interfere with the medical process if they were allowed to be present .

Further, respondents were also asked about the physicians' practices during an active CPR. Which usually lasts 30 minutes. While 55.6% (659) wanted someone from the medical team to inform them about what is happening during the process, 31.55 % (376) would rather wait till the end. 12.7% (150) people said it did not matter.

Table 1

QUESTIONS	RESPONSE YES	FREQUENCY NO
1. Did you witness active CPR for anyone from your family?	14.6%	85.3%
2. Did the physician allow you to be present during CPR?	8.6%	91.4%
3. Would you prefer to be with the medical team in the resuscitation room?	58.9%	40.7%
4. Do you think your presence in the Resuscitation room will interfere with the medical help being provided to your relative?	49.5%	50.3%
5. Do you think your presence during CPR will affect you negatively psychologically in the long term?	54.6%	45%
6. Do you think your presence during CPR will affect you positively psychologically in the long term?	42%	58%
7. Do you think you might interfere with the resuscitation if you are allowed in the treatment room?	30.2%	69.8%
8. Do you think your presence with your relative during CPR will be beneficial to him/her?	48.6%	51.4%

Figure 1: Age distribution

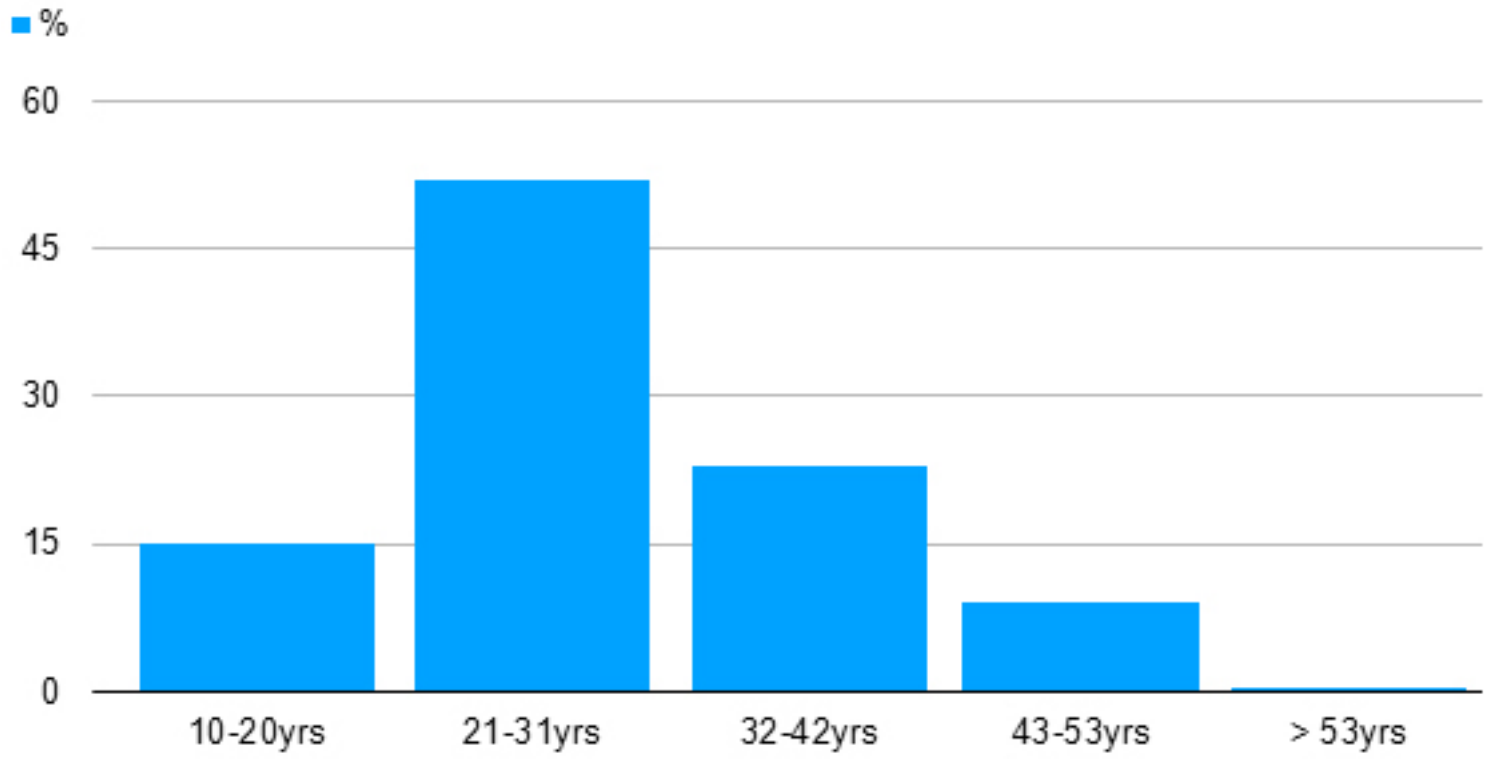
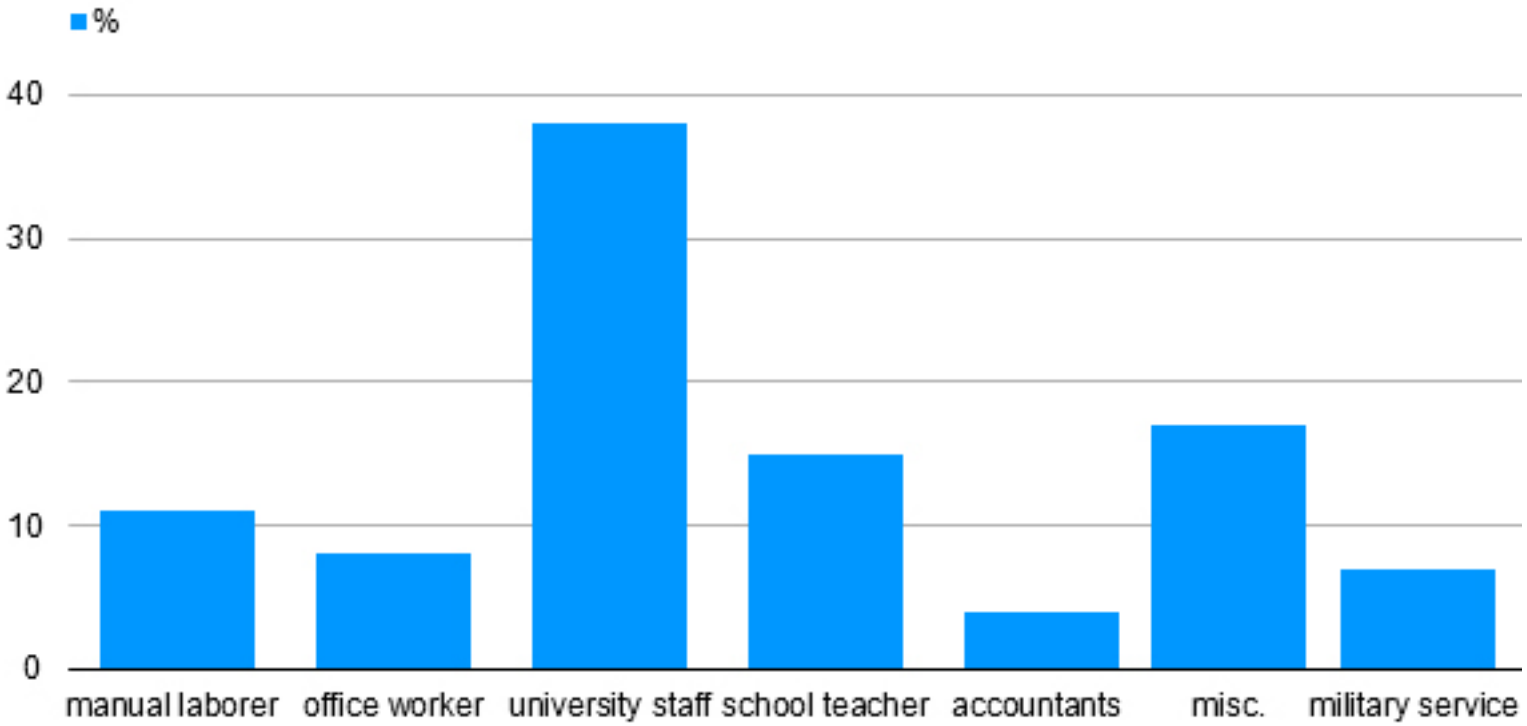


Figure 2: Occupation of respondents



Discussion

This study demonstrated that more than half of the family members (58.9%) expressed a desire to be with their loved ones during resuscitation. However, only less than 15% had actually witnessed an ongoing CPR. The majority (91.4%) of relatives stated this was because the physicians did not allow them to do so. Similar responses have been documented in the past literature conducted by Zakaria et al, [16] Doyle et al.,[2] and Meyers and Eichhorn (7,8). In the Kingdom of Saudi Arabia, Abdul aziz Alshaer et al (18) recently conducted a similar study and found that the majority of patients would like to be offered the option of staying with their relatives during CPR.

The most important and possibly, the most controversial aspect of FPDR is the long term psychological effect on the relatives willing to attend CPR. In our study, less than 50% of people thought it would affect them negatively in the long run. Moreover, around 51.4% of attendants did not feel their presence in the ER would help their relative in any way. This is in contrast to some earlier studies. For example Abdulaziz Alshaer et al (18) found that more than half, i.e., 141 (60.0%) of the respondents believed that their presence might have eased the suffering of the deceased. One hundred and fifty-seven (66.8%) of the family members thought that their presence with the deceased in their last moments could have helped their sorrows and sadness. Meyers et al, (5,6) also suggested relatives would have wanted to be present if they had been given a choice. In fact, his research team continued to examine the relatives' behavior prospectively after they had been present during resuscitation. This research provided compelling evidence that most of the family members would wish to be present at the time of attempted resuscitation and it may in fact, be beneficial in the long term and help them cope better with the stress. More recently, a randomized control trial was conducted by Jabre et al in which family members were randomized into groups allowing Family Presence(FP) and the standard practice. Both the groups were followed and administered a structured questionnaire by a trained psychologist telephonically. His research team found that the FP group had significantly fewer symptoms of PTSD (37 vs 27%, $p=0.01$) and anxiety (23 vs 15%, $p<0.001$) than the control (standard practice) group (9). Follow-up at one year demonstrated that the control group had a higher rate of complicated grief (36 vs 21%, $p = 0.005$) and more major depressive episodes (31 vs 23%, $p = 0.02$) (9).

Another important aspect of FPDR is possibly the physician's attitude and beliefs. In a previous study conducted by us, we found that the majority of the physicians opposed FP during CPR (19). Several concerns were cited by the treating physicians such as that FP might decrease bedside space available for the CPR team, produce staff distraction and performance anxiety, interfere with patient care, jeopardize privacy, and make the decision to discontinue futile CPR difficult. So in our study we enquired from the relatives if they would interfere in the medical aid being provided and majority (69.8%) said no.

There are several important points to consider in this. First and foremost is the process of educating health care providers about the importance of FPDR and alleviate their fears about family interruption during an ongoing CPR. Also successful implementation of this practice will require designated staff which should be available with the designated hospital resuscitation/code teams at all times. These may be someone from the nursing staff or a social worker but these must first be trained on how to provide all the necessary information to the families in the resuscitation room such as explain the interventions, describe in simple terms the meaning of medical terms/jargon, provide information about expected outcomes, supply comfort measures, give an opportunity to ask questions, and if possible, allow them to see, touch, and speak to the patient. These support staff also have an important role to play after the unsuccessful CPR has been completed, to explain or debrief in lay terms the outcome to the family and help them cope with it and if necessary, guide them to a grief counsellor.

Conclusion

This study supports that FPDR has shown promising benefits. Therefore, family members must be offered an option to witness the efforts of the medical team and their wishes must be respected and it is the duty of the health care institutions to facilitate this process.

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3rd November 2021-Abdomen

17th November 2021-Skin Cancer

Acute chest syndrome may not have an atherosclerotic background in sickle cell diseases

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

(1) Specialist of Internal Medicine, MD
(2) Specialist of Ear, Nose, and Throat Diseases, 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 whether or not there is a significant relationship between acute chest syndrome (ACS) and atherosclerosis in sickle cell diseases (SCD).

Methods: All patients with the SCD were included.

Results: The study included 434 patients (222 males) with similar mean ages in male and female genders (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) were also higher in males, significantly. Similarly, 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 in males but not ACS (2.7% versus 3.7%, p>0.05) in the SCD.

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 and alcohol-like strong atherosclerotic risk factors and disseminated teeth losses, COPD, ileus, cirrhosis, leg ulcers, digital clubbing, CHD, CRD, and stroke-like obvious atherosclerotic consequences in male gender, ACS was not higher in them, significantly. In another definition, ACS may not have an atherosclerotic background in the SCD.

Key words: Sickle cell diseases, chronic endothelial damage, atherosclerosis, acute chest syndrome, male gender, smoking, alcohol

Introduction

Chronic endothelial damage may be the leading cause of aging and death by causing tissue infarcts 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 vessels 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, 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 atherosclerotic process are male gender, physical inactivity, excess weight, smoking, alcohol, and chronic inflammatory or infectious processes including sickle cell diseases (SCD), rheumatologic disorders, tuberculosis, and cancers for the development of irreversible 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, stroke, and benign prostatic hyperplasia (BPH) which terminate with early aging and premature death. They were researched under the title of metabolic syndrome in the literature, extensively (1-3). Although the 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, stroke, or BPH due to their fibrotic natures (4-6). Similarly, SCD are severe inflammatory processes on vascular endothelium mainly at the capillary level, terminating with an accelerated atherosclerotic process induced end-organ failures in early years of life (7). We tried to understand whether or not there is a relationship between acute chest syndrome (ACS) and atherosclerosis 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 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 or infectious or traumatic 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, 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 was diagnosed via MRI (8). Autosplenectomy is diagnosed in the absence of any history of surgical splenectomy, ultrasonographically. Associated thalassemia minors were detected with serum iron, iron binding capacity, ferritin, and hemoglobin electrophoresis performed via the HPLC. Systolic BP of the pulmonary artery of 40 mmHg or higher is accepted as pulmonary hypertension (PHT) (9). The criterion for diagnosis of COPD is post-bronchodilator forced expiratory volume in one second/forced vital capacity of less than 70% (10). ACS is diagnosed with the presence of new infiltrates on chest X-ray film, fever, cough, sputum, dyspnea, or hypoxia, clinically (11). 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 the 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, laboratory parameters, and ultrasonographic results. 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 (12, 13). An exercise electrocardiogram is performed in patients with an abnormal electrocardiogram or angina pectoris. Coronary angiography is taken for the exercise electrocardiogram positive patients. So CHD was diagnosed either angiographically or with the Doppler echocardiographic findings as the movement disorders of 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 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, autosplenectomy, and other consequences of the SCD and mean ages of the consequences 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 434 patients with the SCD (222 males and 212 females). Their mean ages were similar in males and females (30.8 versus 30.3 years, respectively, p>0.05). Prevalence of associated thalassemia minors were similar in males and females, too (72.5% versus 67.9%, respectively, p>0.05). Smoking (23.8% versus 6.1%) and alcohol (4.9% versus 0.4%) were much higher in males, significantly (p<0.001 for both) (Table 1). Transfused units of RBC in their lives (48.1 versus 28.5, p=0.000) were also higher in males, significantly. Similarly, disseminated teeth losses (<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 males but not ACS (2.7% versus 3.7%, p>0.05), significantly. There were 11 patients (4.9%) with the symptoms of BPH with a mean age of 41.5 (27-58) years. Additionally, there were 23 patients (10.3%) with priapism with a mean age of 33.4 (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 (19-50) in males and 33.3 (19-47) years in females (p>0.05) (Table 2). On the other hand, when we look at the mean ages of the irreversible consequences, stroke (33.5 years), COPD (33.6 years), PHT (34.0 years), leg ulcers (35.3 years), digital clubbing (35.4 years), CHD (35.7 years), DVT or varices 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 patients

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 patients

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**** or varices or telangiectasias	9.0% (20)	Ns	6.6% (14)
Rheumatic heart disease	6.7% (15)	Ns	5.6% (12)
Avascular necrosis	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)
ACS*****	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 *****Acute chest syndrome

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)
ACS*	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	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¶ or varices 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)*

*Acute chest syndrome †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 an accelerated atherosclerosis induced end-organ failures and a shortened survival in both genders (14, 15). 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 very rare in peripheric blood samples of the SCD with associated thalassemia minors, and overall survival is not affected in hereditary spherocytosis or elliptocytosis. Loss of elasticity is present during whole lifespan, but exaggerated during inflammation, infection, and various stresses of the body. The abnormally hardened RBC induced chronic endothelial damage, inflammation, edema, and fibrosis terminate with disseminated tissue hypoxia and infarcts all over the body (16, 17). As a difference from other causes of chronic endothelial damage, the SCD may keep vascular endothelium particularly at the capillary level, since the capillary system is the main distributor of the abnormally hardened RBC into the tissues (18). 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 (19) whereas they were 30.2 and 33.3 years in the present study, respectively. The great differences may be secondary to delayed diagnosis, delayed initiation of hydroxyurea therapy, and inadequate RBC supports during emergencies in Turkey (20). Actually, RBC supports must be given during all medical or surgical events in which there is an evidence of clinical deterioration in the SCD, immediately (11). RBC supports decrease sickle cell concentration in the circulation, and suppress bone marrow for the production of abnormal RBC. So it decreases sickling-induced endothelial damage, inflammation, edema, and tissue ischemia and infarcts all over the body.

ACS is responsible for a considerable mortality in the SCD (21). According to the literature, it occurs most often as a single episode, and a past history is associated with a high mortality rate (21). Similarly, all of 14 cases with the ACS had just a single episode, and two of them were fatal in spite of the rigorous RBC and ventilation supports and antibiotic therapy in the present study. The remaining 12 patients are still alive without a recurrence at the end of the ten-year follow up period. ACS is the most common between the ages of 2 to 4 years, and its incidence decreases with age (22). Similarly, as a difference from other atherosclerotic consequences, incidence of ACS did not show an increase with aging, and mean ages of the ACS and SCD were 30.3 and 30.5 years in the present study, respectively ($p>0.05$). The decreased incidence with aging may be due to the high mortality rate during the first episode, an acquired immunity against various antigens with aging, and decreased strength of immune response by aging, since an exaggerated immune response may be the major cause of death in the ACS. On the other hand, ACS may also show an inborn severity of

the SCD. For example, its incidence is higher in severe cases such as cases with sickle cell anemia (SCA) or cases with higher white blood cells (WBC) counts (21, 22). Probably, ACS is a complex event, and it does not indicate an absolute diagnosis in the majority of cases. The major clinical problem lies in distinguishing between infections, infarctions, and fat embolisms. For example, ACS did not show an infectious etiology in 66% of cases in the above studies (21, 22). Similarly, 12 of 27 cases of ACS had evidence of fat embolisms in another study (23). But according to our ten-year experiences, the increased metabolic rate during serious infections may also terminate with the ACS. In another word, the ACS may be a relative insufficiency of the lungs during the serious metabolic conditions. On the other hand, an exaggerated immune response against various antigens or abnormal RBC may also be important in the high mortality rates of the ACS. A preliminary result from the Multi-Institutional Study of Hydroxyurea in the SCD indicating a significant reduction of ACS episodes with hydroxyurea therapy suggests that a substantial number of episodes are secondary to the increased numbers of WBC and platelets (PLT) induced vascular endothelial damage (24). Similarly, we strongly recommend hydroxyurea therapy for all patients with the SCD that may also be a cause of the low incidence of ACS among our follow up cases (2.7% in males and 3.7% in females). Additionally, some authors indicated that antibiotics do not shorten the clinical course (25, 26), and RBC support must be given early in the course since it has also prophylactic benefit. RBC support has the obvious benefits of decreasing sickle cell concentration directly, and suppressing bone marrow for the production of abnormal RBC and excessive WBC and PLT. So they prevent further sickling and the exaggerated immune response induced vascular damage in the lungs and all over the body. According to our observations, simple and repeated transfusions are superior to RBC exchange (27, 28). First of all, preparation of one or two units of RBC suspensions in each time rather than preparation of six units or greater provides time to clinicians to prepare more units by preventing sudden death of such high-risk patients. Secondly, transfusions of one or two units of RBC suspensions in each time decrease the severity of pain, and relax anxiety of the patients and their surroundings, since RBC transfusions probably have the strongest analgesic effects during the severe painful crises. Actually, the decreased severity of pain may also be one of the most sensitive indicators of the decreased inflammation all over the body. Thirdly, transfusions of lesser units of RBC suspensions in each time by means of the simple transfusions will decrease transfusion-related complications, including infections, iron overload, and blood group mismatch in the future. Fourthly, transfusion of RBC suspensions in the secondary health centers may prevent some deaths developed during the transport to the tertiary health centers for the exchange. Finally, cost of the simple and repeated transfusions on insurance system is much lower than the exchange which needs trained staff and additional devices.

COPD is the third leading cause of death in the world (29). It is an inflammatory disorder that mainly affects the pulmonary vasculature. Although aging, smoking, and excess weight may be the major underlying risk factors, regular alcohol consumption may also be important in the inflammatory process. For instance, COPD was one of the most common diagnoses in alcohol dependence (30). Furthermore, 30-day readmission rates were higher in the COPD with alcoholism (31). Probably an accelerated atherosclerotic process is the main structural background of the COPD. The inflammatory process of the vascular endothelium is enhanced by the release of various chemicals by inflammatory cells, and terminates with an advanced atherosclerosis and pulmonary losses. Although 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 (32, 33). For example, there may be close relationships between COPD, CHD, PAD, and stroke (34). Furthermore, two-thirds of mortality 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 (35). When the hospitalizations were researched, the most common causes were the cardiovascular diseases again (35). In another study, 27% of mortality were due to the cardiovascular diseases in the moderate and severe COPD (36). As a result, COPD is one of the terminal consequences of the SCD due to the higher prevalence of priapism, leg ulcers, digital clubbing, CHD, CRD, and stroke in the SCD with COPD (37).

Digital clubbing is characterized by an increased normal angle of 165° between the nail bed and nail fold, increased convexity of the nail fold, and thickening of the whole distal finger or toes (38). The exact cause and significance is unknown but chronic tissue hypoxia is highly suspected (39). In the previous study, only 40% of clubbing cases turned out to have significant diseases while 60% remained well over the subsequent years (13). But according to our experiences, digital clubbing is frequently associated with pulmonary, cardiac, renal, or hepatic disorders or smoking which are characterized with chronic tissue hypoxia (4). As an explanation for that hypothesis, lungs, heart, kidneys, and liver are closely related organs which affect each others' functions in a short period of time. On the other hand, digital clubbing is also common in 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 indicate some additional role of male sex on clubbing.

Leg ulcers are seen in 10-20% of patients with SCD (40), and the ratio was 13.5% in the present study. The prevalence of leg ulcers increases with age, male gender, and SCA (41). It is shown that SCA showes a more severe clinic than SCD with associated thalassemia minors (42). Similarly, the prevalence was higher in males (19.8% versus 7.0%, $p<0.001$), and the mean age of the patients with leg ulcers was significantly higher than the others in the present study (35.3 versus 29.8 years, $p<0.000$). These results may indicate effects of systemic atherosclerosis on the leg ulcers. Similarly, the leg ulcers have an intractable nature, and around 97% of ulcers relapse in a period of one year (40). As another evidence of their atherosclerotic nature, the leg ulcers occur in distal areas with less collateral blood flow in the body (40). The abnormally hardened RBC induced chronic endothelial damage, inflammation, edema, and fibrosis at the capillary level may be the main cause in the SCD (41).

Prolonged exposure to the hardened cells due to the pooling of blood in the lower extremities may also explain the leg but not arm ulcers in the SCD. The hardened cells induced venous insufficiencies may also accelerate the process by pooling of causative RBC in the legs, and vice versa. Similarly, pooling of blood may also have some effects on higher prevalences of venous ulcers, diabetic ulcers, Buerger's disease, digital clubbing, and onychomycosis in the lower extremities. Furthermore, the pooling may be the cause of delayed wound and fracture healings in the lower extremities. Beside the hardened RBC, the higher prevalence of smoking and alcohol may also have some effects on the leg ulcers by accelerating the atherosclerotic process in males. Hydroxyurea is the first drug that was approved by Food and Drug Administration for the SCD (18). 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 (20). Its main action may be the suppression of hyperproliferative WBC and PLT in the SCD (43). Although the presence of a continuous damage by hardened RBC on vascular endothelium, severity of the destructive process is probably exaggerated by the higher numbers of WBC and PLT. 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 (44). According to our ten-year experiences, prolonged resolution of leg ulcers with hydroxyurea in most patients may also suggest that the leg ulcers may be secondary to the increased WBC and PLT counts induced prolonged vascular endothelial inflammation and edema at the capillary level. Probably due to the irreversible fibrotic process on the vascular endothelium, hydroxyurea is not so effective in terminal patients with the leg ulcers.

Cirrhosis is increasing in the world, and is the 11th leading cause of death globally (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 (45). NAFLD is a marker of pathological fat deposition combined with a low-grade inflammation that results with hypercoagulability, endothelial dysfunction, and an accelerated atherosclerosis (45). Beside terminating with cirrhosis, NAFLD is associated with higher cardiovascular diseases and overall mortality rates (46). Authors reported independent associations between NAFLD and impaired flow-mediated vasodilation and increased mean carotid artery intima-media thickness (CIMT) (47). NAFLD may be considered as a hepatic consequence of the metabolic syndrome and SCD (14, 48). Smoking may also play a role in the endothelial inflammation in the liver since the inflammatory effects of smoking on vascular endothelium is well-known with Buerger's disease and COPD (49). Increased oxidative stresses, inactivation of antiproteases, and release of proinflammatory mediators may terminate with an accelerated atherosclerosis in smokers. Atherosclerotic effects of alcohol are much more prominent on hepatic endothelium probably due to the highest concentrations of its metabolites in the liver. Chronic infectious or inflammatory processes may also terminate with an accelerated atherosclerosis all over the body. For instance, chronic hepatitis C virus (HCV) infection raised CIMT, and hepatic functions were normalized with the clearance of HCV (50). As a result, beside COPD, ileus, leg ulcers, digital clubbing, CHD, CRD, and stroke, cirrhosis may just be one of the consequences of the metabolic syndrome and SCD.

CRD is increasing all over the world, too (51). The increased prevalence of CRD may be explained by aging of the human being and increased prevalence of excess weight, since CRD may also be one of the consequences of the metabolic syndrome (52). Aging, physical inactivity, excess weight, smoking, alcohol, and chronic inflammatory or infectious processes may be the major underlying causes of the vascular endothelial inflammation in the kidneys. The inflammatory process is enhanced by release of various chemicals by lymphocytes to repair the damaged renal tissues, particularly endothelial cells of the renal arteriols. Due to the prolonged irritations of the vascular endothelium, prominent changes develop in the architecture of the renal tissues with an advanced atherosclerosis and subsequent ischemia and infarcts. Excess weight induced metabolic abnormalities such as hyperglycemia, dyslipidemia, elevated BP, and insulin resistance may cause various cellular stresses by means of acceleration of tissue inflammation and immune cell activation (53). For instance, 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 (52). Increased renal tubular sodium reabsorption, impaired pressure natriuresis, volume expansion due to activations of sympathetic nervous and renin-angiotensin systems, and physical compression of kidneys by visceral fat tissue may just be some of the mechanisms of the increased BP with excess weight (54). Excess weight also causes renal vasodilation and glomerular hyperfiltration, initially serving as compensatory mechanisms to maintain sodium balance due to the increased tubular reabsorption (54). However, along with the increased BP, these changes cause a hemodynamic burden on the kidneys by causing chronic endothelial damage in long term (55). With prolonged excess weight, 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 more rapidly (54). On the other hand, the systemic inflammatory effects of smoking on endothelial cells may also be important in the CRD (56). 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 is not related with the CRD (56), it is not logical, since various metabolites of alcohol circulate even in the renal vasculature, and give harm to the vascular endothelium. Chronic inflammatory or infectious disorders may also terminate with an accelerated atherosclerosis in the kidneys (50). Although the CRD is mainly thought of as an advanced atherosclerotic process of the renal vasculature, there are close relationships between CRD and other consequences of the metabolic syndrome and SCD (57). For instance, the most common causes of death were the stroke and CHD in the CRD again (58). In another definition, CRD may just be one of the consequences of the metabolic syndrome and SCD, again (59).

Stroke is an important cause of death in human beings, and thromboembolism on an atherosclerotic background is the most common mechanism of the stroke. Aging, male gender, smoking, alcohol, excess weight and its consequences, and chronic inflammatory or infectious processes may just be some of the triggering factors of the stroke. Stroke is also a frequent complication in the SCD (60, 61). Similar to the leg ulcers, stroke is higher in the SCA cases (62). Additionally, a higher WBC count is associated with a higher risk of stroke (43). Sickling induced vascular endothelial damage, activations of WBC, PLT, and coagulation system, and hemolysis may terminate with chronic vascular endothelial inflammation, edema, remodeling, and scarring (63). Probably, stroke is a complex and terminal event, and it may not have a macrovascular origin in the SCD. Instead disseminated capillary endothelial inflammation and edema may be much more important in the process. Associated inflammatory or infectious disorders or stressful conditions may precipitate the stroke, since increased metabolic rate during such episodes may accelerate the sickling. On the other hand, 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 endothelial inflammation and edema in the brain (64).

Additional to the accelerated atherosclerotic process, the venous endothelium is also involved in the SCD (65). For instance, varices are abnormally dilated veins with tortuous courses, and they usually occur in the lower extremities. Risk factors include aging, excess weight, 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, DVT or varices or telangiectasias develop. Varicose veins are the most common in superficial veins of the legs, which are subject to higher pressure when standing up, thus the physical examination must be performed in upright position. Although the younger mean ages of the patients in the present study (30.8 and 30.3 years in males and females, respectively), and significantly lower mean body mass index of the SCD patients in the literature (17), DVT or varices 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 (65). Similarly, priapism is the painful erection of penis that cannot return to its flaccid state within four hours in the absence of any stimulation (66). 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 (66). It is seen with hematological and neurological disorders, including the SCD, leukemia, thalassemia, Fabry's disease, spinal cord lesions (hanging victims), and glucose-6-phosphate dehydrogenase deficiency (15, 67, 68). Ischemic (veno-occlusive, low-flow), stuttering (recurrent ischemic), and nonischemic priapisms (arterial, high-flow) are the three types of the pathology (69). Ninety-five percent of the clinical cases are the ischemic (low-flow) type in which blood cannot return adequately from the penis into the systemic circulation as in the SCD, and these cases are very painful (66, 69). 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 (66). Treatment of high-flow type is not as urgent as the low-flow type due to the absence of risk of ischemia (66). RBC support is the treatment of choice in acute phase in the SCD (70). Whereas in chronic phase, hydroxyurea therapy should be the treatment of choice. According to our ten-year experiences, hydroxyurea is an effective drug for prevention of the attacks and consequences if iniatiated early in the course of the disease, but the success rate is low due to the excessive fibrosis around the capillaries if initiated later.

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 and alcohol-like strong atherosclerotic risk factors and disseminated teeth losses, COPD, ileus, cirrhosis, leg ulcers, digital clubbing, CHD, CRD, and stroke-like obvious atherosclerotic consequences in male gender, ACS was not higher in them, significantly. In another definition, ACS may not have an atherosclerotic background in the SCD.

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Sickle cell anemia versus sickle cell diseases in adults

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

(1) Specialist of Internal Medicine, MD
(2) Specialist of Ear, Nose, and Throat Diseases, 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 and clinical severity of sickle cell anemia (SCA) alone or sickle cell diseases (SCD) with associated alpha- or beta-thalassemias in adults.

Methods: All adults with the SCA or SCD were studied.

Results: The study included 441 patients (215 females). The prevalence of SCA was significantly lower than the SCD in adults (29.0% versus 70.9%, p<0.001). The mean age and female ratio were similar in the SCA and SCD groups (31.2 versus 30.5 years and 52.3% versus 47.2%, p>0.05 for both, respectively). The mean body mass index was similar in both groups, too (21.5 versus 21.7 kg/m2, p>0.05, respectively). On the other hand, the total bilirubin value of the plasma was higher in the SCA, significantly (5.7 versus 4.4 mg/dL, p= 0.000). Whereas the total number of transfused units of red blood cells in their lives was similar in the SCA and SCD groups (43.6 versus 37.1 units, p>0.05, respectively).

Conclusion: The SCA alone and SCD are severe inflammatory processes on vascular endothelium particularly at the capillary level, and terminate with an accelerated atherosclerosis and end-organ failures in early years of life. The relatively suppressed hemoglobin S synthesis in the SCD secondary to the associated thalassemias may decrease sickle cell-induced chronic endothelial damage, inflammation, edema, fibrosis, and end-organ failures. The lower prevalence of the SCA in adults and the higher total bilirubin value of the plasma in them may indicate the relative severity of hemolytic process, vascular endothelial inflammation, and hepatic involvement in the SCA.

Key words: Sickle cell anemia, sickle cell diseases, thalassemias, chronic endothelial damage, atherosclerosis, end-organ failure, metabolic syndrome

Introduction

Chronic endothelial damage may be the leading cause of aging and death. Probably whole afferent vasculature including capillaries are mainly involved in the process since much higher blood pressure (BP) of the afferent vessels 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, 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 atherosclerotic process are male gender, physical inactivity, excess weight, smoking, alcohol, and chronic inflammatory or infectious processes including sickle cell diseases (SCD), rheumatologic disorders, tuberculosis, and cancers for the development of irreversible 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, stroke, and benign prostatic hyperplasia (BPH) which terminates with early aging and premature death. They were researched under the title of metabolic syndrome in the literature, extensively (1-3). Although the early withdrawal of the causative factors may delay terminal consequences, the endothelial changes cannot be reversed after the development of obesity, HT, DM, PAD, COPD, CRD, CHD, stroke, or BPH due to their fibrotic natures (4-6). Similarly, SCD are severe inflammatory processes on vascular endothelium mainly at the capillary level, terminating with an accelerated atherosclerosis and end-organ failures in early years of life (7). We tried to understand prevalence and clinical severity of sickle cell anemia (SCA) alone or SCD with associated alpha- or beta-thalassemias in adults.

Materials and Methods

The study was performed in the Medical Faculty of the Mustafa Kemal University between March 2007 and June 2016. All adults with the SCA or SCD with associated thalassemias were included into the study. The SCA and SCD are diagnosed with the hemoglobin electrophoresis performed via high performance liquid chromatography (HPLC). Medical histories including transfused units of red blood cells (RBC) in their lives were learnt. A complete physical examination was performed, and the body mass index (BMI) was calculated by the Same Physician instead of verbal expressions. Weight in kilograms is divided by height in meters squared (8). A check up procedure including a peripheral blood smear and total bilirubin value of the plasma was performed. Associated thalassemias are diagnosed by the complete blood count, mean corpuscular volume, serum iron, iron-binding capacity, ferritin, hemoglobin electrophoresis via HPLC, and genetic testing in required cases. Eventually, all patients with the SCA and SCD were detected. Mann-Whitney U test, Independent-Samples t test, and comparison of proportions were used as the methods of statistical analyses.

Results

The study included 441 patients (215 females). The prevalence of the SCA was lower in the adults (29.0% versus 70.9%, $p<0.001$). The mean age and female ratio were similar in the SCA alone and SCD groups (31.2 versus 30.5 years and 52.3% versus 47.2%, $p>0.05$ for both, respectively). The mean BMI was similar in both groups, too (21.5 versus 21.7 kg/m2, $p>0.05$, respectively). On the other hand, the total bilirubin value of the plasma was significantly higher in the SCA (5.7 versus 4.4 mg/dL, $p= 0.000$). Whereas the total number of transfused units of RBC in their lives was similar in the SCA alone and SCD groups (43.6 versus 37.1 units, $p>0.05$, respectively) (Table 1).

Table 1: Characteristic features of the study cases

Variables	Patients with SCD*	*p*-value	Patients with SCA†
Prevalence	*70.9% (313)*	*<0.001*	*29.0% (128)*
Mean age (year)	30.5 ± 10.3 (14-59)	Ns‡	31.2 ± 9.0 (17-58)
Female ratio	47.2% (148)	Ns	52.3% (67)
BMI§ (kg/m²)	21.7 ± 3.8 (14.3-46.4)	Ns	21.5 ± 2.8 (14.5-29.9)
Total bilirubin value (mg/dL)	*4.4 ± 5.4 (0.6-55.2)*	*0.000*	*5.7 ± 4.6 (0.8-26.7)*
Transfused units of RBC¶	37.1 ± 50.7 (0-339)	Ns	43.6 ± 55.6 (0-434)

*Sickle cell diseases †Sickle cell anemia ‡Nonsignificant ($p>0.05$) §Body mass index ¶Red blood cells

Discussion

SCD are chronic inflammatory processes on vascular endothelium terminating with an accelerated atherosclerosis induced end-organ failures in early years of life (9, 10). SCD are characterized by sickle-shaped RBC which are caused by homozygous inheritance of hemoglobin S (Hb S). They are chronic hemolytic anemias including SCA alone and SCD. The SCD are subdivided as sickle cell-Hb C, sickle cell-beta-thalassemias, and sickle cell-alpha-thalassemias. Together with thalassemias, SCA alone and SCD are particularly common in malaria-stricken areas of the world. The responsible allele is autosomal recessive that located on the short arm of the chromosome 11. Glutamic acid is replaced with valine in the sixth position of the beta chain of the Hb S. Under stressful conditions including cold, surgical operations, pregnancy, inflammations, infections, emotional distress, and hypoxia, presence of a less polar amino acid promotes polymerisation of Hb S, which distorts RBC into sickle shaped structures with a decreased elasticity. The decreased elasticity may be the major pathology of the diseases, since the normal RBC can deform to pass through capillaries easily and sickling is very rare in peripheric blood samples of the SCD with associated thalassemias. Additionally, overall survival is not affected in hereditary spherocytosis or elliptocytosis. In another word, Hb S causes RBC to change their normal elastic and biconcave disc shaped structures to hard and sickle shaped bodies. RBC can take their normal shape and elasticity after normalization of the stressful conditions, but after repeated cycles of sickling and unsickling, they become hard bodies, permanently, and the chronic endothelial damage and hemolysis develop. So the lifespan of the RBC decreases up to 15-25 days. The abnormally hardened RBC induced chronic endothelial damage, inflammation, edema, and fibrosis terminate with disseminated tissue hypoxia and infarcts all over the body (11, 12). As a difference from other causes of chronic endothelial damage, the SCD may keep vascular endothelium particularly at the capillary level, since the capillary system is the main distributor of the abnormally hardened RBC into the tissues (13). The hardened cells induced chronic endothelial damage builds up an advanced atherosclerosis in much younger ages, and the life expectancy of the SCA alone cases is decreased by 25 to 30 years (14). On the other hand, thalassemias are chronic hemolytic anemias, too and 1.6% of the population are heterozygous for alpha- or beta-thalassemias in the world (15). They are autosomal recessively inherited disorders, too. They result from unbalanced Hb synthesis caused by decreased production of at least one globin polypeptide chain (alpha, beta or delta) that builds up the normal Hb. HbA1 is composed of two pairs of alpha and beta chains that represents about 97% of total Hb in adults. Alpha-thalassemias result from decreased alpha chain synthesis, and beta-thalassemias result from decreased beta chain synthesis. The relatively suppressed Hb S synthesis in the SCD with associated thalassemias may decrease sickle cell-induced chronic endothelial damage, inflammation, edema, fibrosis, and end-organ failures. The higher white blood cells (WBC) ($p=000$) and platelets (PLT) counts ($p=007$), pulmonary hypertension ($p<0.05$), digital clubbing ($p<0.05$), and autosplenectomy ($p<0.001$) and the lower mean hematocrit value ($p<0.000$) may also indicate the severity of chronic inflammatory process on vascular endothelium in the SCA alone (16). As also observed in the present study, the total bilirubin value of the plasma may have prognostic significance due to the higher prevalences of ileus, digital clubbing, leg ulcers, pulmonary hypertension, cirrhosis, CRD, and exitus in patients with the plasma bilirubin values of 5.0 mg/dL or greater (17). The significantly lower prevalence of the SCA alone in adults and the higher total bilirubin value of the plasma in them may indicate the relative severity of hemolytic process, vascular endothelial inflammation, and hepatic involvement in the SCA alone (17).

RBC support must be given during all medical or surgical events in which there is an evidence of clinical deterioration in the SCD, immediately (18). For example, antibiotics do not shorten the clinical course of the acute chest syndrome (ACS) (19), and RBC support must be given early in the course since it has additional prophylactic benefits. RBC support has the obvious benefits of decreasing sickle cell concentration directly, and suppressing bone marrow for the production of abnormal RBC and excessive WBC and PLT. For example, a significant reduction of ACS episodes with hydroxyurea therapy suggests that a substantial number of episodes are secondary to the increased numbers of WBC and PLT (20). So RBC support prevents further sickling and an exaggerated immune response induced vascular endothelial damage all over the body. According to our experiences, simple transfusions are superior to RBC exchange (21, 22). First of all, preparation of one or two units of RBC suspensions in each time rather than preparation of six units or greater provides time to clinicians to prepare more units by preventing sudden death of such high-risk patients. Secondly, transfusions of one or two units of RBC suspensions in a short period of time decrease the severity of pain, and relax anxiety of the patients and surroundings, since RBC transfusions probably have the strongest analgesic effects during the severe painful crises. Actually, the decreased severity of pain may also be an indicator of the decreased vascular inflammation all over the body. Thirdly, transfusions of lesser units of RBC suspensions in each time by means of the simple transfusions will decrease transfusion-related complications including infections, iron overload, and blood group mismatch in the future. Fourthly, transfusion of RBC suspensions in the secondary health centers can prevent some deaths developed during the transport to the tertiary health centers for the exchange. Finally, cost of the simple transfusions on insurance system is much lower than the exchange which needs trained staff and additional devices.

COPD is the third leading cause of death in the world (23). It is an inflammatory disorder that mainly affects the pulmonary vasculature. Although aging, smoking, and excess weight may be the major underlying risk factors, regular alcohol consumption may also be important in the inflammatory process. For instance, COPD was one of the most common diagnoses in alcohol dependence (24). Furthermore, 30-day readmission rates were higher in the COPD with alcoholism (25). Probably an accelerated atherosclerotic process is the main structural background of the COPD. The inflammatory process of the vascular endothelium is enhanced by the release of various chemicals by inflammatory cells, and terminates with an advanced atherosclerosis 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 (26, 27). For example, there may be close relationships between COPD, CHD, PAD, and stroke (28). Furthermore, two-third of mortality 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 (29). When the hospitalizations were researched, the most common causes were the cardiovascular diseases again (29). In another study, 27% of mortality cases were due to the cardiovascular diseases in the moderate and severe COPD (30). 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 with COPD (31).

Digital clubbing is characterized by an increased normal angle of 165° between the nail bed and nail fold, increased convexity of the nail fold, and thickening of the whole distal finger or toes (32). The exact cause and significance is unknown but chronic tissue hypoxia is highly suspected (33). In the previous study, only 40% of clubbing cases turned out to have significant diseases while 60% remained well over the subsequent years (34). But according to our experiences, digital clubbing is frequently associated with pulmonary, cardiac, renal, or hepatic disorders or smoking which are characterized by chronic tissue hypoxia (4). As an explanation for the hypothesis, lungs, heart, kidneys, and liver are closely related organs which affects each other in a short period of time. On the other hand, digital clubbing is also common in the SCD, and its prevalence was 10.8% in another study (16). 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 indicate some additional role of male sex on clubbing (16).

Leg ulcers are seen in 10-20% of patients with SCD (35), and the ratio was 13.5% in the above study (16). The prevalence of leg ulcers increases with age, male gender, and SCA alone (36). It is shown that SCA alone represents a more severe clinic than SCD with associated thalassemias (37). Similarly, the prevalence of leg ulcers was higher in males (19.8% versus 7.0%, $p<0.001$), and the mean age of the patients with leg ulcers was significantly higher than the others in the above study (35.3 versus 29.8 years, $p<0.000$) (16). These results may indicate effects of systemic atherosclerosis on the leg ulcers. Similarly, the leg ulcers have an intractable nature, and around 97% of ulcers relapse in a period of one year (35). As another evidence of their atherosclerotic nature, the leg ulcers occur in distal areas with less collateral blood flow in the body (35). The abnormally hardened RBC induced chronic endothelial damage, inflammation, edema, and fibrosis at the capillary level may be the main cause in the SCD (36). Prolonged exposure to the hardened cells due to the pooling of blood in the lower extremities may also explain the leg but not arm ulcers in the SCD. The hardened cells induced venous insufficiencies may also accelerate the process by pooling of causative RBC in the legs, and vice versa. Similarly, pooling of blood may also have some effects on the higher prevalences of venous ulcers, diabetic ulcers, Buerger's disease, digital clubbing, and onychomycosis in the lower extremities. Furthermore, the pooling may be the cause of delayed wound and fracture healings in the lower extremities. Beside the hardened RBC, the higher prevalences of smoking and alcohol may also have some effects on the leg ulcers by accelerating the atherosclerotic process in males. Hydroxyurea is the first drug that was approved by Food and Drug Administration for the SCD (13). 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 (38). Its main action may be the suppression of excessive proliferation of WBC and PLT in the SCD (39). Although the presence of a continuous damage by hardened RBC on vascular endothelium, severity of the destructive process is probably exaggerated by the higher numbers of WBC and PLT. 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 (40). According to our ten-year experiences, prolonged resolution of leg ulcers with hydroxyurea may also suggest that the leg ulcers may be secondary to the increased WBC and PLT counts induced prolonged vascular endothelial inflammation and edema at the capillary level. Probably due to the irreversible fibrotic process on the vascular endothelium, hydroxyurea is not so effective in terminal patients with the leg ulcers.

Cirrhosis is increasing in the world, and is the 11th leading cause of death globally (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 (41). NAFLD is a marker of pathological fat deposition combined with a low-grade inflammation that results with hypercoagulability, endothelial dysfunction, and an accelerated atherosclerosis (41). Beside terminating with cirrhosis, NAFLD is associated with higher cardiovascular diseases and overall mortality rates (42). Authors reported independent associations between NAFLD and impaired flow-mediated vasodilation and increased mean carotid artery intima-media thickness (CIMT) (43). NAFLD may be considered as the hepatic consequence of the metabolic syndrome and SCD (9, 44). Smoking may also take role in the endothelial inflammation in the liver since the inflammatory effects of smoking on vascular endothelium is well-known with Buerger's disease and COPD (45). Increased oxidative stresses, inactivation of antiproteases, and release of proinflammatory mediators may terminate with an accelerated atherosclerosis in smokers. Atherosclerotic effects of alcohol are much more prominent on hepatic endothelium probably due to the highest concentrations of its metabolites in the liver. Chronic infectious or inflammatory processes may also terminate with an accelerated atherosclerosis all over the body. For instance, chronic hepatitis C virus (HCV) infection raised CIMT, and hepatic functions were normalized with the clearance of HCV (46). As a result, beside COPD, ileus, leg ulcers, digital clubbing, CHD, CRD, and stroke, cirrhosis may just be one of the several atherosclerotic consequences of the metabolic syndrome and SCD.

CRD is increasing all over the world, too (47). The increased prevalence of CRD may be explained by aging of the human being and increased prevalence of excess weight, since CRD may also be one of the consequences of the metabolic syndrome (48). Aging, male gender, physical inactivity, excess weight, smoking, alcohol, and chronic inflammatory or infectious processes may be the major underlying causes of the vascular endothelial inflammation in the kidneys. The inflammatory process is enhanced by release of various chemicals by lymphocytes to repair the damaged renal tissues, particularly endothelial cells of the renal arteriols. Due to the prolonged irritations of the vascular endothelium, prominent changes develop in the architecture of the renal tissues with an advanced atherosclerosis and subsequent ischemia and infarcts. Excess weight induced metabolic abnormalities such as hyperglycemia, dyslipidemia, elevated BP, and insulin resistance may cause various cellular stresses by means of acceleration of tissue inflammation and immune cell activation (49). For instance, 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 activations of sympathetic nervous and renin-angiotensin systems, and physical compression of kidneys by visceral fat tissue may just be some of the mechanisms of the increased BP with excess weight (50). Excess weight also causes renal vasodilation and glomerular hyperfiltration, initially serving 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 by causing chronic endothelial damage in long term (51). With prolonged excess weight, 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 rapidly (50). On the other hand, the systemic inflammatory effects of smoking on endothelial cells may also be important in the 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 is not related with the CRD (52), it is not logical, since various metabolites of alcohol circulate even in the renal vasculature, and give harm to the renal vascular endothelium. Chronic inflammatory or infectious disorders may also terminate with an accelerated atherosclerosis in the kidneys (46). Although the CRD is mainly be thought as an advanced atherosclerotic process of the renal vasculature, there are close relationships between CRD and other atherosclerotic consequences of the metabolic syndrome and SCD (53). For instance, the most common causes of death were the stroke and CHD in the CRD again (54). In another definition, CRD may just be one of the several atherosclerotic consequences of the metabolic syndrome and SCD, again (55).

Stroke is an important cause of death in human being, and thromboembolism on an atherosclerotic background is the most common mechanism of its development. Aging, male gender, smoking, alcohol, excess weight and its consequences, and chronic inflammatory or infectious processes may just be some of the several accelerating factors. Stroke is also a frequent complication in the SCD (56, 57). Similar to the leg ulcers, stroke is higher in the SCA alone (58). Additionally, a higher WBC count is associated with a higher risk of stroke (59). Sickling induced vascular endothelial damage, activations of WBC, PLT, and coagulation system, and hemolysis may terminate with prolonged vascular endothelial inflammation, edema, remodeling, and scarring (59). Probably, stroke is a complex and terminal event, and it may not have a macrovascular origin in the SCD. Instead disseminated capillary endothelial inflammation and edema may be much more important in the stroke. Associated inflammatory or infectious disorders or stressful conditions may precipitate the stroke, since increased metabolic rate during such episodes may accelerate the sickling. On the other hand, 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 endothelial inflammation and edema in the brain (20).

Although the accelerated atherosclerotic process, the venous endothelium is also involved in the SCD (60). For instance, varices are abnormally dilated veins with tortuous courses, and they usually occur in the lower extremities. Risk factors include aging, excess weight, 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, deep venous thrombosis (DVT) or varices or telangiectasias develop. Varicose veins are the most common in superficial veins of the legs, which are subject to higher pressure when standing up, thus the physical examination must be performed in upright position. Although the younger mean ages of the patients in the above study (30.8 and 30.3 years in males and females, respectively) (16), and significantly lower mean BMI of the SCD patients in the literature (12), DVT or varices 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 (60). Similarly, priapism is the painful erection of penis that cannot return to its flaccid state within four hours in the absence of any stimulation (61). 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 (61). It is seen with hematological and neurological disorders, including the SCD, leukemia, thalassemia, Fabry's disease, spinal cord lesions (hanging victims), and glucose-6-phosphate dehydrogenase deficiency (10, 62, 63). Ischemic (veno-occlusive, low-flow), stuttering (recurrent ischemic), and nonischemic priapisms (arterial, high-flow) are the three types of the pathology (64). Ninety-five percent of the clinical cases are the ischemic (low-flow) type in which blood cannot return adequately from the penis into the systemic circulation as in the SCD, and these cases are very painful (61, 64). 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 (61). Treatment of high-flow type is not as urgent as the low-flow type due to the absence of risk of ischemia (61). RBC support is the treatment of choice in acute phase in the SCD (65). Whereas in chronic phase, hydroxyurea therapy should be the treatment of choice. According to experiences, hydroxyurea is effective for prevention of the attacks

and consequences if iniatiated early in the course of the SCD, but the success rate is low due to the excessive fibrosis around the capillaries if initiated later.

As a conclusion, the SCA alone and SCD with associated thalassemias are severe inflammatory processes on vascular endothelium particularly at the capillary level, and terminate with an accelerated atherosclerosis and end-organ failures in early years of life. The relatively suppressed hemoglobin S synthesis in the SCD secondary to the associated thalassemias may decrease sickle cell-induced chronic endothelial damage, inflammation, edema, fibrosis, and end-organ failures. The lower prevalence of the SCA in adults and the higher total bilirubin value of the plasma in them may indicate the relative severity of hemolytic process, vascular endothelial inflammation, and hepatic involvement in the SCA.

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Frailty : Update on Diagnosis Evaluation and Management Part 2

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, evaluation, management

Background

With age, frailty becomes a more prevalent health problem. Frailty is prevalent in community-dwelling older adults at a rate ranging from 4.9 percent to 27.3 percent worldwide, reaching 50% in those >80 years of age (1). As a result, frailty is becoming a more critical factor for physicians to consider when caring for elderly patients. This paper discusses how to diagnose frailty in a variety of healthcare settings.

The Comprehensive Geriatric Assessment (CGA) is currently used to assess frailty in elderly patients (2). This is a multifaceted, multidisciplinary diagnostic procedure aimed at identifying a variety of medical, functional, and psychological problems in elderly patients. The objective is to develop a care plan. By converting qualitative elements to quantitative elements, the procedure enables the measurement and analysis of a complex situation (that of the frail elderly person) (scores). The CGA's utility is well established: when combined with targeted action, it improves patients' functional state (3) and cognitive performance (3,4), reduces medical costs (5,6), hospital utilization, and the number of institutional placements (4). However, the effects on mortality are debatable (4). Numerous studies have demonstrated the beneficial effects of this type of evaluation in primary care (7-9). The CGA's utility appears to be well established. The element that appears to be discriminatory is the way health-care interventions are organized around the elderly patient. Several organizational models are being tested following the screening and assessment of frail elderly patients. The preliminary findings are encouraging (10).

Although there is no universally accepted operational definition of frailty, two conceptual models dominate the field: the Frailty Index (FI) (11) and the Frailty Phenotype (FP) (12). Frailty is defined as a state by the FI as an accumulation of deficits over time. The FI's deficits encompass a diverse range of physical and psychosocial conditions and diseases (1). Frailty is defined by the FP as a syndrome defined by a predefined set of five criteria: involuntary weight loss; exhaustion; slow gait speed; inadequate handgrip strength; and sedentary behavior. (12).

A common feature of frailty tools is that they take biological age into account rather than chronological age alone. This is consistent with the biopsychosocial model of primary care, and its application may aid in identifying those at increased risk of negative outcomes and promoting equity of access to services (13). The frailty model's ability to capture risk and biological age in this manner has pushed the boundaries of care for the most vulnerable members of a population. This advancement, combined with the increasing prevalence, has prompted international consensus guidance to recommend frailty screening during routine clinical encounters (14,15).

Frailty Identification

Frailty is not a natural part of aging; it is a chronic condition similar to diabetes or Alzheimer's disease. Frailty should be recognized in order to improve outcomes and avoid unwarranted harm. Identifying people who are frail can aid in improving outcomes for both specific interventions and long-term management of health needs. Simple tests can be used to detect frailty, but should always be followed by a more detailed clinical assessment.

The central issue with frailty is the possibility of serious adverse consequences following an apparently minor stressor event or change. The severity of frailty varies (individuals should not be labelled as being frail or not frail but simply that they have frailty). Individuals' frailty states are not static; they can improve or deteriorate. Any interaction between an older person and a health or social care professional should include a frailty assessment.

Frailty is frequently reversible, at least in its early stages, prior to the onset of functional impairment (16). Thus, early identification, typically during the pre-frail stage (17), is critical for assisting individuals in regaining function and avoiding adverse outcomes associated with the syndrome. Despite the critical nature of frailty diagnosis, there is no conclusive evidence or consensus regarding whether screening should be implemented routinely in various settings, whether an age threshold should be established (18), or which domains should be investigated (19). Indeed, there is scant evidence to support the use of primary healthcare services for frailty screening, surveillance, or monitoring at the population level (20). Despite this, the Royal College of Physicians, the French Society of Geriatrics and Gerontology (21,22), and the British Geriatrics Society (8) all advocate for opportunistic or targeted frailty screening. Numerous brief instruments exist to screen for and assess frailty, but no consensus on how to define frailty exists, limiting our ability to quantify it (16, 23,24). Given the syndrome's multidimensional characteristics, a variety of instruments with varying features have been validated and can be used in a variety of clinical settings. Among these instruments, some are designed solely for the purpose of detecting physical frailty, while others have a broader scope (Table 1). The primary limitation of all of these instruments is that they make no recommendation for intervention based on their score.

Frailty screening

Currently, the Comprehensive Geriatric Assessment (CGA) is considered the gold standard for frailty assessment (26). However, it was not designed for this purpose and may not accurately reflect frailty, as its original purpose was to detect disability (12). As a result, a modified CGA may be more useful in identifying frailty (8, 13). CGA is critical for developing tailored interventions, despite the fact that it is time consuming and requires specialized input. PHC may be the optimal location for frailty screening (23). To this end, it is necessary to emphasize the importance of PHC physicians and specialists receiving appropriate training on how to detect frailty (15), in order to conduct appropriate frailty screenings (16). There are an increasing number of examples of healthcare professional education programs on frailty (16). These are backed up by interprofessional learning guidelines, which are critical to frailty education (17). For instance, in Ireland, the National Frailty Education Program, which aims to educate a broad range of healthcare professionals across all healthcare settings about the fundamentals of frailty, was successfully implemented (18). There is a need for a similar approach in other countries

Table 1: Selection of frailty screening and assessment instruments comparing uni- and multi-dimensional scales

Unidimensional	Multi-domain and multidimensional
Frailty Phenotype	Frailty index
Gait Speed	Clinical Frailty Scale
Timed-Up-and-Go Test	Groningen Frailty indicator
INTER-FRAIL	Edmonton Frail Scale
Short Physical Performance Battery	Gerontopole Frailty Screening Tool
Frail scale	Frail Elderly Functional Assessment
	Prism-7-Questionaaire
	Kihon Checklist
	Tiburg frailty index
	Comprehensive Frailty Assessment Instrument

Table 2-Prism 7 Questions

1- Are you more than 85 years?
2- Male?
3- In general do you have any health problems that require you to limit your activities?
4- Do you have someone to help you on a regular basis?
5- In general do you have any health problems that require you to stay at home?
6- In case of need, can you count on someone close to you?
7- Do you regularly use a stick, walker or wheelchair to get about?

to equip healthcare professionals with the necessary skills and knowledge about frailty, as well as to ensure early detection and appropriate management of this condition.

There are a variety of tests available for determining frailty, but their accuracy is unknown. There are several straightforward tests for identifying frailty (e.g. walking speed, grip strength, and simple questionnaires) that can be used in conjunction with a phenotype model, cumulative deficit model, or comprehensive geriatric assessment.

PRISMA 7 Questionnaire - a seven-item questionnaire used in previous frailty studies that is also suitable for postal completion. A score of greater than three is considered to indicate frailty.

Walking speed (gait speed) - Gait speed is typically expressed in meters per second and has been measured in research studies over distances ranging from 2.4 to 6 meters. Gait speed was measured over a 4-meter distance in this study.

The timed up and go test (TUGT)- determines the time required to stand from a standard chair, walk three metres, turn, walk back to the chair, and sit.

Self-Reported Health - which was assessed in the study by asking participants to rate their health on a scale of 0-10. Frailty was defined using a cut-off of less than 6.

GP assessment - in which a GP determined whether a participant was frail or not based on a clinical examination.

Multiple medications (polypharmacy) - a condition in which a person is considered frail if they take five or more medications.

The Groningen Frailty Indicator questionnaire - a 15-item questionnaire on frailty that can be completed via mail. A score of greater than four indicates the possibility of moderate-severe frailty.

Frail Questionnaire- The five-item Fatigue, Resistance, Ambulation, Illnesses, and Weight Loss (FRAIL) questionnaire has been extensively validated throughout the world (20). The FRAIL questionnaire used the term "illness" rather than the Fried frailty phenotype's physical inactivity.

Frailty Phenotype Questionnaire- Kim et al., (27) developed a five-item questionnaire (The Frailty Phenotype Questionnaire) to detect the Fried frailty phenotype accurately. The new questionnaire demonstrated acceptable diagnostic accuracy for the Fried frailty phenotype (area under the curve=0.89), as well as a high sensitivity (81.7 percent) and specificity (88.7 percent) (82.5 percent). (27). As with the Fried frailty phenotype, those scoring "0" on the Frailty Phenotype Questionnaire are considered robust, those scoring 1 or 2 are considered pre-frail, and those scoring 3 or more are considered frail.

Discussion

While several definitions of frailty exist, they do not yet assist in operationalizing the concept (16). Involving international experts from diverse backgrounds, including health and social care professionals, academics, and older adults, could be the first step toward achieving broad agreement on a definition. Additionally, no consensus has been reached on the dimensions that must be examined in order to arrive at an operational definition (20). Due to the heterogeneity of frailty definitions and the varied characteristics of frailty, the same person can be both frail and not frail, depending on the domains investigated. We argue that reaching consensus on an operational definition does not necessarily require finding a single definition that applies to all health and social care settings, but rather that all professionals, including public health professionals, must have a shared understanding and a multidimensional approach to defining and recognizing the condition. Contextual terms such as social frailty, nutritional frailty, physical frailty, and cognitive frailty may also be beneficial in increasing understanding of the frailty concept of vulnerability to adverse events (28,29).

At the moment, there is a dearth of data on frailty screening and assessment at the population level (18). Additionally, we argue that implementing population-level screening would necessitate upskilling existing staff and additional research evaluating the approach's effectiveness and cost-effectiveness in primary care and public health. Secondary care's role (e.g., hospital-based Geriatricians) and how it can complement community-based services must also be clarified. Identifying and labeling individuals as frail without a compelling reason to do so risks causing harm in and of itself. Defining a concept has an effect on how we identify it (30) and provides it with a clear meaning, which has ramifications in everyday life. Labeling people as frail may have ramifications for how society views and interacts with them (31). This may have an effect on how individuals view themselves and their role in society, as well as in the familial setting. It is critical that people feel valued and can participate fully in daily life, even when they are recognized as frail. To accomplish this goal, society must foster environments that enable frail people to feel socially engaged while minimizing social stigma. As a result, frailty affects not only health-care services, but also social services and communities as a whole. Additionally, there is a need for improved communication between individuals with frailty and their supports in order to assist people in contributing in every aspect of life, regardless of their level of frailty. This is a critical approach to frailty that professionals in PHC and public health should strive to achieve. Additionally, communication with the public about frailty is necessary. It is critical to conduct public health campaigns emphasizing that this is a condition that is influenced by the life course. As it is critical to identify frailty early, we argue that additional frailty research involving individuals younger than 65 years old is necessary, as this will aid in identifying frailty in its earliest, prodromal stage, commonly referred to as pre-frailty (25, 32). Public health campaigns combined with interventions targeting pre-frail individuals may result in more favorable outcomes, as reserve capacities are still sufficient to maintain functional abilities at this stage (33).

Population-level interventions centered on education and utilizing a public health approach are also appropriate. Again, these interventions should begin early and focus on younger individuals before frailty sets in. Although the optimal strategy for frailty intervention is not yet clear, the biopsychosocial model is the most appropriate for providing a holistic assessment of the patient. Recognizing which domains (physical, cognitive, nutritional, psychological, social, and economic) contribute to function loss would serve as a proxy for health-care utilization and enhance the quality of patient-centered care (34), thereby favoring population-level targeted prevention and management strategies. Education is critical to ensuring that providers and older adults alike are well-positioned to benefit from these approaches. Evidence suggests that awareness of frailty's prevention and reversibility, or "malleability," is low (34); thus, in light of the world's aging societies and high rates of frailty in all countries (35), there is a need to raise awareness at all levels (i.e., micro, meso, macro). In this sense, frailty should no longer be confined to settings associated with geriatric medicine. For instance, the majority of healthcare specialties manage older adults with complex needs, which necessitates a broader understanding of the patient's overall health status (36), rather than a disease-specific approach. Additionally, even if impairment is detected in one domain, frailty's increased vulnerability puts individuals at risk for rapid deterioration in other domains as well. This requires prevention rather than reaction and the adoption of a person-centered, community-focused public health model. When caring for frail older adults, a holistic approach is necessary. Thus, public health personnel should be educated about the multifaceted nature of frailty, trained to identify it, and made aware that it is not just a clinical concept, but also a societal issue that can be addressed in an individual's environment and social relationships. Additionally, public health professionals can contribute to community-level education and training on frailty, fostering community-based interventions that assist older adults and caregivers in preventing and managing frailty. Similarly, policymakers must be more cognizant of the role of frailty and develop policies that promote seamless care for those with complex needs and enhance individuals' ability to self-manage (37). The importance of providing integrated care at the population-health level cannot be overstated (38). Care fragmentation makes it impossible to adequately address all facets of frail individuals' complex needs.

Socioeconomic inequalities have a significant impact on the development of frailty and on the outcomes of frail individuals. Frailty is typically associated with a lower socioeconomic status; frail individuals tend to be less educated and earn less money (12, 39). This demonstrates how social factors have a significant impact on health. Additionally, the absence of a shared assessment of environmental and social factors, which are reported infrequently in currently available multidomain frailty instruments, may contribute to a misleading approach to meeting the true needs of frail individuals and populations (40). Services must be able to intervene to address the social determinants of health, which are frequently overlooked, particularly in healthcare settings, as an integral part of an individual's well-being. Traditional health care systems, with their siloed structure and a strong hospital-centric, cure-first culture, must be refocused in order to adapt to populations' new complex and chronic care needs. To accomplish this, we must

implement the framework for reimagining healthcare around PHC that was outlined in 1978 in the Alma-Ata Declaration and reaffirmed in 2018 in the Astana Declaration (41). Public health, primary health care, and social services must be at the forefront of frail older adults' care management, promoting integrated care and a life-course approach to health. Intermediate care, which was developed to facilitate the integration of acute and post-acute care and to provide a breadth of health and social services to bridge care for older and frail adults with complex needs (42), may facilitate the management of frail adults' complex needs. It has been demonstrated that it has an effect on healthcare outcomes, including hospitalizations, though additional research, particularly at the population level, is required (43). Thus, while it has been asserted that "complex problems necessitate complex solutions" (44), we assert that complex needs necessitate holistic and integrated care.

Conclusion

Frailty affects a large number of older adults, and its prevalence increases with age. Frailty is a spectrum of severity, and certain interventions such as exercise that improves strength and balance, as well as addressing nutritional deficiencies, can help reduce it. Frailty refers to an individual's increased risk of suffering a negative outcome as a result of a minor change in their circumstances or health, and it is critical that health and social care staff recognize this.

Frailty can be recognized either as a result of the clinical condition with which the individual presents or as a result of an active search for it using gait speed, a timed up and go test, or a brief questionnaire.

Once frailty is recognized, the most effective management strategy is a comprehensive geriatric assessment. This includes a comprehensive medical examination and appropriate referral to other specialist disciplines (including geriatricians), as well as care and support planning. Each person living with frailty should have their own care and support plan, which should be shared with other health and social care professionals with whom they interact.

Thus, frailty assessment provides a theoretical framework within which primary care physicians can develop a systematic approach to assessing and treating elderly patients with complex multimorbidity. The importance of frailty measurement tools is bolstered by a global dearth of critical information and evidence about the elderly's health, which impedes the development and evaluation of appropriate policies and programs for them. Frailty measurements can provide useful information in general, but this requires the use of a valid instrument.

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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.

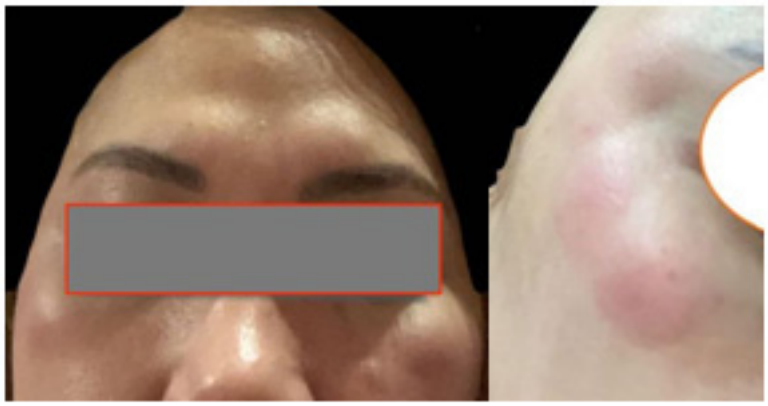

Figure 1

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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