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Editorial

Dear readers,

I am ecstatic to present you the first issue of 2023 by the Turkish Medical Student Journal.

This is our most international feature yet, with papers submitted by authors from five different countries in total, spreading to three continents. This is particularly remarkable for us since one of our most prominent missions is to reach out to medical students all around the world and provide a platform for them to publish their valuable work.

I would also like to extend my warmest welcome to our new editors joining us this year. Our editorial board continues to evolve, change and adapt thanks to our ever-growing family.

Thank you for your interest in our journal, hope to meet you again in our next issue.

Beliz Koçyiğit
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REVIEW

VARIABILITY IN THE INNATE BEHAVIOR OF DISGUST: A BRIEF REVIEW

Muhammad Ikrama, Muhammad Usama, Shifa Israr

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ABSTRACT

Disgust is a feeling of revolt or rejection of something at an emotional level. It has been debated over the past century whether this feeling of disgust is innate or not. Inherited behaviors are often described as being distinct from those behaviors that we acquire through experience. A large majority of evolutionary biologists describe this primitive behavior of disgust as being innate. It must be stated that these innate behaviors are in some aspect modified by the environment we live in. A review of disgust patterns will help us better describe the approach to some gastrointestinal infections. Patterns of disgust shown by different individuals, certainly, are distinct from each other. This is because the disgust systems of different individuals react discretely to certain stimuli and these systems evolve over the life of an individual. It is clear that disgust sensitivities vary among people and much evidence suggests that present theories are not particularly accurate in describing the variability in this so-called innate behavior. Therefore, we cannot label a pattern as being strictly innate or not innate. Some features or elements of every emotional pattern, including disgust, are innate, and some are not. These intricacies need to be explored by further research as this may help us approach some gastrointestinal infections in a way that addresses the root cause.

Keywords: Disgust, behavior, infection

INTRODUCTION

Disgust is a feeling of revolt or rejection of something on an emotional level. It has been debated over the past century whether this feeling of disgust is universal (implying some evolutionary basis) or not. Darwin (1) was the first one to suggest that this pattern is universal; however, not only Darwin but also renowned Professor Plutchik (2) describes disgust as one of the basic, primitive human instincts. Many studies support this idea of the universality of disgust (3, 4). Innate or instinctive behavior is a stereotyped, hereditarily determined characteristic of a species that is distinct from acquired behavior but open to evolutionary analysis, as described by Lorenz (5, 6).

Motivation for Studying Disgust

Disgust sensitivities vary across the world, and so do hygienic measures. The rate of gastrointestinal infections can be related to the gastronomic affairs of people from a certain place (1, 7, 8). This may help us better understand why some infections occur more in certain regions. This will also help us approach the problem that addresses the root cause for a lot of gastrointestinal diseases, which as this research suggests, might lie somewhere in the problem of disgust.

The Nature of Innateness

First of all, it should be differentiated what makes a behavior instinctive. Inherited behaviors are often described as being distinct from those behaviors that are acquired through experience (9). It is necessary to elaborate on the question of which criterion we have to suggest whether a certain behavior pattern is innate or not. Do these innate patterns develop exclusively before birth? The answer is no. As described by Grohmann (10), there is post-natal maturation of these innate behaviors. Behaviors are too complex to be characterized under a single classification of being "innate" or "not innate", rather it must be said that behaviors have certain elements that are innate and certain elements that are not. One might say that

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innate behavior is something that develops without practice or influence of environmental factors (11). Or such behavior is displayed by individuals when they are raised in isolation. Quite a few such experiments have been conducted in which different animals have been isolated to study the innateness of their behaviors (12). It must be stated that these innate behaviors are in some aspect modified by the environment we live in. Some behaviors may be over-expressed, and some may be repressed, as suggested by a number of previous research studies (5, 11, 13). It is also necessary to ascertain the fact that labeling a pattern as being "innate" is mere wordplay, and it sheds no light on the developmental aspects of such behaviors. Most of the criteria for considering a pattern innate are arbitrary (14).

Innateness of Disgust

A large majority of evolutionary biologists describe the primitive behavior of disgust as being innate (1-3). They believe disgust to be an adaptive measure evolved to avoid diseases or parasite-contaminated food. They argue that disgust is a universal driver of pathogen avoidance behavior in humans (7, 8). We may agree with this idea, considering disgust is a major factor that is responsible for some people to eat specific meals (picky eaters). In most of the scenarios, the elicitors of disgust are implicated in the transmissibility of pathogens (9). It seems that the relationship between disgust stimuli and the corresponding disease sources is reasonably consistent throughout humanity (1, 7, 8).

People tend to avoid meals which had elicited disgust sometime in the past (8). A study that supposedly supports this idea of the innateness of disgust suggests that people frown when they are disgusted and have a specific pattern of facial movements that limit the extent to which the surface of the eye is exposed to pathogens (15). Some have suggested that this facial pattern is to increase the visual acuity so that the potential pathogenic substance can be better examined. This interpretation also supports the pathogen-avoiding behavior (16). Furthermore, the feeling of disgust makes a person avoid physical contact with the substance that elicits such a response (17). This suggests that our behavioral immune system depends on disgust to guide it (18).

It is suggested that disgust sensitivities are higher in areas where the rate of infectious diseases is higher. This is supported by a study that showed people living in an area with higher infection rates scored higher on disgust sensitivity compared with people living in an area with lower infection rates (19, 20). A study conducted by Tybur et al. (21) in 2016 measured disgust sensitivities in about 11,000 participants from 30 nations and provided similar results; i.e. higher disgust sensitivities in the individuals belonging to the nations with higher infection rates. Curtis et al. (22) conducted a study in which he found that disgust sensitivities (of pictures collected by him) did not vary across many nations. The sample size under question was more than 30,000 individuals. This result is striking because it contradicts the results of previous research, but there is a way to reconcile them (21). It might be said that the people with lower disgust sensitivities that lived in high-infection areas developed more resistance to infectious stress rather than developing greater disgust sensitivities (23).

Variability in Disgust

Patterns of disgust shown by different individuals are distinct from each other. This is because disgust systems of different individuals react discretely to a certain stimulus, and these systems evolve and improve over the life of an individual (24, 25). A study was conducted globally where over 38,000 participants were asked to rate, on a Likert scale of 0-5, how disgusting a series of so-called disgusting pictures (including those of sick people, body fluids, and crowded trains) were to them. It yielded that people in different areas of the world showed a great degree of variability (mean standard deviation: 0.83) (21).

Trait-based Differences

It is known that individuals deviate in their behavioral patterns from each other because they have different traits as shown by the fact that obsessive compulsive disorder is often associated with too much disgust sensitivity (26). On the contrary, people with Huntington's disease show lesser disgust sensitivity (27). These trait-based differences are important factors for variation in disgust sensitivities. In addition, as described earlier in this review, people learn from their environments; they evolve and modulate their disgust sensitivities to better cope with the environment (11, 13).

Cultural Background

Culture is the pool of beliefs, customs, and traditions that has developed over time of a particular group of people in a particular area at a particular period (28). Disgust may be a product of a person's cultural background, thus showing environmental effects on human behaviors (13). A person's culture is thought to play a significant role in determining disgust sensitivities, even more so than heredity, which is discussed in more detail under the next heading (29).

Genetics and Learning

Some studies have shown that a person's disgust sensitivities depend heavily on their parent's disgust sensitivities (30-32). This is because the children observe and learn from their parents' behaviors (33, 34). Davey et al. (34) showed that parents and their children show similar scores on the disgust scale. This implies that genetics, along with the environment, has a significant effect on the disgust sensitivities of individuals. A study was conducted on a sample of 38 monozygotic twins and 34 dizygotic twins (29). Disgust scores of those monozygotic ones were similar to those of the dizygotic ones ($p<0.05$) (29). This showed that heredity is not as statistically significant a factor as compared to environment or culture (29). Another study that tested 131 monozygotic twin pairs showed that about half of the disgust sensitivity variations were due to

genetics. These findings strengthened the view that genes are a major factor controlling disgust sensitivities (35).

CONCLUSION

As described earlier, the results of the study that measured disgust sensitivity in over 30,000 individuals showed that disgust sensitivities are very similar among people across the nine regions of the world (22). If disgust was an adaptive measure evolved to avoid parasitic infestations or infections, then the results of the experiment would have been completely different. Still, the possibility of this cannot be completely ruled out, as disgust does prevent one from eating unhygienic meals, as well as the contrasting results of Tybur et al.'s (21) study (22).

It is clear that disgust sensitivities vary among people, and much evidence suggests that the aforementioned theories are not particularly accurate to describe the variability in this so-called innate behavior.

So, what are the reasons behind disgust variability? It seems that the following factors can help to determine peoples' disgust sensitivities: Culture, trait-based variations, general hygiene behavior, genetics.

Some features or elements of every pattern including disgust are innate, and some are not innate. More intricacies need to be explored by further research on this pattern of disgust, keeping in mind the factors stated above.

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REVIEW

CURRENT TREATMENT APPROACHES IN ANKYLOSING SPONDILITIS

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ABSTRACT

Ankylosing spondylitis (AS) is a multifactorial rheumatic disease. In today's developing treatment conditions, Non-steroidal anti-inflammatory corticosteroid injections, tumor necrosis factor alpha inhibitors, and disease-modifying antirheumatic drugs offer solutions to patients. In addition to traditional treatments, the effects of nutrition and exercise on ankylosing spondylitis are still being investigated. Genetic factors are also effective on ankylosing spondylitis and are among the factors that should not be forgotten. In this review, we wanted to contribute to the literature by explaining the treatment options that have developed in recent years and the factors affecting the disease.

Keywords: Arthritis, treatment, spondylitis

INTRODUCTION

Ankylosing spondylitis (AS) is a chronic, systemic, inflammatory disease of unknown cause, with a worldwide prevalence of up to 0.9%, which characteristically affects the spine, sacroiliac joint, enthesis, and in some patients, joints other than the axial skeleton (1). The calculation of the Bath AS Activity Index (BASDAI) is widely used to evaluate the activity of the disease (2). This index is based on the assessment and scoring of 6 criteria related to the axial skeleton, peripheral joints, systemic symptoms, and morning stiffness by the patient using a visual analog scale (2). It is known that AS is mostly seen in young men and first appears with symptoms of sacroiliitis (1). Approximately 9/10 patients are found to be positive for the *HLA-B27* gene. However, it is thought that there is no significant difference in the progression of the disease between patients with and without the *HLA-B27* gene (3).

Treatment is generally symptomatic, as a therapeutic approach to address the underlying cause of inflammation in Ankylosing spondylitis is currently not possible. The main purpose of treatment is minimizing pain and preventing morning stiffness and deformities as much as possible. Protecting the posture, physical appearance, and psychosocial health of patients from the effects of the disease is also important (2). Although non-steroidal anti-inflammatory drugs (NSAIDs) are the gold standard in treatment, they are symptomatic treatment options rather than curative (3). Sulfasalazine (SSZ) is a second-line therapy and positive results have been observed in patients with peripheral arthritis (4). Although methotrexate has been found useful in some studies, this has not been proved in controlled studies (1). On the other hand, biological agents have gone beyond symptomatic improvement and become the prominent option in the treatment of the disease in recent years (4). Anti-tumor necrosis factor-alpha (anti-TNF-α) agents target the inflammation mechanism of the disease (1). Treatment with these agents resulted in rapid and significant improvement in the clinical course and laboratory findings in placebo-controlled studies (3). It has been observed that serum vitamin D levels in

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patients with AS are lower than healthy individuals (4). Vitamin D, which has been evaluated as a hormone in recent years, is thought to have a regulatory function on the immune system as well as its role in Calcium - Phosphorus metabolism and bone mineralization (5). This raises the question of how vitamin D plays a role in the progression of AS rather than in the etiology of the disease (5). In addition to medical treatment options, physical exercise is just as important as medical treatment (4). Strengthening the muscles, maintaining the posture, and minimizing the feeling of stiffness increase the patient's quality of life and slow the progression of the disease (3).

REVIEW

Non-steroidal Anti-inflammatory Drugs

Non-steroidal anti-inflammatory are the first-line drugs in all symptomatic AS patients unless it is contraindicated (3). Patients whose symptoms persist despite NSAID therapy are candidates for transition to other treatments (4). This includes cases where at least two different NSAIDs have been used at the maximum recommended dose for at least two weeks, but the disease has not regressed, or the patient has had side effects from the treatment (4).

The aim of NSAIDs is to reduce pain and inflammation by inhibiting the cyclooxygenase enzyme (COX). According to the selectivity of COX-1 and COX-2 isoenzymes, NSAIDs are grouped as traditional NSAIDs (ibuprofen, ketoprofen, indomethacin, naproxen, etc.), and specific COX-2 inhibitors NSAIDs (rofecoxib, celecoxib, etc.) (5). Non-selective and specific COX-2 inhibitor NSAIDs are the most effective treatment group, but it would be beneficial to prefer low-dose NSAIDs due to the observed adverse effects on gastrointestinal, renal, and cardiovascular systems (5). On the other hand, the highest dose (150 mg diclofenac sodium) is preferred by experts for the treatment to be useful (4). As a result of much important evidence, it was seen that all groups of NSAIDs had similar effects and benefits, and that there was a significant difference compared to the placebo group at three months of use (5). In a study evaluating the compliance rates of patients to drugs, it was found that the compliance rates of the patients were 53% to NSAIDs, 65-70% to steroids, and 60-100% to disease-modifying anti-rheumatic drugs (DMARDs), respectively (6). Patients were more nonadherent to NSAIDs than steroids and DMARDs (6). The most common causes of non-compliance were thoughts on the drugs' side effects such as organ failures, gastrointestinal tract damages, and forgetfulness (7). The most common factors that ensured compliance in patients were fears of exacerbation of the disease, reduction of symptoms, and expected side effects (7). When remission is analyzed in AS, it has been proven that NSAIDs provide remission at a rate of 9-35%, reduce mortality, and regress in radiological progression (7). The use of NSAIDs is recommended if medically necessary (8). When the treatment protocols were examined in a study conducted on 23 patients, it was determined that 3.8% of the patients were not receiving treatment, 16.8% were only using NSAIDs, 65.4% were receiving single DMARD, 6.6% were receiving dual DMARD (SSZ + Methotrexate + NSAID), and 7.4% were treated with a biologic agent (anti-TNF-α + NSAIDs) (8).

Corticosteroid Therapy

Systemic glucocorticoids have no place in the treatment of AS. However, short-term medium/high-dose glucocorticoids can be used in patients with axial involvement. Injection therapy of glucocorticoids is recommended in areas of local inflammation in the musculoskeletal system and can be preferred especially in patients with sacroiliitis who have axial pain (6). A randomized double-blind placebo-controlled study investigated the efficacy of two different oral doses of prednisolone (20 and 50 mg/day) versus the placebo group and showed that the short-term efficacy of 50 mg oral prednisolone was superior to the placebo group (8). Another study on steroid usage evaluated the safety and efficacy of slow-release prednisone in 41 patients with AS according to the Assessment in SpondyloArthritis International Society classification criteria (9). According to the results of the study, after three months of treatment with 5 mg of prednisolone at night, significant reductions in spinal and peripheral pain, morning stiffness, and acute phase reactants levels were observed (7, 8).

TNF-alpha Inhibitor Therapy

Tumor necrosis factor (TNF) has an important role in many inflammatory diseases (9). TNF has two forms as alpha and beta and binds to TNF 1 and 2 receptors in the cell nucleus (9). It is produced by macrophages, then destroyed and converted to its soluble form (9). This form causes an inflammatory and immune response in the cell by initiating the release of many cytokines and apoptosis pathways (9, 10).

The use of anti-TNF-α drugs in patients who did not respond to conventional treatment has revealed dramatic results (11). Anti-TNF-α samples approved by the United States Food and Drug Administration for use in the treatment of AS are infliximab, adalimumab, etanercept, golimumab, and certolizumab pegol (11). These anti-TNFα agents can be preferred as second-line therapy in patients who have not benefited sufficiently from NSAIDs (11). Clinically and radiologically significant curative effects of anti-TNF-α were detected in patients with AS (10). With this treatment, inflammation in the axial skeleton was decreased, and satisfactory results were observed in Bath Ankylosing Spondylitis Functional Index (BASFI) and BASDAI scores (12).

In a study of 133 patients treated with NSAIDs and SSZ in Republic of Korea, the treatment results of 69 patients were very successful, and the treatment was not changed (group A). Low back pain persisted in the remaining 64 patients, and their treatment was arranged as anti-TNF-α (group B) (12). When the patients and their radiological parameters were followed for six months, BASDAI, erythrocyte sedimentation rate (ESR), and C-reactive protein (CRP) were evaluated clinically, and significantly more lumbar lordosis was detected in patients in

group B compared to patients in group A. Although no significant difference was observed in other radiological parameters, clinically, patients in group B showed more positive results in ESR, CRP, and BASDAI scores than in group A (13).

In a study conducted in China, 39 patients treated with etanercept and 41 patients treated with infliximab were evaluated for treatment efficacy at 12 and 24 weeks. Clinically, both drugs appeared to have positive effects on the Schober test, morning stiffness, and BASDAI and BASFI scores (14).

Since the side effects of anti-TNF-α drugs are mostly mild, changing the treatment is usually not required. However, dangerous side effects such as severe infection can be observed (11). More than 10% of patients have headaches, injection site reactions, and infusion reactions (11). In addition, anemia, mild elevation in liver function tests, upper respiratory tract infection, and geographic information system problems may occur (10).

Disease-modifying Anti-rheumatic Drug Therapy

Disease-modifying anti-rheumatic drugs are popular in the treatment of patients with AS because they are beneficial in peripheral rather than axial symptoms (15). SSZ is a synthetic drug formed by the bonding of sulphapyridine, a sulfonamide derivative, and a 5-aminosalicylate, an anti-inflammatory salicylate derivative, with an azo bond (16). The efficacy of this drug has been recognized, especially in HLA-B27-positive arthropathies (16). They can be used for therapeutic purposes and to prevent anterior uveitis in patients with early stages of the disease, elevated erythrocyte sedimentation rate, and peripheral arthritis (15). The most common side effects of SSZ include acute hemolytic anemia, leukopenia, thrombocytopenia, nausea, vomiting, rash, and fever (16).

In a randomized controlled study conducted by Khanna Sharma et al. (16), the study group was started with 500 mg of SSZ twice a day and this amount was increased by 500 mg per week to the target dose of 2 g/day. The control group was given a similar-looking placebo. The total duration of treatment in this study was six months. Comparing the mean change in BASDAI scores at six months follow-up, 61.3% of patients in the treatment group had at least 50% (17). In the study, when the mean changes in disease activity were evaluated based on the AS Disease Activity Score, BASDAI, and, Bath AS Metrology Index (BASMI), it was observed that there was a betterment of 80% (17). As the second-line therapy after NSAIDs, SSZ additionally can reduce systemic inflammation and mediate reduction of cardiac risk (17). Another study investigated whether cardiovascular disease was the primary cause of death in patients with AS. In this 10-year population-based case-control study, in which 3,766 AS patients with coronary artery disease were included as the control group, coronary artery disease developed in 8.4% of AS patients (18). According to the results of the study, it was shown that the use of SSZ at an average dose of 0.5 mg/day was negatively associated with the development of coronary artery disease in patients with AS (18). In addition, a positive correlation was found. A group of researchers declared that lumber spine Bath AS Radiology Index scores in AS patients without polymorphonuclear leukocytes showed a lower degree of sacroiliitis (19). They also included sulfasalazine in their studies and had positive results at the end of 4 months. It has been observed that SSZs reduce the transcription of HLA-B27 by decreasing the levels of IFNγ, interleukin-17, and TNF-α. However, although the disease progression could be improved with this treatment, it did not reverse the spinal damage (20).

Janus Kinase inhibitors have just joined the treatment of AS. They belong to the group of DMARDs (20). They are considered disease-modifying because they reduce the progression of damage in the joints (20).

Interleukin-17 inhibitors such as secukinumab have started to be used in the treatment of AS (20). In addition to having a pronounced effect on patient recovery, they also slow down the damage caused by the disease (20).

Exercise

Chronic inflammatory diseases that primarily affect the joints and musculoskeletal system, such as AS, cause functional damage because of joint destruction, comorbid conditions, and side effects of drugs over time (20). Despite the developments in pharmacological treatments in recent years, a permanent solution has not been found yet for the functional losses and the deterioration in the quality of life caused by rheumatic diseases (20). For this reason, it is recommended to do exercises related to the joint and muscle group involved, in addition to drug treatment, to slow down the progression of the disease and protect their functional capacities (20). In order to adapt to the planned exercise program for the patient, it should initially be done under the supervision of a physician (21). In the following periods, patients' lifelong participation in exercise should be ensured by admonishing the participation of relatives and starting to see the results of physical rehabilitation (21).

It was obtained that home exercise for 30 minutes a day, at least 5 days a week, can slow progression of the disease (20). However, outcomes related to the quality of life are controversial (20, 21). It was observed that the aerobic capacity of patients with AS was lower than healthy people, and it was found to be directly correlated with the impairment of physical condition (21). Another study conducted in Turkey showed the benefit of adding aerobic exercise to conventional exercise on physical capacity (22). When aerobic exercise training is together with clinical pilates exercises, it reduces disease activity, but increases spinal mobility upper extremity flexibility, dynamic balance, forced vital capacity, quality of life, and fatigue severity (22). It was also concluded that restrictive type respiratory failure and emerging insufficiency in patients with AS can be prevented by correct and effective exercise (23).

Nutrition

Although recent studies suggest that there may be a relationship between AS and intestinal microflora, no clear evidence has been obtained from the studies (24). In a control group study in which probiotics were used, it was observed that the probiotics cause a decrease in inflammation values, and BASDAI and BASFI scores, but it did not create a statistically significant result that would provide definitive information (24).

Smoking is also a factor that reduces the life comfort of AS patients. The underlying reason for this decline is that smoking drastically changes the stage and progression of the disease. At the same time, a relationship between smoking and syndesmophyte formation has been demonstrated by magnetic resonance imaging. Eventually, it has been observed that AS is not directly related to nutrition, except for these two nuances. Several studies on the subject are ongoing. Vitamin D, an anti-inflammatory and immune modulatory hormone, regulates bone metabolism by playing a role in calcium and phosphorus metabolism (25). The relationship between AS and vitamin D is a subject of studies since vitamin D manifests itself in AS in case of deficiency (25). In conclusion, vitamin D is seen as an important parameter in the treatment approach and follow-up of patients with AS, and its replacement should be performed if necessary (25).

DISCUSSION

Although the negative effects of high-dose NSAID use on the gastrointestinal, cardiovascular, and renal systems were reviewed in a study, it was concluded that high doses of NSAIDs (150 mg diclofenac sodium) should be used in the treatment of AS and it was found beneficial in this review article (7). Despite the results that corticosteroid treatment did not make a significant difference for AS, there is a study in which 50 mg prednisolone was used for AS treatment and it was effective (15). Another treatment option, SSZs, may become the primary treatment for other patients with predominant peripheral symptoms (16). However, the report of a larger randomized controlled trial showing that this drug provided significant improvement in rheumatologic patients with peripheral joint involvement failed to show a similar outcome in AS patients (26). Son et al. (12) stated that after a 5-year period, anti-TNF-α did not have significant radiological effects. However, in this review, it is clear that anti-TNF-α has positive effects radiologically, especially on lumbar lordosis. We concluded that anti-TNF-α drugs are more effective than other drugs in AS patients. Anti-TNF-α agents are important drugs to be preferred in cases that do not respond to conventional treatment, but they are more expensive than other agents (22). However, despite its high cost, it is an effective option for suitable patients due to its better clinical outcomes compared to other agents (26). As a result of the studies we examined, it was understood that the exercise program added to the medical treatment in AS had positive effects on the flexibility, muscle strength, and aerobic capacity of the person (20). However, in the reviewed systematic review of Soy Buğdaycı and Paker (19), it was mentioned that the effects on pain, stiffness, and increased quality of life are low. In addition to exercise, there are studies on the relationship between AS and nutrition, in which smoking significantly worsens the course of the disease, and probiotics and vitamin D have positive effects on the musculoskeletal system (25). However, meaningful statistics could not be reached that would provide definitive information (24, 25).

CONCLUSION

In today's developing treatment conditions, non steroidal anti inflammatory drugs, corticosteroid injections, tumor necrosis factor alpha inhibitors and disease-modifying antirheumatic drugs offer solutions to patients. In addition to traditional treatments, the effects of nutrition and exercise on AS are still being investigated. Genetic factors are also effective on AS and are among the factors that should not be forgotten. In this review, we wanted to contribute to the literature by explaining the treatment options that have developed in recent years and the factors affecting the disease. Treatments in AS are various, therefore every patient should be cared with a multidisciplinary approach.

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ORIGINAL ARTICLE

A RELIABLE WAY FOR DIGITIZATION AND INTEGRAL ANALYSIS OF PAPER ELECTROCARDIOGRAM

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ABSTRACT

Aims: In this paper, we aim to present our designated digitization tool and interrogate its reliability and feasibility by comparing ST shift, ST area, T-amplitude, and QT interval measurements from three observers.

Methods: Fifty ST elevation myocardial infarction electrocardiograms were digitized and analyzed offline by three investigators blindly via in-house developed software in MATLAB environment. Measurements were compared with analysis of variance and Friedman's test, and correlations were quantified via Pearson's and Spearman's tests.

Results: Six electrocardiogram records were excluded prior to digitization due to inadequate quality. Mean ST shift (0.19±0.27, 0.21±0.27, 0.19±0.27 mV, p=409), ST area (0.0841±0.1069, 0.0885±0.0981, 0.0871±0.1113 mV sec, p=0.792), T-amplitude (0.59±0.42, 0.59±0.40, 0.57±0.38 mV, p=0.071), and QT interval measurements (0.35±0.07 sec, 0.36±0.06 sec, 0.36±0.05 sec, p=0.256) of three observers were not statistically different. All observer pairs showed significant and substantial correlations in all four parameters with correlation coefficients ranging between 0.803-0.974 (p<0.001 was for all correlations between each paired observer).

Conclusion: Digitization of paper electrocardiogram records enables integral (area) analysis in paper records and more detailed analysis for researchers with paper electrocardiogram archives or lack of signal recording opportunity. Our designated publicly available tool can be reliably used in this process.

Keywords: Electrocardiogram, digitization, myocardial infarction, ST segment area, integral

INTRODUCTION

Electrocardiogram (ECG) is a widely employed, low-cost diagnostic tool that holds an irreplaceable place in current clinical practice. In the era of data digitization, most clinics continue to use paper records. This lack of digital data inevitably prevents researchers from postprocessing recorded ECG into more usable forms in a context-dependent manner, which is especially important in experimental and novel concepts.

Digitization of paper ECG (p-ECG) records may enable researchers to expand their analysis beyond simple voltage and interval assessment to include more complex examinations including static and dynamic indices such as ST area (integral). Integral analysis of ECG segments has been previously assessed in several studies and repeatedly shown to be relevant in physiopathological aspects (1-6). Additionally, processing of records (e.g., noise removal, ensemble averaging, magnification of amplitudes) becomes possible.

In this context, we aim to present our designated digitization tool and interrogate its reliability and feasibility by comparing ST shift, ST area, T-amplitude, and QT interval measurements of three observers.

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MATERIAL AND METHODS

ECG Records

We have used the strongly anonymized, publicly available, and open ECG records of Khan et al. (7). Ethical statements and conditions for the use of this open dataset can be found in the related data article (8). ECG segmentation was made in concordance with American Heart Association/American College of Cardiology recommendations (9). The end of the ST segment (=T wave beginning) for ST integral calculation was determined as previously described (1). The digitization process necessitates two steps. Firstly, plot representing the ECG signal on paper should be extracted. For the first part of the task, we integrated a previously designed code by Jung (10), which creates 2-dimensional matrices depicting the plot via pixel-level color detection on images (in our case scanned p-ECG records), that enables plotting any given images on Cartesian coordinate system. Next, calibration as well as amplitude, interval, and integral analyses of interested segments are made by the MATLAB software (MATLAB R2021b, The MathWorks, Inc., Natick, Massachusetts, United States), this software enables the user to select predefined segments by clicking or brushing following the on-screen shown directions (11). Figure 1 shows an example of the digitization process.

Protocol

After visual evaluation, one investigator picked and cropped an ECG segment with manifest ST shifts consisting of three consecutive beats in each of 50 ECG records of acute myocardial infarction. Three other investigators (intern doctors) blindly digitized and analyzed the cropped ECG parts. Another investigator merged and analyzed the data.

Statistical Analysis

Standard statistical tests were used. Continuous variables were expressed as mean ± standard deviation. The normality of variables was assessed quantitively by Shapiro-Wilks test and visually by histogram. Correlation coefficients were calculated with Pearson's and Spearman's tests for parametric and non-parametric data, respectively. Bland-Altman analysis was conducted to examine mean differences in observer pairs. One-Way analysis of variance (ANOVA) and Friedman's tests were used to assess intergroup differences in parametric and non-parametric data, respectively. Paired t-test was used when comparing repeated measurements from the same observer. PA p-value of <0.05 was considered statistically significant. All data were blindly analyzed offline using SPSS (v28.0.1.1 IBM).

RESULTS

Six ECG records were excluded prior to digitization by the principal investigator due to the lack of a stable isoelectric line in the cropped ECG part. Forty-four ECGs were digitized and analyzed by three blinded investigators.

ECG Characteristics

Electrocardiogram characteristics and comparisons between mean measurements are demonstrated and compared in Table 1 and Figure 2. Figure 3 shows a correlation between paired observers. Bland-Altman plots for ST shift and ST Integral of paired observers are provided in Figure 4.

ST Shift

Mean ST shifts were 0.19±0.27, 0.21±0.27, and 0.19±0.27 mV for observers 1, 2, and 3, respectively, and it did not significantly vary between observers (Friedman's test, p=0.409). Measured ST shift magnitudes were highly correlated between observers (observer 1-2: r= 0.974, p<0.001; observer 1-3: r= 0.940, p<0.001; observer 2-3: r= 0.951, p<0.001).

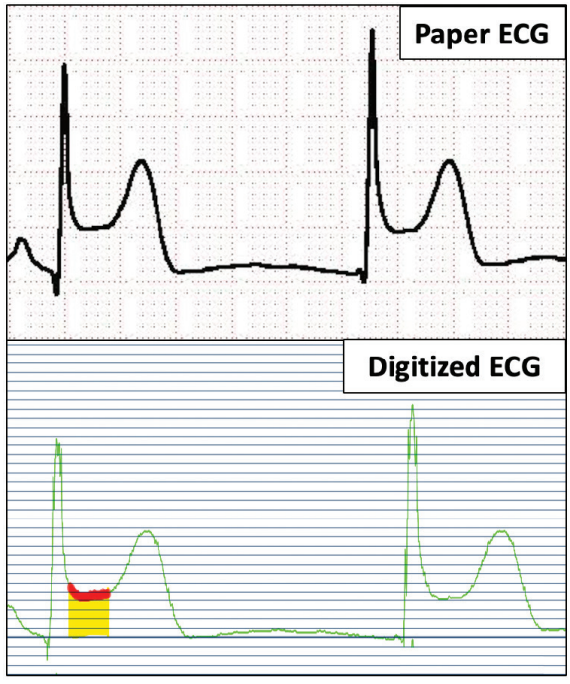

Figure 1: Paper ECG record (top) and ST integral (yellow area) analysis on digitized version (bottom) (Horizontal lines are not calibrated).

ECG: Electrocardiogram

Table 1: Comparison of mean measurements.

	Observer 1	Observer 2	Observer 3	P value
ST shift (mV)	0.19±0.27	0.21±0.27	0.19±0.27	0.409
ST area (mV sec)	0.0841±0.1069	0.0885±0.0981	0.0871±0.1113	0.792
T-amplitude (mV)	0.59±0.42	0.59±0.40	0.57±0.38	0.071
QT (sec)	0.35±0.07	0.36±0.06	0.36±0.05	0.256

One-Way ANOVA (ST area) and Friedman's tests (others) for parametric and non-parametric measurements, respectively.

ST Segment Integral

Mean ST integral were 0.0841±0.1069, 0.0885±0.0981, and 0.0871±0.1113 mV sec for observers 1, 2, and 3, respectively, and measurements were not statistically different from each other (ANOVA, p=0.792). Remarkable intergroup correlations were observed. Correlation coefficients (r) were 0.940 (O1-O2, p<0.001), 0.915 (O1-3, p<0.001) and 0.888 (O2-3, p<0.001).

T-amplitude

Differences between measured T-amplitude values were statistically insignificant (0.59±0.42, 0.59±0.40, 0.57±0.38 mV for O1, O2, and O3, respectively: Friedman's test: p=0.071). Remarkable interobserver correlations were present (O1-O2: 0.840, O1-O3: 0.871, O2-O3: 0.982; p<0.001).

QT Interval

All measurements obtained from 3 observers were significantly correlated with each other, and the mean differences were irrelevant (O1: 0.35±0.007 sec, O2: 0.36±0.06 sec, O3: 0.36±0.05 sec; Friedman's test p=0.256). Finally, correlation coefficients were remarkable in each observer pair (O1-O2 r: 0.841, O1-O3 r: 0.803, and O2-O3 r: 0.888, p<0.001).

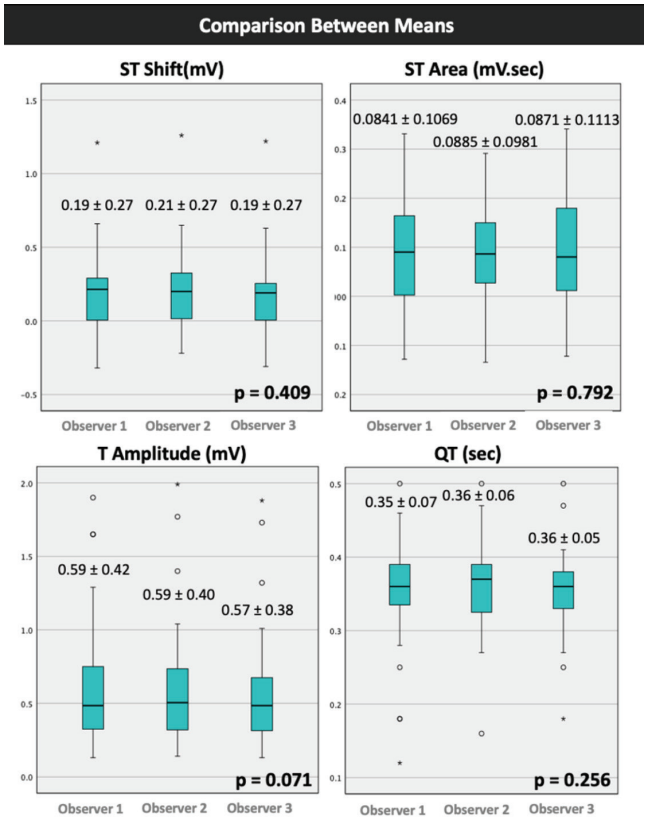

Figure 2: Comparison of mean measurements between 3 observers. ANOVA and Friedman's tests were used for parametric (ST area) and non-parametric data (others), respectively. The difference between mean values of measured ST shift, ST area, T-amplitude, and QT were not statistically significant. N=44 for all observers.

Intraobserver Reliability

In 44 ECGs, repeated ST shift measurements of observer 2 significantly correlated to initial measurements (r: 0.99 p<0.001), and mean measurements were numerically identical (0.21±0.27 mV vs. 0.21±0.27 mV, p=0.309).

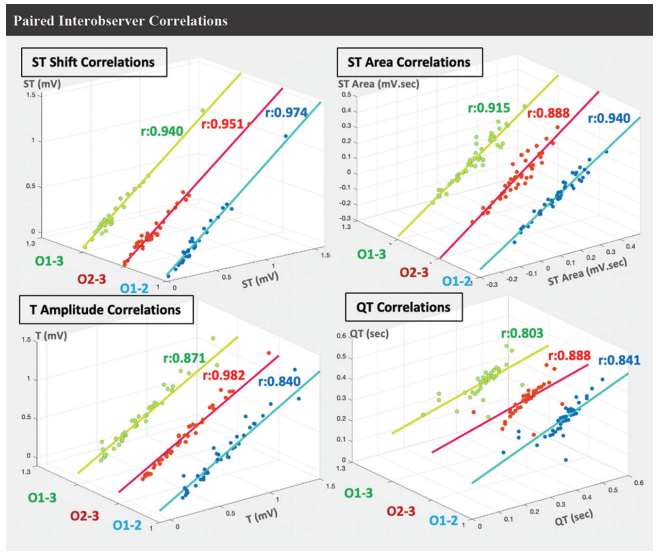

Figure 3: Paired correlations between observers 1, 2, and 3 (O1, O2, O3). Correlations between O1 and O2 were demonstrated with blue line, O2-O3 with red line, O1-O3 with green line. All demonstrated correlations coefficients were statistically significant (p<0.001). N=44 for all observers.

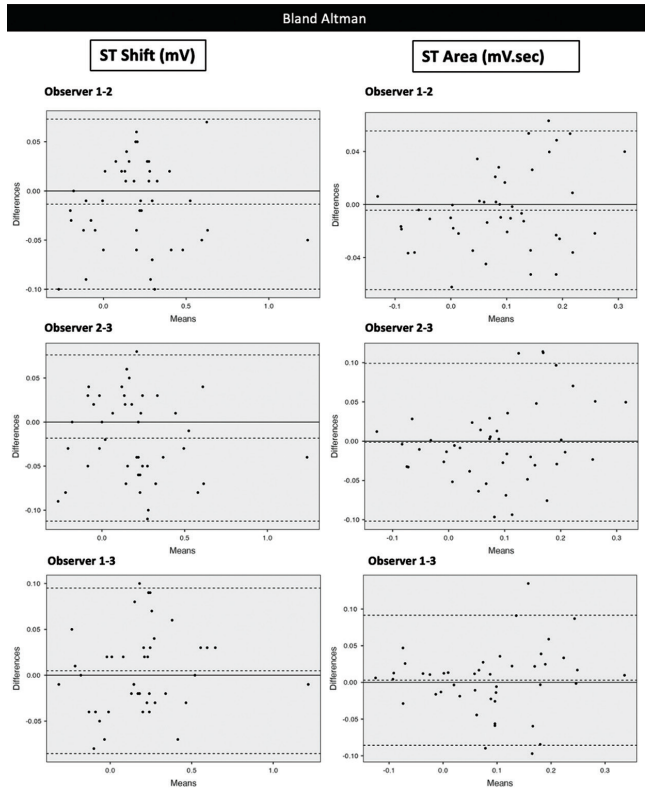

Figure 4: Bland-Altman plots for ST shift, ST area, T-amplitude and QT values of observer pairs.

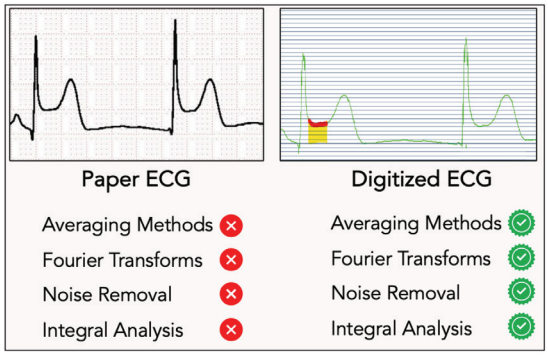

Figure 5: Paper ECG and digitized ECG.
ECG: Electrocardiogram

DISCUSSION

In this study, we have compared ST shift, ST integral, T-amplitude, and QT interval measurements from p-ECG records digitized by a simplistic in-house developed software by three investigators. In all four parameters, the measurements of three observers showed significant and substantial correlations and there were no statistically significant differences in measured values. In the light of these results, we propose that our publicly available software can be reliably used in p-ECG digitization and analysis.

Integral analysis of ECG segments has been previously assessed in several studies and repeatedly shown to be relevant in physiopathological aspects (1-6). Bigler et al. (1) have recently demonstrated that ST integral in intracoronary ECG has remarkable sensitivity for myocardial ischemia. On the other hand, postprocessing of ECG with a miscellanea of techniques has been assessed in several concept studies so far, including root mean squared ECG for long QT syndrome detection, signal averaged ECG inducible ventricular tachycardia prediction, and Fourier transforms for cardiovascular pathology classification (12-14). All of these inherently necessitates digitized version of ECG (Figure 5). In parallel, researchers wishing to utilize their p-ECG archives to train machine learning models share the same need. With the use of publicly available p-ECG digitization tools, researchers with large p-ECG archives can utilize these methods.

Future Directions

We aim to deploy a fully automated follow-up version of this software by employing machine learning algorithms, which is required for more rapid digitization of large p-ECG archives.

Limitations

Comparison between measurements of experienced cardiologists could reinforce the reliability of the software.

CONCLUSION

A simplistic software can reliably digitize p-ECG records, which can enhance cardiovascular research by enabling inclusion of p-ECG records in experimental research that otherwise would be limited to signal ECG.

Ethics Committee Approval: N/A

Informed Consent: N/A

Conflict of Interest: The authors declared no conflict of interest.

Author Contributions: Concept: A.T., Design: A.T., Y.A., İ.K., F.S., M.İ.B., A.Y.D., D.T., Ç.K., Data collection or processing: A.T., Y.A., İ.K., F.S., M.İ.B., A.Y.D., D.T., Ç.K., Analysis or Interpretation: A.T., Y.A., İ.K., F.S., M.İ.B., A.Y.D., D.T., Ç.K., Literature Search: A.T., Y.A., İ.K., F.S., M.İ.B., A.Y.D., D.T., Ç.K., Writing: A.T., Y.A., İ.K., F.S., M.İ.B., A.Y.D., D.T., Ç.K.

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ORIGINAL ARTICLE

DIFFERENT REPORTING PATTERNS OF AUTHOR AFFILIATIONS: A CROSS-SECTIONAL EVALUATION OF PUBLICATIONS FROM AN EGYPTIAN MEDICAL ACADEMIC INSTITUTE

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ABSTRACT

Aims: Inappropriate presentation or reporting of the authors' affiliation may deprive their institution of the research credit for the published work. The study's primary aim was to detect possible patterns of author affiliations being misreported by evaluating the PubMed-indexed publications of Qena Faculty of Medicine, a representative of North African and Egyptian academic institutions, over one year.

Methods: A PubMed search was limited to one year to search for publications from South Valley University, Qena Faculty of Medicine, and Qena University Hospital. The resulting articles were examined to evaluate the contribution of Qena Faculty of Medicine and Qena University Hospital's different departments and the patterns of author affiliations reporting. Author affiliation reporting was divided into three main patterns: I: Missing affiliation information, II: Mistakes in affiliation reporting, and III: Inconsistent affiliation reporting.

Results: For the included 77 articles, there were 59 (76.6%) articles with authors from only one department, 9 (11.7%) with two, 4 (5.2%) with three, and 5 (6.5%) with four. The contribution of all departments totals up to 109 articles. Pattern II was seen in 47 (43.1%) articles and was the most common pattern, followed by pattern III in 31 (28.4%) articles and pattern I in 16 (14.6%) articles.

Conclusion: Certain patterns of misreporting authors' affiliations were detected. Identifying such patterns will help avoid them and protect institutions from being deprived of their research credit. Further evaluation of other faculties and universities on a broader scale is highly encouraged.

Keywords: Egypt, authorship, organizational affiliation, research activities, researchers

INTRODUCTION

Individual researchers, as well as academic institutions, are put under the pressure of the "publish or perish" dictum (1). The rate of scientific publications and citations has been an area of great attention in most universities (2). As the quality and quantity of research being produced determine the ranking and reputation of these academic centers (3).

The scientific activity of an institution or an individual researcher is measured by different indicators (4). A common indicator is the number of their publications and citations they get, preferably in high-ranking well-respected journals (4-6). These measurements are primarily based on scientific publications, especially those included in major databases, such as the Web of Science (6).

According to the Research Organization Registry (ROR), affiliation describes any formal relationship between a researcher and an organization associated with researchers, including but not limited to their employer, educator, funder, or

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scholarly society (7). They also define a research organization as an organization that conducts, produces, manages, or touches research (7). An author may have single or multiple affiliations (1). However, it is generally agreed that the affiliation should be reported according to where the research work was performed (1, 8). Bachelet et al. (9) reported on misrepresenting authors' affiliations by evaluating Scopus-indexed articles published in 2016 from Chilean universities. The researchers reported that they could not validate the authors' affiliations in 38% of the cases, and the authors considered this as a possible case of authorship misconduct and fraud (1, 9). Furthermore, inappropriate presentation or reporting of the authors' affiliation may deprive the affiliated institution of getting the research credit for the published work (1, 9).

To the best of our knowledge, authors' affiliation reporting patterns were not evaluated in our area. Hence, the primary objective of the current cross-sectional study is to detect the possible patterns of authors' affiliation reporting by evaluating PubMed-indexed publications over one year from the Qena Faculty of Medicine (QFM) as a representative of North African and Egyptian academic institutions. The secondary objective is to document the incidence of research output contribution from QFM's various departments during the same period. We hypothesized that possible mistakes could be detected in these reporting patterns.

MATERIAL AND METHODS

Setting

Qena Faculty of Medicine, including Qena University Hospital (QUH), is one of the faculties of South Valley University (SVU), Egypt (10).

South Valley University was established in 1995, and QFM started its undergraduate education in the academic year of 2007-2008 (10). QFM has been active for 14 years, making it one of the youngest Egyptian medical schools (11). It comprises a total of 32 departments (22 clinical, 10 academic), where the clinical departments, such as general surgery and internal medicine, work mainly in the QUH, carrying out clinical activities related to patient care. In contrast, the academic departments, such as microbiology and histology, mainly have operations that do not involve direct patients care. The working staff members in both departments are responsible for teaching undergraduate and postgraduate medical curricula and supervising research activities carried out as a part of Master's and Medical Doctorate degrees or independent research projects.

Search Strategy

We conducted a PubMed search limited to one year, starting from January 2020 to the end of December 2020. By using the advanced search option, we searched articles by affiliation using three search terms 1- "SVU", 2- "Qena Faculty of Medicine", and 3- "QUH". The search results were downloaded in three forms: As a citation list opened in the Endnote program, as an Excel sheet containing the characteristics of each article, and as full abstracts containing the authors and their affiliation data.

The citation list downloaded to the Endnote program was used to find duplicates, which were later deleted. The search results for term 1 were confirmed to contain all the search results for terms 2 and 3 as well, thus, the final analysis was carried out only for the resulting articles of search term 1.

The official names of the QFM's departments were collected from the faculty's official website's departments directory (http://www.svu.edu.eg/faculties/med/en/faculty-departments/), which were later compared with the department names reported in the authors' affiliation sections of the published articles.

Extracting the Results of Interest

We examined all the final studies to define the authors' exact affiliation and authors' departments for articles from QFM or QUH. A publication was credited to a QFM if at least one contributing author was affiliated with it at the time of publication. For the articles from the QFM or QUH, we defined the contributing departments, the incidence of contribution, and the percentage of clinical and academic departments; then we compared the presented name of the affiliated department with its official name in the QFM department names directory. To ensure the accuracy of the data collected, the most senior author revised the extracted data by reviewing randomly selected abstracts.

Defining the Patterns of Affiliation Reporting

Each author independently reviewed the abstracts of the published articles from QFM and QUH in order to form an opinion on the possible controversies and mistakes in reporting the affiliations. A meeting was carried out among the authors to discuss the suspected patterns of affiliation reporting in the articles. It was agreed on to divide the articles into three different patterns. Each pattern will have a number of sub-patterns that indicate possible forms of affiliations' misreporting (Table 1).

Statistical Analysis

Description of data as frequencies and percentages for qualitative variables were performed. No further statistical analysis was needed.

We downloaded the search results from the PubMed database in the form of an Excel sheet with details of the articles, an option offered by the PubMed database. We used this Excel sheet to organize the data and then reported simple explanations of numbers and percentages.

RESULTS

The search for term 1 (SVU) resulted in a total of 261 articles, while using the search terms 2 (QFM) and 3 (QUH) resulted in 20 and 9 articles, respectively. It is noteworthy that the search terms 2 and 3 (29 articles) resulted in 62.3% fewer QFM articles compared to the results obtained from search term 1, which resulted in 77 articles that were included in the analysis.

Of the 77 articles published from QFM and QUH, three (3.9%) articles were in collaboration with other SVU faculties, two with the faculty of veterinary medicine, and one with the faculty of science. Collaborations between different QFM departments were as follows: Authors from only one department (59, 76.6%), two (9, 11.7%), three (4, 5.2%), and four (5, 6.5%) departments, this provides a total contribution of all departments as 109 articles from clinical and academic departments, 83.8% and 16.2%, respectively. The share of each department in the total publications is shown in Figure 1.

Regarding the detected patterns, the sub-patterns of authors' affiliation reporting are each shown with an example in Table 2 (12-21). The most commonly occurring pattern was pattern II, where the authors mistakenly reported their affiliations in 47 (44.8%) articles.

DISCUSSION

Universities are complex academic organizations, serving to create knowledge by conducting scientific research and educational activities, then transferring the generated knowledge to students through tutoring and training, as well as passing this knowledge on to society (6, 22). Participation in scientific research and subsequent publishing of the scientific literature are considered the main factors in improving a university's reputation and ranking, which helps acquire accreditation and increases research funding (6, 9, 23). Misreporting the authors' affiliation in the published scientific articles might deprive universities or academic institutions of this research credit (1, 9).

The main finding of this study is that there exist specific patterns, including mistakes and variations, in the reporting of author affiliations. In 44.8% of the reviewed articles, the authors misreported their departments' names or mentioned a division or a unit that is not present on the official faculty website. Per our investigation, a report with the same aim as ours was not published in an Egyptian University before. We expect that this study's findings will also apply to other universities, and the protocol used can be reproduced by other researchers.

Some universities and academic institutions implement specific measures to improve their research output, such as funding and support to the researchers (24). However, to give back to these institutions, the individual researcher's task is to correctly report their affiliation, securing the research credit to their institution (23).

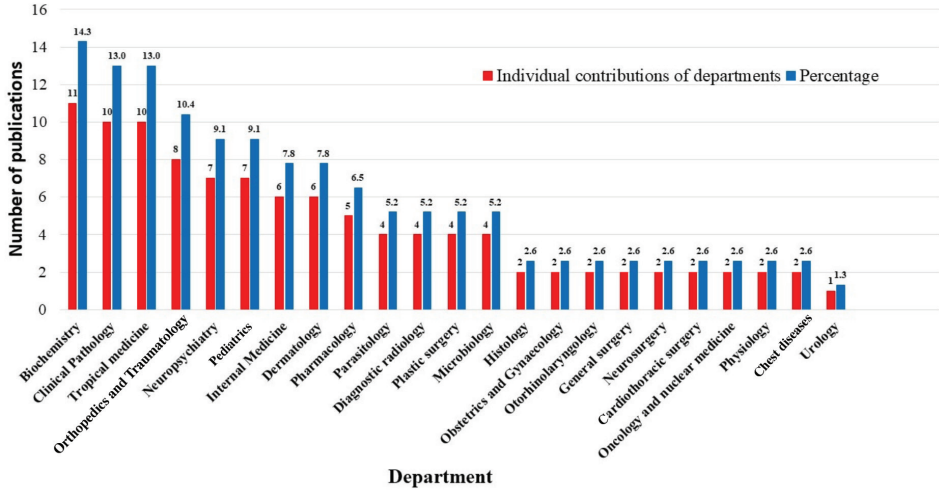

Figure 1: Department contribution to the publications from QFM.

QFM: Qena Faculty of Medicine

Table 1: Possible affiliation reporting patterns.

Pattern	Description	Possible presentation forms (sub-patterns)
I	Missing affiliation information	A- Missing faculty name (authors mentioned the department only).
		B- Missing the department name (author mentioned being affiliated to QFM or QUH).
II	Mistakes in affiliation reporting	A- Department affiliation was presented but different from the QFM website departments directory.
		B- Reporting affiliation to a department or a division that was not present in the QFM website departments directory.
III	Inconsistent affiliation reporting	A- Reporting as being affiliated either to the QFM (for academic departments) or QUH (for clinical departments).
		B- The same department name was written in different forms in the same article.
		C- Department name is presented but different among various articles.

QFM: Qena Faculty of Medicine, QUH: Qena University Hospital

There is an increasing interest in measuring universities' academic performance and ranking them nationally and internationally (25). Universities in non-English speaking countries, such as Egypt, may be ranked lower due to the fact that most of the vital reference databases contain very few non-English scientific publications (25, 26). This poses a larger burden on faculties of medicine, as almost all of their publications are published in the English language, which helps their respective universities to be recognized among these databases (27).

Although measuring the research productivity of an academic institution or an individual researcher is not a straightforward process, they are considered easier to measure compared to other academic activities such as teaching and community development (22, 27). So research output is not only the gold standard for evaluation but also the most reliable variable (22, 27).

Why is Evaluation and Diagnosis of Such Affiliation Misreporting Patterns Important?

Correct identification of the department and the faculty that an author is affiliated with will help acquire research credit for that particular institution (28). This credit is not only required for international ranking, but also for national competition and for increasing visibility to research societies (28). An example of the patterns we noticed is when a researcher mentioned the name of a department without reporting the faculty name (Pattern I A), "Department of Obstetrics & Gynaecology, SVU". The exact name of this department is shared with different faculties in the same university, namely: The faculty of medicine and the faculty of nursing (12, 29). Another example was when the authors reported that they were affiliated with QFM or QUH without mentioning a department (Pattern I B). This can occur when an undergraduate researcher is a co-author of such a publication (30). However, if a researcher is affiliated with a department that they did not mention, this will deprive that department of taking credit for that research (9).

As our research pool was a medical faculty with an associated university hospital, the question of whether reporting the affiliation as the faculty or the university hospital was raised, as detected in pattern III A. For the academic departments, it was clear that all the authors reported their affiliation as QFM. However, a dilemma was present among the clinical departments. Some authors reported being affiliated to QFM only, and some reported being affiliated to QUH only, as an example of pattern III A.

Two of the authors in one article were from the same clinical department; however, they reported different affiliations, QFM and QUH. This caused the publishing journal to consider both authors as affiliates of two different bodies, which might confuse the reader into thinking that these two authors were from separate departments. A different presentation was reported as an example of pattern III C, where one of the authors from a clinical department reported being affiliated with both QFM and QUH and reported it as "QFM and University Hospital". One important point we noticed in our study was that we missed some of the QFM scientific literature during the search process while using different search terms. When the search terms were limited to the faculty and the university hospital only, we noticed a loss of 62.3% of the articles compared to using the university name as the search term. This means that if someone

Table 2: Examples of the affiliation reporting patterns and their incidence.

Pattern	Example	Incidence (n=109) [Number (%)]
I A	In a study by Leduc-Robert et al. (12), one of the authors reported its affiliation as "Department of Obstetrics & Gynecology, SVU" without reporting the faculty name; the issue with this pattern is that the same department is present in other faculties, such as the nursing faculty.	16 (14.7%)
I B	In a study by Mahdy et al. (13), one of the authors reported his affiliation as "QUH" without reporting the department; in another study by Shehata et al. (14), one of the authors reported his affiliation as "Faculty of Medicine, SVU".	
II A	The clinical pathology department is the department's official name in the QFM directory. However, in a study by Suliman et al. (15), one of the authors reported his affiliation as "Clinical Pathology and Laboratory Medicine Department". In another study by Hetta et al. (16), one of the authors reported it as "Department of Clinical and Chemical Pathology".	47 (43.1%)
II B	In a study by El-Abd Ahmed et al. (17), one of the authors reported his affiliation as "Department of Pediatric Surgery, Pediatric Surgery Unit", while neither the name of the department nor the name of the unit is present in the QFM departments directory.	
III A	When reporting the affiliation as a clinical or an academic department, the affiliation should be for QUH or QFM, respectively. In a study by Baseer et al. (18), all the authors were from the Pediatric department, which is a clinical department. However, one of the authors reported being affiliated with QFM, while the others reported QUH as their affiliation.	31 (28.4%)
III B	In a study by Ibrahim et al. (19), two of the authors were affiliated with the same department; however, one author reported his affiliation as "Dermatology, Andrology, and Venereology, QFM" while the other author reported it as "Dermatology, Venereology, and Andrology, QUH".	
III C	In a study by Khalifa and Ahmed (20), the authors reported the department name as "Orthopaedic açnd Traumatology Department, QFM and University Hospital". In contrast, in another study (by one of the two authors listed in the previous article) (21), the author in this article reported his affiliation as "Department of Orthopaedic Surgery, SVU".	

QFM: Qena Faculty of Medicine, QUH: Qena University Hospital, SVU: South Valley University

is looking for the research output of QFM, about two-thirds of the already published work will be missed during this search, this is mostly due to incorrect affiliation reporting.

We admit that this study has several limitations. Firstly, we investigated only one faculty and with a specific time limit of one year; however, we considered this study a preliminary report to raise awareness of the existence of such a problem and initiate further studies on a larger scale which should contain a larger sample size. Secondly, we used only one search engine (PubMed) to find the articles. The reason for doing so is that, besides PubMed being known as one of the oldest and most popular scientific indexing databases, amount of articles indexed in PubMed is used as a measurement by some Egyptian faculties to decide whether to offer someone a promotion (31). Furthermore, it offered the ease of using search filters, such as searching by affiliation only, and the results could be downloaded in various forms, which enabled easier data processing. Research on the entirety of a specific institution's research output can be carried out by detecting publications in journals that are indexed in leading global indices such as the Science Citation Index, Web of Science, or Scopus, their equivalents. However, the disadvantage of using the previously mentioned indices is that they list only a small number of journals (27). Lastly, the use of academic e-mail or researcher identifiers, such as ORCID, by the authors could not be assessed because the corresponding author was not affiliated with QFM in some articles; therefore, their e-mail addresses were not provided. Additionally, an ORCID ID was not mandatory for some journals.

Some recommendations to avoid affiliation reporting diversity detected in the current study include implementing new policies by the universities, governmental and institutional organizations through the Ministry of Higher Education to ensure a uniform and accurate presentation of affiliations (25). Ministry of Higher Education and relevant authorities should provide accurate and standardized translations of the institutions' and departments' names. A separate affiliation protocol should be included for undergraduate students or interns who publish their work, as they are affiliated with the faculty and not with a specific department. Evaluating the research performance of certain academic institutions using previous evaluation models, such as the one recommended by Caminiti et al. (32), can be beneficial. From the researchers' side, they should be encouraged to use their academic e-mail addresses and researcher identifiers, such as ORCID, as suggested by Bachelet et al. (9). From journals' and specialized communities' perspectives, the publication process should include verifying the authors' affiliation before submitting manuscripts. As Gould (33) discussed, further affiliation reporting and verification should be offered by specialized communities such as ROR. Gould (33) also stressed the importance of correctly reporting affiliations and the role of creating ROR IDs for the research institutions, which prevents researchers from losing any of their work.

CONCLUSION

Specific patterns of authors' affiliation reporting mistakes and diversity were detected in our study. Identifying such patterns will help avoid them in future publications and prevent depriving a particular institution of its research credit. A checkpoint verifying the authors' affiliation before manuscript submission may benefit many institutions. Further studies evaluating the authors' affiliation reporting patterns in other universities on a broader scale are highly encouraged.

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CASE REPORT

SOLITARY METASTASIS MASQUERADING AS PRIMARY COLON CARCINOMA ON FDG PET-CT IN A TREATED PATIENT OF BREAST CARCINOMA

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ABSTRACT

Breast cancer is the most common malignancy among women across the globe. Despite receiving treatment, patients may develop recurrence and metastasis. Breast cancer most commonly metastasizes to the bones, lungs, liver, lymph nodes, and brain structures. Metastasis to the gastrointestinal tract is rare, with only a few cases reported in the literature. F18-fluorodeoxyglucose positron emission tomography-computed tomography is performed to localize occult metastasis and suspected recurrence of breast carcinoma that remain undetected in conventional imaging techniques despite rising tumor markers. This case report describes an unusual course of the disease in a patient treated for breast cancer with late presenting colon metastasis mimicking primary colon cancer on fluorodeoxyglucose positron emission tomography-computed tomography. This case demonstrates that fluorodeoxyglucose positron emission tomography-computed tomography can identify the occult metastatic site in patients with breast cancer even at a rare site such as the colon; however, histological evaluation is required to differentiate between breast cancer metastasis to the colon and primary gastrointestinal malignancy.

Keywords: Breast cancer, PET-CT scan, neoplasm metastasis, recurrence

INTRODUCTION

The most common type of cancer amongst women is breast cancer (BCa) and it has recently surpassed lung cancer to become the most common malignant neoplasm overall worldwide (1, 2). The current demographic trend indicates that BCa will pose an even greater public health threat in years to come (3). The most frequently diagnosed type of cancer in women in Pakistan is BCa and one in nine women is at risk of being diagnosed with this morbidity (3). Nearly 12% of patients diagnosed with BCa eventually develop metastatic cancer despite receiving standard treatment including surgery, cytotoxic chemotherapy, radiotherapy, and hormonal treatment (4). Metastasis to common sites such as bones, skin, lungs, liver, and brain is a frequent cause of death and morbidity among BCa patients (1). Although rare, metastasis to the gastrointestinal tract (GIT), spinal cord, and meninges have also been reported (5). Colorectal metastasis may mimic a primary large bowel cancer; however, the metastatic disease should be considered whenever a patient presents with gastrointestinal symptoms such as chronic bowel obstruction, particularly in BCa patients with aggressive tumor biology or receptor-negative diseases (6, 7). Occult metastasis of breast cancer may pose a challenge when serum tumor markers such as CA 15-3 show a rising pattern indicating disease recurrence, and when both clinical examination and conventional imaging modalities fail to identify a site of recurrence or metastatic disease (8).

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Fluorodeoxyglucose labeled with positron emitter fluorine-18 is used for combined positron emission tomography-computed tomography (PET-CT) in the evaluation of oncologic conditions. Studies have shown that FDG PET-CT plays an important role in the detection of locoregional and distant recurrence as well as in monitoring the response to therapy in patients with BCa (6, 9).

This report presents the case of a patient who previously underwent treatment for BCa, and then developed metastasis eight years after completing treatment with chemotherapy. Initially suspected because of a rise in CA 15-3 level, which led to FDG PET-CT detected metastasis to a rare site in the colon mimicking a primary carcinoma.

CASE REPORT

A 45-year-old female was diagnosed with invasive ductal BCa after a lump in the left breast was evaluated in December 2012. After thorough investigation including mammography, ultrasound of breasts, bone scan, and ultrasound of abdomen and pelvis revealed stage IIIA BCa, the patient underwent left mastectomy and nodal dissection in December 2012. Following the operation, the patient received six cycles of adjuvant chemotherapy that included fluorouracil, adriamycin, and cyclophosphamide followed by three-dimensional conformation radiation therapy of the chest wall delivering 50 Gray of radiotherapy. The treatment was completed in October 2013. Since the histology of the surgical specimen demonstrated estrogen receptor positive status, the patient was advised hormonal therapy comprising tamoxifen 20 mg once a day orally. Patient continued to receive oral tamoxifen during the follow-up period of eight years without any significant adverse effects. During the patients' follow-up evaluation in March 2021, CA 15-3 serum level was found to be 40.5 U/mL, which was higher compared to the normal reference range of 30 U/mL. The serum level of CA 15-3 was 61.3 U/mL in October 2021, demonstrating a further rise since March 2021. The patient underwent several procedures for the detection of recurrence including mammography of the right breast, bone scan, chest CT scan, and abdominal and pelvic ultrasonography, but the results did not reveal any evidence of recurrence. FDG PET-CT scan was performed for further evaluation after the patient's consent was taken. FDG PET-CT was conducted after intravenous administration of 315 MBq of FDG followed by a whole body scan using ST Discovery (GE) PET-CT scanner adopting acquisition protocol as per European Association of Nuclear Medicine guidelines. The scan revealed an abnormal focal area of hypermetabolic wall thickening involving hepatic flexure/proximal transverse colon with mild haziness of adjacent omental fat, which was considered significant for primary malignant neoplasm (Figure 1). After informed consent, a colonoscopy was performed, and biopsy specimens were obtained from the diseased site that revealed malignant neoplastic tissue growth. Biopsy report revealed metastatic ductal carcinoma features with 100% estrogen receptor positivity consistent with metastatic BCa to colon (Figure 2).

The authors made an application for a waiver to the institutional review board to share the learning experience with the scientific community. The institutional review board studied the application and the case report, and decided its' unusual findings may increase awareness among the medical community of rare sites of metastasis from BCa that develop years after standard treatment including surgery, chemotherapy, and radiotherapy. The review board found that a waiver in this case would not adversely affect the right and welfare of the concerned patient. Hence, a waiver was granted for this case report.

DISCUSSION

The range of patients presenting with distant metastasis at the time of the first diagnosis, that is de novo metastatic breast

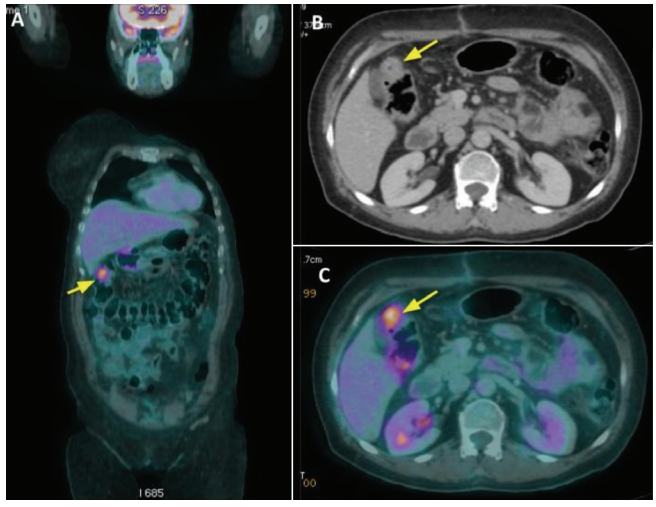

Figure 1: Focal region of increased metabolic activity (yellow arrow) demonstrating standardized uptake value of 8 involving hepatic flexure of colon on fused coronal **(A)** and fused axial **(C)** images of FDG PET-CT. Corresponding axial CT image **(B)** from PET-CT scan demonstrate focal thickening of colon wall (yellow arrow).

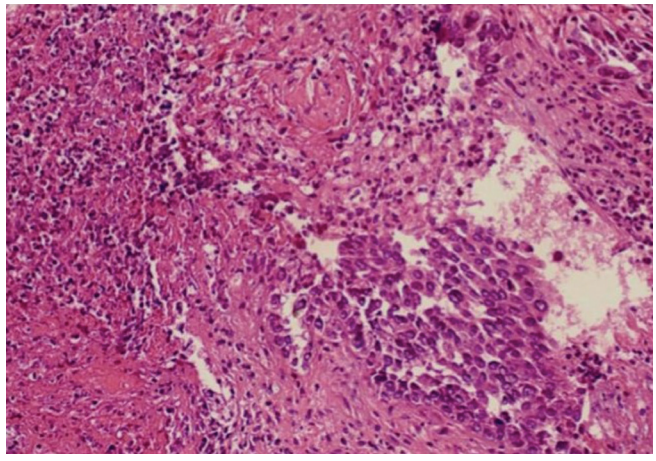

Figure 2: Histological analysis of surgical specimen after biopsy of colon mass that was detected on fluorodeoxyglucose positron emission tomography-computed tomography demonstrated diffuse sheets of ductal differentiation favoring metastatic invasive ductal carcinoma.

cancer, varies from 10-25% in low to middle-income countries to 3-6% in high-income countries (10). However, analogous to our case, a large fraction of patients who are metastasis-free at the time of the first presentation eventually develop distant metastasis despite receiving standard treatment for BCa (11). Although the most common sites for distant metastasis are bones, lungs, liver, and brain, some rare cases of GIT metastasis have been reported in the literature (5). The most frequent organ involved in GIT metastasis is the stomach and involvement of the colon is quite rare (11). Unlike upper GIT metastasis, which often causes symptoms such as vomiting, dysphagia, and abdominal pain earlier in the course of the disease, lower GIT metastasis may remain asymptomatic or produce mild symptoms, which was the case with our patient (12). In a published series, metastasis to colon in primary BCa patients were found in only 20 out of 720 cases (13, 14). Also, Taal et al. (15) have reported 17 cases of colorectal metastasis from BCa over a study period of 15 years. The primary tumor in most of the cases reported by Taal et al. (15) histologically belonged to lobular carcinoma. Unlike our case, the majority of cases with GIT metastasis have been found in patients with lobular type of BCa. Aggressive biology, poor response to standard therapy, and higher propensity of metastasizing to other organs have been identified as possible causes of such behavior of lobular type of BCa (11). Few reports in recently published literature have documented detection of GIT metastasis in BCa patients with invasive ductal carcinoma histology type (16, 17). It is hypothesized that longer survival of patients after effective chemotherapy allows development of metastases in a relatively less aggressive invasive ductal variety of BCa as well. Generally, a mean interval of 53 months after completing primary treatment has been documented among patients who present with GIT metastasis (15). In another study, Schwarz et al. (18) reported 7 cases with metastatic BCa mimicking a GIT primary. The reported average interval in this series was 6 years between diagnosis of BCa and GIT metastasis, and the average survival time after presenting with GI symptoms was 12 months. In our patient, the interval between development of distant metastasis after the completion of primary treatment with chemotherapy and radiotherapy was approximately 9 years. This may be attributed to the suppressive effect of hormonal therapy, as the patient had estrogen receptor positive disease and used oral therapy. It appears from the literature that BCa patients with metastasis to GIT are uncommon, and therefore presence of prior history of malignancy does not necessarily imply GIT metastasis. To differentiate between primary and metastatic tumors involving GIT, histopathological comparison between histological specimens of BCa and GIT features is mandatory. The morphological similarity to the previous BCa and the absence of dysplasia in adjacent colonic epithelium is considered metastatic growth rather than colon primary. Immunohistochemistry analysis also plays an important role in differentiating primary colon carcinoma from GIT metastasis of BCa (11).

FDG PET-CT is not recommended as the primary diagnostic procedure in BCa as the sensitivity of FDG PET-CT ranges between 64-96% and specificity between 73-100% (19). However, it has the potential to be useful for the detection of distant metastases with a reported sensitivity of 80-100% and specificity of 75-100% (20). In another report, the sensitivity and specificity of FDG PET-CT were shown to be better than the sensitivity and specificity of conventional imaging for detecting distant metastatic disease (21). The FDG PET-CT may be particularly useful in patients with biochemical evidence of recurrence or with occult metastasis in whom conventional imaging remains unsuccessful in the detection of the metastatic site.

Local recurrences may be treated by surgery and radiation followed by systemic therapies. The GIT involvement in metastatic BCa represents a systemic disease in which hormonal therapy and chemotherapy, along with surgery, have been reported to produce a favorable response. FDG PET-CT in such cases is considered useful in ascertaining solitary or limited disease and excluding multiple or widespread metastatic deposits.

This case presents an unusual case of colonic metastasis from BCa, and thus adds to the fact that although isolated GIT metastases are very rare, metastatic disease should be taken into consideration whenever a patient demonstrates biochemical evidence of recurrence with or without GIT symptoms. FDG PET-CT localizes solitary colonic the metastatic from BCa accurately; however, histology of the surgical specimen remains the gold standard in differentiating primary colon carcinoma from metastatic deposit of BCa.

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CASE REPORT

SWOLLEN LIMBS AND DELAYED ECCHYMOSIS: UNEXPECTED ENCOUNTER WITH ACQUIRED HEMOPHILIA A

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ABSTRACT

Acquired hemophilia A is a rare disorder and may be first encountered anywhere from the primary care setting, emergency departments, and like in this case report, orthopedic clinics. This case report is about an elderly patient with comorbidities not usually associated with acquired hemophilia A, initially presented with left wrist swelling following a bee sting, which later turned into ecchymosis. The later presentation of ecchymosis prompted the clinician to investigate the coagulation profile, which led to a referral to the hematology team for further workup, and the subsequent diagnosis of acquired hemophilia A. Considering the high mortality rate of AHA, high index of suspicion, early management, and prompt referral to a hematology team are very important.

Keywords: Autoimmunity, ecchymosis, hemophilia A

INTRODUCTION

Acquired hemophilia A (AHA) is a rare disorder with an annual incidence of 1.48 cases per 1 million healthy individuals per year in the United Kingdom (UK) (1). The usual initial presentation of patients diagnosed with AHA is bleeding events, which may be spontaneous, or associated with trauma, surgery, and the peripartum period (2). Skin, deep muscle, and mucosal tissues are common sites of bleeding (2). Given the rarity of the disease and its unfamiliarity among clinicians, diagnosis is challenging and often delayed (2). While AHA is rare, patients presented with swollen limbs are common with vast differentials. This is a case report of an elderly patient diagnosed with AHA who initially presented with vague swelling of limbs with delayed ecchymosis.

CASE REPORT

A 64-year-old male patient with a history of diabetes mellitus, hypertension, and dyslipidemia initially presented to the clinic with complaints of left forearm swelling associated with intermittent neuropathic pain from elbow toward the hand following a bee sting one week ago. Initial examinations of the left upper limbs revealed a firm, erythematous, and warm diffuse swelling over the wrist extending to distal forearm. It was associated with numbness over the ulnar aspect of the left hand and forearm. He was initially treated for forearm cellulitis and completed a course of antibiotics. Following the treatment, the swelling reduced, but the numbness persisted although it was intermittent and had less frequency. The patient underwent electromyography, which revealed normal results.

At the patient's follow-up visit, the ulnar nerve neuropathy symptoms were found to be resolved. Although patient's ulnar nerve neuropathy symptoms were resolved, he had vague discomfort over his left leg and both of his forearms. There were multiple ecchymoses of varying ages and sizes seen in the bilateral upper limb and left thigh (Figure 1). Diffuse swelling over the anterior aspect of the left leg was also present. The patient denied any prior trauma. Blood investigations revealed an isolated prolonged activated partial prothrombin time (APTT) of 85.2 seconds (normal range 32.4-42 seconds). Ultrasound of the left leg revealed no focal lesion or collection. He was referred to the hematology team to investigate further the cause of

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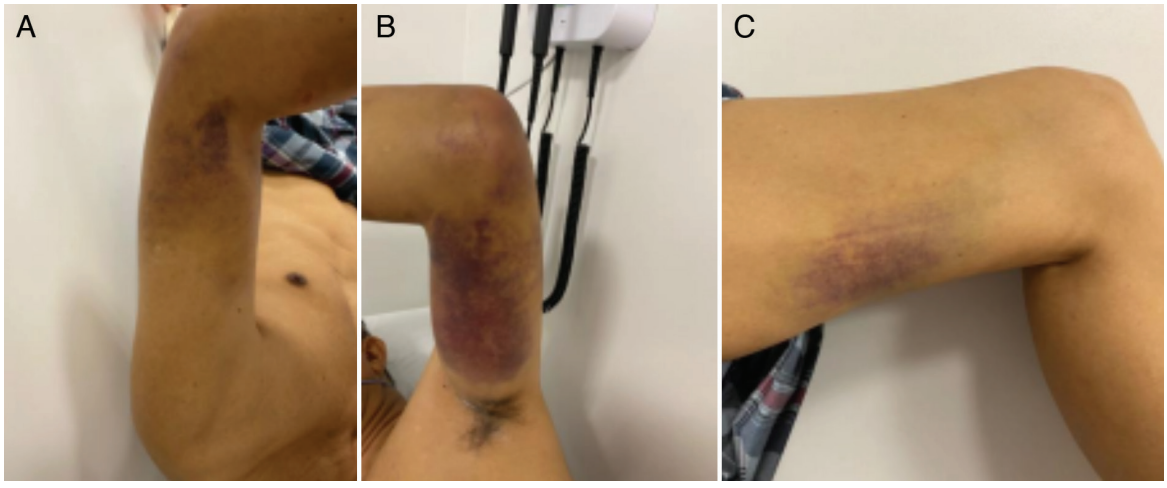

Figure 1: Multiple ecchymoses during first follow-up visit noted at the lateral and medial aspect of left arm, and medial aspect of left thigh.

isolated prolonged APTT and was investigated as an outpatient.

One month later, he presented to the emergency department with a complaint of worsening left forearm swelling and pain. Symptoms were associated with extensive ecchymosis over the left upper limb, which was extending from forearm to mid-arm. The patient denied any trauma. He still had vague discomfort over his left leg. Examination of his left upper limb showed diffuse swelling of left upper limb from forearm distally to mid-arm proximally, which was firm, and tender upon deep palpation, limiting his elbow range of motion. Extensive ecchymosis over the medial aspect of the forearm to the mid-arm was also present. Neurovascularity of the left upper limb was intact. There was also ecchymosis over his left thigh, which did not worsen since previous visit. He was admitted to the ward for observation of the swelling. Ultrasound of the left forearm revealed an intramuscular hypoechoic lesion that was likely an intramuscular hematoma. Blood investigations revealed persistent isolated prolonged APTT, non-correctable mixing study, low factor VIII of 1.3% (normal range 50-150%) with the presence of factor VIII inhibitor at 18.4 Bethesda unit. The hematology team reviewed him in the ward and diagnosed him with AHA with bleeding tendency. Initial treatment started by the hematology team included intravenous vitamin K and tranexamic acid, transfusion of fresh frozen plasma, cryoprecipitate, prothrombin complex concentrate, oral prednisolone, and cyclophosphamide. He was then transferred to a hematological center for further treatment and workup for the diagnosis of AHA.

DISCUSSION

Initial presentation of a swollen limb with a precipitating factor such as an insect sting, as seen in this report, usually does not require the clinician to investigate any hematological disorder. The extensive bruising that the patient later developed was the eliciting factor behind the clinician's investigation of the coagulation profile, which lead to a referral to the hematology team for further workup, and, subsequently, the diagnosis of AHA. The exact period that the patient developed the disease is not known.

Acquired hemophilia A is a rare disorder with an incidence of 1.48 cases in 1 million healthy individuals per year in the United Kingdom (1). According to a UK study, 63% of the cases are elderly with ages between 65 to 80 years old (1). 43% to 63% of the patients who do not have underlying diseases are at risk of getting AHA (1, 2). In terms of gender, there is a higher incidence in females compared to males, with incidence rates of 57% and 42%, respectively; although in older age groups, incidence of AHA is higher in males (1, 2). In the female age group between 20-40 years old, most cases of AHA are pregnancy related (1-3). Development of AHA can be linked to multiple factors such as malignancies, autoimmune diseases, pregnancy, infections, and drugs (1-3). However, more than half of the time AHA is idiopathic (1-3).

The exact pathophysiology of AHA remains unclear (4). However, it is known to be associated with the production of antibodies that affect the function of factor VIII in the coagulation cascades due to immune system dysfunction and the inhibition of thrombin generation and fibrin clot formation because of factor VIII deficiency (3, 4). These deficiencies will lead to the presentation of bleeding events in patients with AHA (3, 4). In AHA, the autoantibodies involved are mostly in the immunoglobulin G1 and immunoglobulin G4 classes. These antibodies will bind to factor VIII epitopes and affect the binding of factor VIII to von Willebrand factor, the formation of intrinsic rename complexes, and the interaction of factor VIII with phospholipids (3, 4).

Diagnosis of AHA is precipitated by bleeding events most of the time (89%) with most common being spontaneous bleeding (77.4%), while others are associated with trauma, surgery, and the peripartum period (2). With regards to sites of bleeding, common sites include skin, deep muscle, and mucosal bleeding, with incidence rates of 53.2%, 50.2%, and 31.6%, respectively

(2). Other sites of bleeding include hemarthrosis and intracranial bleeding, which are rare (4.9% and 1.1%) (2). The mortality rate is considerably high, which is up to 27.9% (2). In this case report, the patient developed a bleeding tendency following a bee sting, which may be considered a minor trauma precipitating the bleeding tendency. There are, however, some case reports with regards to insect sting or bites that lead to the diagnosis of AHA (5, 6).

A local case series of AHA summarizes that the disease has a different initial presentation. Two out of the 5 cases reported have initial presentations of spontaneous extensive skin bruising, while other cases have presented with prolonged bleeding after a dental procedure, post-natal vaginal bleeding, and bilateral lower limb weakness (7).

Treatment of AHA includes control of bleeding, inhibitor eradication, treating the underlying disorders, and prevention of trauma. Hemostatic management includes bypassing agents and strategies to increase the level of circulating factor VIII. Bypassing agents are commonly used as first-line treatment and it includes prothrombin complex concentrate. Inhibitor eradication with immunosuppressive therapy should be undertaken as soon as the diagnosis has been made. The options for immunosuppressive therapy include steroids, cytotoxics (cyclophosphamide, azathioprine, or combination therapy), rituximab, cyclosporin A, plasmapheresis, and FVIII immune tolerance (3).

Acquired hemophilia A is rare and it has a high mortality rate. This case report focuses on the importance of clinical suspicion, early management, and prompt referral to the hematology team.

Ethics Committee Approval: N/A

Informed Consent: An informed verbal consent was obtained from the patient.

Conflict of Interest: The authors declared no conflict of interest.

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