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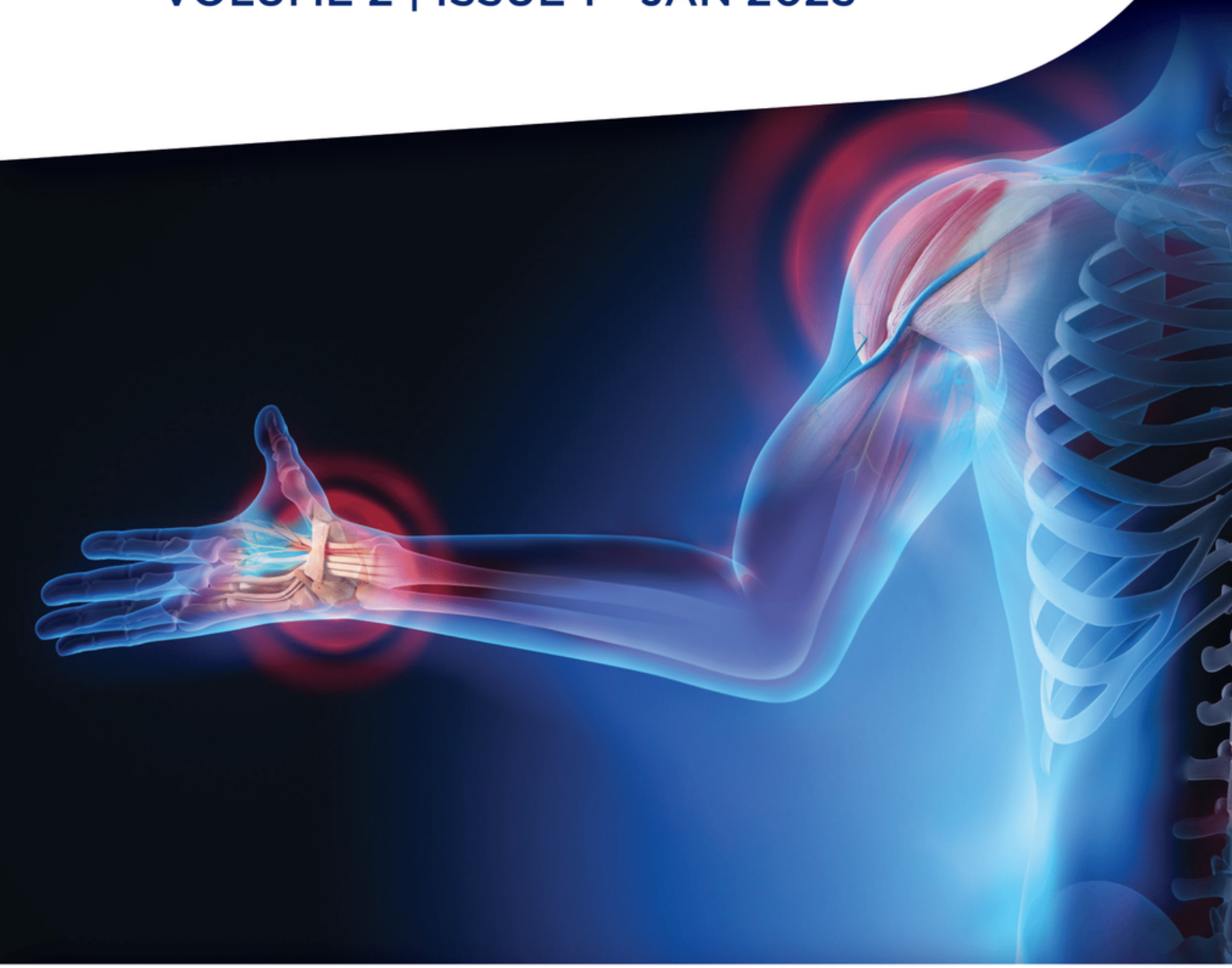

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Barriers to capacity building amongst physicians in the Sri Lankan health sector - a point of view

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Vision and mission statement of Sri Lanka College of Internal Medicine states that it hopes to achieve a nation with a premier health service through excellence in internal medicine by undertaking a mission to deliver healthcare with a holistic approach (1). Holistic care addresses physical, emotional, social and spiritual wellbeing of the patient and is succinctly given in a quote of the famous physician Sir William Osler - father of modern medicine - *"It is much more important to know what sort of a patient has a disease than what sort of a disease a patient has" (2)*. The theme of the College for the year 2022 was enhancing clinical excellence, capacity building and humane care (1). Although there are many barriers the College has to circumvent to achieve these goals, the discussion to follow will focus only on barriers to capacity building amongst physicians in Sri Lanka and how we may overcome some of those barriers.

I have no conflicts of interest and what I am expressing are my own personal observations and opinions based on my experience of four decades as a medical teacher and a physician trainer, and wisdom gained during fifty years as a doctor. Some contents in this article are based on my experiences, observations and comments of my fellow trainers/trainees alone and cannot be supported with references due to dearth of accessible Sri Lankan studies.

As defined by the United Nations; capacity building is the process of developing and strengthening the skills, abilities, pathways and resources that organisations and communities need to survive, adapt, and thrive in a fast-changing world (3). An essential ingredient in capacity building is transformation that is generated and sustained over time from within; transformation of this kind goes beyond performing tasks to changing culture, mindsets and attitudes. Therefore, during capacity building, we not only have to perform tasks but change culture, mindsets and attitudes with a lasting impact among healthcare workers. Even leading economies in the world have shortcomings in capacity building. Sri Lanka's health sector has many. Capacity building programmes have to operate at state level, institutional level, team level and finally at the level of the individual healthcare worker.

Main organisations that are directly concerned with capacity building in Sri Lankan healthcare include, Ministry of Health, hospitals, community healthcare services and medical faculties. Organisations lead two lives akin to two parts of an iceberg (organisational iceberg) the visible part and the unseen/submerged part or to put across differently; the visible formal public one, as described in organisational charts and procedure manuals; and the submerged informal one, which is the lived experience of the organisation (4). The formal public or didactic one includes, mission, goals, plans, structures, policies, assets, resources, rules and procedures. The informal or experiential aspects include unofficial working arrangements, social networks at work, and battles for influence and authority and it is breakdown or issues in these aspects that often lead to disruption in capacity building programmes despite availability of resources.

Several important barriers to capacity building can be identified within the healthcare services in Sri Lanka. These include inconsistent drive and poorly

sustained efforts; non-adherence to timelines/deadlines, lack of protected time; insufficient collaboration across colleges; insufficient incentives; Continuing Professional Development (CPD) being not mandatory for promotions and for licence to practise. Other important factors are dearth of human resources (5); brain drain out of the country and within the country (6); leadership issues; inadequate mentoring, supervision and feedback; poor team effort; dearth of physical resources; cultural barriers; hierarchical structure; poor recognition of interprofessional education; socio-political issues; lack of a policy on capacity building in the Ministry of Health and negative forces from trade unions. I will discuss possible solutions to overcome some of these barriers in the remaining section of the article.

Protected time for CPD activities and merit for such activities should be encouraged to support capacity building. Inability to provide protected time can be due to understaffing, especially in the periphery. The Ministry should avoid internal brain drain leading to overstaffing of larger hospitals at the expense of smaller hospitals. Colleges and the Ministry should recognize CPD points of trainees and trainers' roles of consultants, when awarding fellowships and appointments to Teaching Hospitals.

Another factor that can impede capacity building is physician burnout. Recent study done amongst postgraduate doctors working in Colombo has shown a high prevalence of burnout (7). It is up to the doctors themselves to prevent burnout or recognise red flags at early stages and take remedial measures. Giving priority to self-care, avoiding chronic work overload, avoiding rumination of thoughts and living your values can help to prevent or minimise burnout. Role of the Ministry would be to prevent work overload and professional colleges should offer counselling services.

As mentioned earlier, capacity building takes place also at individual level and its magnitude is highest during the internship. Doctors learn a lot during the internship. Learning continues from medical school to internship and beyond. Interns learn many professional skills and professional behaviours from their consultants and other trainers and it is important for them to be good role models (8). To enhance capacity building at individual level, trainees should also be given regular feedback for formative purposes (9).

Leadership and team issues can impede capacity building. In Sri Lanka, medical services in hospitals are fragmented into several wards, overlooked by different specialists. This leads to too many leaders and teams with different visions and missions and loss of synchrony. As a result, there is no unified road map for capacity building. Should we follow the model in developed countries with one team for each specialty and one leader - the clinical director? This approach is more effective and efficient for capacity building. When there is no proper leadership, it can cause teams to function ineffectively, becoming a barrier to capacity building. For effective teamwork; there should be clarity of team identity and objectives, explicit roles of members; with effective team processes involving sound decision making, good communication and constructive debate with good leadership and appropriate inter-team working (4).

Inadequate clinical governance in our hospitals is another barrier for capacity building. Clinical governance can be defined as 'the framework through which healthcare organisations are accountable for continuously improving the quality of their services and ensuring high quality of care'. Clinical governance encompasses clinical audit, risk management, clinical effectiveness, quality assurance, staff development, and research and development (10). These areas need to be addressed by the ministry and professional colleges.

Every year, when the College instals its new office bearers, the focus changes and a new theme is taken on board (1). It takes a few months to get going and the term of office lapses without leaving much time for reflection, evaluation of progress and feedback. This is true of most professional colleges in Sri Lanka. This approach which is similar to aiming at a moving target is inefficient and it can be an impediment to progress. Longer tenure of office as in Royal Colleges of Physicians

and/or expert committees as in Sri Lanka Medical Association would be more effective and efficient.

Uncontrolled private practice can be a barrier for capacity building. It can affect a physician's capacity building such as self-directed learning as well as capacity building undertaken on his/her trainees, in addition to upsetting the work-life balance.

This article is an attempt to sensitise the reader to important barriers to capacity building in healthcare in Sri Lanka and advocate measures that may be taken to overcome some of them. The intention of this article was to create awareness and not to point a finger at any individual, professional colleges or the Health Ministry. Having pointed out many barriers, I would like to end on a positive note. Sri Lanka provides a good health service despite limited resources but we should continue to strive for excellence. Our doctors are of international standard. I hope physicians and physician trainees would consider barriers described as stepping stones to excellence and strive to achieve the vision of the College of achieving a nation with a premier health service through excellence in internal medicine.

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Ethics review of research: is there a need?

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Abstract

Ethics review of a research protocol by an independent ethics review committee (ERC) is an integral aspect in the conduct of research and aims to safeguard the rights, welfare and wellbeing of research participants. The ethical review process can be time consuming for both the researcher and the members of the ERC and may be considered unnecessary where the risk is minimal. This article discusses the need to regulate research through ethics review, the key issues that are important in such reviews and discusses how the problems that may arise in this process can be reduced.

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Key words: Medical research, Ethics review

Introduction

Research aims to obtain generalizable knowledge relevant to man by means of a scientifically respectable methodology (1). Medical progress must, therefore, include studies that ultimately involve human subjects but this goal should not take precedence over the rights and interests of individuals who take part in such research (2). Unlike in therapeutic interventions that aim to benefit patients, the functional outcome of research is to extend or further develop knowledge and these outcomes are unpredictable (1,3). This uncertainty is the fundamental characteristic of research and makes accurate assessment of risks and benefits of research difficult (3). The benefits of research are mostly to others than those taking the risks of research and research participants may directly benefit only at times (3).

In this article I will discuss the arguments for and against regulation of research through ethics review. I will also highlight some of the problems faced during the ethics review process and discuss how these problems can be minimised.

Should research be regulated?

Research that involves human participants, especially when it is medical research, is closely regulated compared to other types of research and is more so when it involves interventions -i.e. clinical trials (3). The regulation is considered necessary as research involves individuals with rights and interests that may be affected by activities pertaining to the research (1). Research regulation occurs through both administrative and ethics approval prior to commencement of research and periodic monitoring thereafter where necessary. However, it is often felt that research is overregulated and is counterproductive, as it tends to discourage researchers (4). Regulation could also add to the cost of the research which would be significant in low resource settings (3).

There are many historical examples on exploiting human participants during research and initial guidelines related to research ethics – e.g., the Nuremberg code and the Belmont report - were developed in response to such abuse and resultant scandals. An important measure to

reduce such abuse was the introduction of a structured ethics review process where the protocol was reviewed by an independent body (2). While the older ethical issues appear less now, newer issues have arisen with new developments in Science, for example bio banks and data sharing, and these must be addressed with minimal delay to avoid harm to research participants. Ethics review of proposed research is only one way of minimising harm to research participants.

Ethics review of research

Ethics review of research has expanded globally over the last 50 years and plays an important role in research regulation. In many instances this is the 'final hurdle' to be cleared before research can commence. Medical research in almost all countries now must undergo a review by an Institutional Review board (IRB) or an Ethics Review Committee (ERC). The approval by an ERC is also a prerequisite for publication in high-impact journals and this has been the driving force for the expansion of ethics review of medical research seen globally and locally.

In many instances, the issues raised by ERCs during the review process are not unique to research, the same issues may be seen in day-to-day life too. However, by virtue of being 'research' these issues can have a different impact. While risks may only be possible but not definite in any planned research, it is important that steps are taken to reduce their occurrence (3). Risks become more important when the procedures involved in research introduce new risks that are not otherwise present (3).

A key aspect in ethics review is the evaluation of risk-benefit ratio. Both the investigators and the ERCs are required to ensure that the risks are appropriately identified, and measures are instituted to ensure minimal discomfort/harm to study participants. While even healthy volunteers have suffered critical illness during research due to interventions, most research that is done both globally and locally carry minimal or moderate risks to participants (5). Yet, the ethics review process remains the same and even if the protocol is presumed to be of minimal risk it must be evaluated by an independent body to ensure a favourable risk- benefit ratio to participants (2, 6). Consider for example, questionnaire-based Knowledge-Attitudes-Practices (KAP) studies which are usually considered to be of minimal risk. However, if the questions asked are of a sensitive nature that has the potential to cause distress to the participant, the risk-benefit ratio changes and could vary from moderate to severe. The same applies for audits and would depend on what is being audited and who has access to the data that will be perused (6). Auditing a registry of HIV positive patients will carry a different risk-benefit ratio to an audit on medical records to determine the door-to-needle time for thrombolytics at an emergency department. A blanket exception from ethics review for research simply because it is an audit or is questionnaire based is therefore inappropriate.

Research involving human subjects carries some risk to all research participants, this risk can vary from minimal to severe. An important aspect in the ethics of risk management is whether the person who is subjected to a risk also benefits from that risk (7). When the participant does not directly benefit from the research but will only help to find generalizable knowledge, minimising such risks becomes more important. Research ethics and a review by an ERC, aims to ensure a favourable risk-benefit ratio, the autonomy of and justice to study participants (2,6). The informed consent process and the ability to withdraw from the research at any time without penalty give participants some control over the risks they undertake (3). However, the quality of information given and the ability to understand that information plays a major role in this process.

The difference between research and therapy is an important distinction that must be made as people may at times be unaware that they are participating in research and not being treated for the disease they have (8). This 'therapeutic misconception' may cause people to take risks without truly understanding them and violates the autonomy of the research participant as an informed and autonomous decision must be taken to participate in research (8).

Both the researcher and the ERC must ensure that the information given to participants accurately reflects what will be done during research and that it is given in a manner the participants can understand. This highlights the need to submit the information sheets in English and the vernacular of the community involved for perusal by the ERC. It is mandatory that all translations are consistent and contain all necessary information regarding the research. The perusal of information sheets, especially those in the vernacular, which is what will be given to participants, is one method of ensuring accurate transfer of information to participants to enable them to make an informed and autonomous decision. The process of obtaining consent must also be clearly stated in the protocol and must be evaluated by ERCs to ensure that participants make their decisions voluntarily and without coercion.

Overcoming problems related to ethics approval process

While ERCs aim to provide protection against research subjects being harmed, the time spent in getting ethics approval prior to commencing research and thereafter for any protocol amendments, is considered too long by many researchers (3,4).

The delays in obtaining ERC approval can be multifactorial. In a study to determine reasons for resubmissions to an ERC in Sri Lanka, protocol related issues accounted for 66.3% of instances while issues related to informed consent accounted for 29.5% (9). The correct methodology is important to ensure accurate and generalizable results and ensures the scientific validity of research (2,6). Issues in methodology accounted for 46% of instances in the Sri Lankan study (9). These could have been easily avoided if the applicants had paid attention to methodology during the development of protocol and by ensuring that all relevant documents were included at the time of submission (9).

A major cause for delays is the need to get approval from multiple ERCs when research must be conducted at different sites (10). The need to obtain multiple ERC approvals for the same research can be overcome if there is reciprocity for the ethics approval given by another ERC (11). While it happens to some extent in Sri Lanka with hospital based ERCs accepting the ethics approval given by the ERCs of medical faculties affiliated to these hospitals, it is done in an ad hoc manner. However, to be effective and mutually acceptable, all ERCs should function at a consistent level in relation to the reviews done. Given the constraints faced by ERCs, especially with regards to time commitment of ERC members who perform their functions as additional work from their regular occupations and on a voluntary basis, this is hard to achieve. A way forward is to develop an acceptable method to evaluate and accredit all ERCs in the country that evaluate biomedical research. Of the many ERCs in the country, only 9 have undergone an external evaluation process and 8 of these are those affiliated to medical faculties.

A major criticism against ERCs is that they assess the scientific validity – i.e the methodology. Scientific validity is important to ensure that the findings are valid and generalizable and therefore will benefit the society at large (1,2,6). Without scientific validity, the research lacks social value and must not be conducted (6). Many countries have separate research/scientific committees that evaluate methodology of a protocol, and this would make the work of the ERC easier. In the absence of any other body to ensure scientific rigour, it becomes a task for the ERC to evaluate the methodology and ensure that scarce resources and participants are not exploited. Conducting both scientific and ethical reviews by a single committee, provided the expertise is available to do so, may also reduce the time taken for review.

Another criticism against ERCs is the differences in decisions or comments that may be given for the same protocol by different ERCs for protocols that need multi-site approval (12). Given the plurality of different views represented on an ethics committee and the variety of experience and expertise in considering and identifying ethical issues in research, some of these variations are to

be expected (3). While there are some well-known and agreed-upon standards in research ethics, there are also many ethical issues where a single agreed-upon answer is not possible. The level of expertise and experience of members of ERCs will also contribute to differences seen in reviews by different ERCs (12). These differences may be minimised to some extent with continued training of ERC members and a uniform external evaluation process of all ERCs in the country to ensure appropriate and comparable standard of review.

A major concern for both researchers and the ERCs is when the time spent to review is disproportionate to the risks involved in the proposed study. There are arguments for and against a proportional ethical review where it is proposed that the ethics review should be proportional to the level of risks represented by the research (13-15). While this sounds attractive, this method runs the risk of missing important potential risks that are identified by a discussion between ERC members (15). Currently the ERCs have the option for exempting protocols that do not pose any risks to participants from review while conducting an expedited review for protocols that carry no more than minimal risks to participants (6,16). However, both these processes must be conducted by the ERCs and not by the researcher as the ethical judgement about his/her project could be clouded by the conflicts of interests that arise by virtue of being the researcher whose objectives would be different to that of the participants. If properly conducted, the expedited reviews will reduce full board reviews of low-risk protocols by ERCs but would add to the workload of individual members involved with such expedited review processes. For such processes to be effective, the protocols must identify and address ethical issues correctly and the documentation should be complete at the time of submission to the ERC.

The many arguments against research regulation were widely stated during the recent COVID-19 pandemic. Epidemics/pandemics require rapid answers to hitherto unexpected problems. Research into these questions is essential and is an integral aspect in management of epidemics (6). Any delay in finding answers could have catastrophic outcomes. ERCs adapted to the situation by conducting accelerated/rapid reviews with minimal delays. An accelerated review is done under exceptional circumstances and is identical to the usual full board review. Only the time taken for the process usually by the ERCs was reduced. Most delays that occurred during the ethics reviews at these times were due to poorly prepared protocols as the researchers were trying to conduct studies quickly on COVID. Pandemics are no exception to research rigour, and it is essential to uphold the ethical principles that are practised at other times (6). Conducting research in these situations is challenging as there is a need to generate knowledge quickly while maintaining public trust and overcoming practical obstacles to implementing research (6). These challenges need to be carefully balanced with the need to ensure the scientific validity of the research and uphold ethical principles in its conduct (6).

Conclusion

Regulation of research by way of administrative activities or ethical review should not be a barrier for conducting good quality research that provides generalizable knowledge which will benefit people. Given the conflicts of interests of the researchers that may arise due to their objectives being at variance with those of participants, ERCs could act as a vehicle to allow researchers to fulfil their ethical obligations to research participants. Careful planning of the study and discussing the issues with the ERCs, expedited review of protocols that carry no more than minimal risks to participants and reciprocal recognition of reviews done by similar ERCs can help to minimise much of the delays that can occur during ERC review processes. A laissez-faire attitude to ethics review must not be the answer.

Conflict of interest: CAW is chairperson of the Forum for Ethics Review Committees in Sri Lanka, the Chairperson of the ERC of the Sri Lanka Medical Association and a former member and Chairperson of the ERC of the Faculty of Medical Sciences, University of Sri Jayewardenepura. The views expressed are her own.

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Carpal tunnel syndrome with shoulder symptoms; is it a different entity?

A prospective cohort study comparing recovery patterns following decompression

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Abstract

Background: Carpal tunnel syndrome (CTS) may present with atypical proximal symptoms other than hand symptoms.Among proximal symptoms, shoulder symptoms are most distant to the site of compression and leads to a battery of investigations to exclude other pathologies. The recovery patterns of proximal symptoms have not been studied following carpal tunnel decompression.

Methods: A prospective cohort study was conducted to compare the recovery patterns between subgroup-A; CTS patients (n=55) with shoulder symptoms, with subgroup-B; patients (n=55) without shoulder symptoms. A pre-tested questionnaire was administered prior and after the surgery and information was gathered on day-7, day-14 and day-21.

Results: Of 110 patients, 81.8% were females. The mean age(±SD) of the total population was 49.2(±10.6), that of subgroup-A was 48.7(±10.3), and subgroup-B was 49.7(±11) years. They were predominantly right-handed (82.7%), 73% had their dominant hand affected while 74.5% were affected bilaterally at presentation. All had hand symptoms: numbness in 94.5%, pain in 85.4%, tingling of hand in 66.3% and all-three symptoms in 57.2%. In subgroup-A, pain was the predominant shoulder symptom which appeared before hand symptoms in 34.5%, after in 47.3% and simultaneously in 18.2%. It was aching-type in 91%. The pain radiated proximally (neck and scapula) in 61.8% and to the arm in 81.8%. The recovery rates (RR) of hand symptoms following decompression on day-7 were 41.8% in subgroup-A and 40.0% in subgroup-B. RR of hand symptoms in subgroup-A and subgroup-B on day-14 were 72.7% and 70.9%, while on day-21 were 83.6% and 85.5% respectively. RR of shoulder symptoms in subgroup-A were 38.2% on day-7, 65.4% on day-14, and 78.2% on day-21.

Conclusions: Near identical RR of hand and shoulder symptoms were seen between the two subgroups after decompression, which indicates CTS with shoulder symptoms is not a different entity.

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Key words: Carpal tunnel syndrome, shoulder symptoms, recovery rates, decompression, CTS

Introduction

In the early twentieth century, carpal tunnel syndrome (CTS) was recognized as acroparesthesia. In 1906 Farquhar Buzzard and W. W. Keene suggested treating this with resecting the first rib (1). This theory of brachial plexus plexopathy persisted till the mid twentieth century. Subsequently, several surgeons started publishing their results to show a more distal reason for compression (2). This treatment focused on the carpal tunnel as the point of compression. A landmark paper by Cannon and Love in 1946 described the surgical treatment at the wrist level for CTS (3). Later, numerous studies by Brain and Phalen popularised the current understanding (4). The term “carpal tunnel syndrome” first appeared on print in 1953 by Kremmer et al (5).

Atypical proximal symptoms may have led to the uncertainty of the site of compression in CTS. Among atypical proximal symptoms, shoulder symptoms are the most distant to the site of compression and clinically more relevant (6). The shoulder symptoms in patients with CTS have been reported to be around 6.3 to 19% in different populations (7,8). The presence of atypical proximal symptoms and the different characteristics of shoulder symptoms are thought to be due to different pathophysiological reasons (9). The median nerve has three main anatomical variations at its formation, different patterns of branching and variable cross communications with other nerves (9, 10).

The specific treatment for CTS is decompression of the carpal tunnel at the wrist. Though the recovery patterns of distal hand symptoms are described following decompression, the data on recovery from proximal symptoms are scarce. This study mapped the recovery patterns seen among CTS patients with shoulder symptoms in comparison to those without shoulder symptoms. We also studied the characteristics of proximal symptoms including shoulder symptoms. Study of the recovery patterns of proximal symptoms following decompression helps to indirectly prove the causal relationship of origin of symptoms and potentially minimise unwanted and expensive investigations done to exclude other pathologies when a patient presents with shoulder symptoms due to CTS.

Methods

This prospective cohort study was conducted from January 2018 to January 2019 at the department of plastic surgery of a tertiary care institution in Sri Lanka . Patients diagnosed with CTS who would undergo decompression surgery were recruited for the study. They were referred from the departments of medicine and neurology after evaluation for CTS. Each one of them had undergone electromyogram (EMG) and nerve conduction study (NCS) to confirm CTS and to exclude other neuropathies. An individual who had clinical syndrome of median nerve (MN) compression confirmed by neuro-electrophysiological study was considered as a case of CTS.

Comprehensive neck and upper limb examination was carried out by a trained physician. Cervical X-ray and ultrasound examination of the shoulder joint was carried out when clinically indicated. The following categories were excluded from the study: patients with diagnosed cervical radiculopathy, two or more compression neuropathies, other painful pathologies e.g., trigger finger, post trauma or active synovitis, active inflammatory arthropathies. All the subjects who fulfilled the above criteria and consented for the decompression surgery were enrolled. Informed written consent was taken for the study and consent for surgery was taken separately. A pre-tested, interviewer administered questionnaire was designed to extract necessary data from the individual subject prior to the surgery. The latter part of the questionnaire was completed following the decompression surgery over the phone. Symptoms of CTS were categorised according to the two regions involved: hand/forearm symptoms (below elbow) or shoulder/arm symptoms (above elbow). Patients were divided into two groups accordingly: both shoulder/arm and hand/forearm symptoms (subgroup-A) and patients with only hand/forearm symptoms (subgroup-B). Symptoms were further studied in detail in relation to onset, radiation, severity, nature, resolution, and associated other symptoms.

Post-op evaluation was done on day-7, day-14 and day-21. The resolution of symptoms following the surgery were recorded. Null-hypothesis of "there was no difference between the two groups in the recovery pattern after decompression surgery" was tested. Statistical Package for Social Sciences (SPSS) software version 20 was used for the analysis of data. Descriptive statistics were used to describe population parameters. Complete recovery rates in the subgroups at the three points were calculated. Significant differences between subgroups were calculated using the chi-square test. The ethical clearance was obtained from the ethical review committee of the institution.

Results

Out of 110 patients, 81% were females (female: male ratio was 4:1). The mean age (SD) was 49.2 (±11) years. They were predominantly right handed (83%). Carpal tunnel syndrome was evident bilaterally at presentation in 83% while unilateral in 17%. The condition had predominantly affected the dominant hand in 73%. The population was divided into subgroup-A (n=55) and subgroup-B (n=55). The mean (±SD) age of subgroup-A and subgroup-B were 48.7 (±10.3) years and 49.7 (±11.0) years respectively. The prevalence of diabetes mellitus among subgroup-A was 18.2% while subgroup-B was 16.4%. Hypertension was reported as 18.2%, while hypothyroidism was reported as 3.6% in each subgroup.

Hand symptoms

Hand symptoms were present in all the patients. The reported symptoms were numbness, pain and tingling sensation of the hand which were reported in 95%, 85.4% and 66.3% respectively. All three symptoms were present in 57.3%.

Shoulder/arm symptoms

Patients with both shoulder and hand symptoms were identified as (n=55) subgroup A. Pain was the only symptom related to the shoulder region among them. Shoulder pain appeared before, after and almost simultaneously with hand symptoms in 34.5%, 47.3% and 18.2% respectively. Shoulder pain extended further proximally to the neck and/or scapular region in 14.5%. The majority (81.8%) experienced arm pain in addition to shoulder pain. Shoulder pain was mild in 12.7%, moderate in 52.7% and severe in 34.5%. The majority (91%) experienced an aching type pain while the rest had pricking type (5.4%) or burning type (3.6%).

Decompression outcome

Recovery rates of hand symptoms were recorded independently from recovery rates of shoulder symptoms on day-7, day-14 and day-21 following carpal tunnel decompression. Then the recovery rates of hand symptoms were compared with shoulder symptoms in subgroup A. Recovery rates of distal and proximal symptoms were nearly identical and not statistically significant (Table 1).

Table 1 - Complete recovery rates of hand and shoulder symptoms of patients with both symptoms in subgroup A (n=55)

	Day 7	Day 14	Day 21
Hand symptomsrecovery rate (%)	41.8	70.9	85.5
Shoulder symptomsrecovery rate (%)	38.2	65.4	78.2
p value	0.69	0.54	0.32

Table 2 - Complete recovery rates of hand symptoms in the two subgroups (subgroup A - patients with both shoulder and hand symptoms, subgroup B - patients with only hand symptoms)

	Day 7	Day 14	Day 21
Subgroup A - hand symptomsrecovery rate (%) n=55	41.8	70.9	85.5
Subgroup B - hand symptomsrecovery rate (%) n=55	40.0	72.7	89.1
p value	0.84	0.83	0.56

Recovery rates of hand symptoms in day-7, day-14 and day-21 following carpal tunnel decompression were recorded, and compared between subgroup A and subgroup B. Recovery rates were not significantly different between the two subgroups in our study (Table 2).

Discussion

Our study showed near identical complete recovery rates of hand symptoms in CTS patients with or without shoulder/arm symptoms following decompression surgery. Recovery rate of hand symptoms on day-7 among patients without shoulder symptoms was 40.0% whilst among patients with shoulder symptoms was 41.8%. Recovery rates of hand symptoms were 72.7% and 70.9% on day-14 , while recovery rates were 89.1% and 85.5% on Day-21 respectively. Complete recovery rates of shoulder symptoms on day-7, day-14 and day-21 were 38.2%, 65.4%, 78.2% respectively.

A wide variation in clinical presentation of CTS may have contributed to the historical confusion in describing the syndrome. Clinical symptoms of the hand remain consistent and well understood. In our study population, the presence of hand symptoms was a universal finding among participants. In previous studies, paresthesia/numbness of hand was reported in >95% of patients with CTS (11,12,13). Similarly in our study, symptoms of numbness, pain and tingling of hand were reported in 95%, 85.4% and 66.3% respectively.

However, the symptoms of CTS are not only limited to the hand. These compression symptoms may extend proximally up to the shoulder girdle. Out of proximal symptoms the shoulder symptoms remain poorly described. The frequency of shoulder symptoms vary from one study to another from 6.3-19% in different populations. (7)

Patients belonging to subgroup A had symptoms not only limited to the hand region but extending proximally to the shoulder/arm region. All of them had pain in the shoulder, but the nature, severity and the timing were different. There are limited reports on the character of the shoulder symptoms up to now. This group of patients have described it as an aching type of pain. It is quite different from the hand symptoms. At the same time the majority has described it as a moderate to severe type of pain. Character of radiation is poorly understood and the timing of the symptom may vary. In our population, shoulder pain appeared in one third of patients (34.5%) before hand symptoms. Rest of the population reported shoulder symptoms after and almost simultaneously with hand symptoms. They described the pain as radiating towards the arm, neck or even scapula. In 1973, Kummel et. al. described the presence of radiating shoulder pain in CTS (8). The presence of shoulder pain could alert the clinician to an alternative diagnosis or

additional pathology. Therefore, proximal symptoms can take the patient and the clinician towards a battery of expensive, unnecessary and inconclusive investigations.

This referred pain or recently described retrograde neuropathic pain (RNP) is thought to have a neurological reason. There are mainly three theories explaining the RNP. The convergence theory is a phenomenon that has been demonstrated in various other nerves (14). It explains the possibility of combining specific pathways that carry sensory information from related regions to the brain. When extrapolating this to the MN, the sensory pathway of the hand and shoulder could be carried in the same nerve (15). Evidence from cadaveric studies for this phenomenon is limited. However it could be explained by the Hiltons law applied to the musculocutaneous nerve (MCN). The mystery of a subset of patients with shoulder pain could also be explained by the existence of interconnections between MCN and MN as described in cadaveric studies(16).

The second theory states that the pain fibres of the MN and the efferent fibres of the shoulder could potentially be sharing a second order neuron. This could be triggering the brain to misinterpret the shoulder as a site of origin of the pain (17). Another theory of unmasking the shoulder pain pathways following activation of these pain fibres at the wrist level could be adopted from the original description (18). Moreover, the individual variations in perception of shoulder pain may be explained by combination of all these mechanisms or in different combinations and/or in different intensity. Our study conforms to above theories and observations by showing similar recovery rates of shoulder symptoms on par with hand symptoms in patients with carpal tunnel syndrome.

A systematic review conducted in 2008 revealed that complete or marked improvement occurs in 70-90% of patients by one year following treatment for CTS (19). Recovery rate of hand symptoms by day-21 in our study was 85- 89%. Recovery rates of hand symptoms between the two groups showed no significant difference. Therefore, despite having an additional shoulder symptom both groups appeared identical. Furthermore, shoulder symptoms recovered at the same rate. There was no statistically significant difference in their hand-symptom recovery rates and shoulder-symptom recovery rates. These results have two implications to patients with CTS. First, patients with typical shoulder symptoms of CTS have a good recovery following MN decompression at the carpus. Secondly, recovery from hand symptoms and shoulder symptoms of CTS may take up to a few weeks for complete resolution. Which means that there is no immediate complete resolution in many patients.This is explained by the nerve symptoms that are thought to have the ability to register themselves along the pathway (20).

Despite those individual variations, clinicians should offer early decompression and assess potential resolution of shoulder symptoms for a few weeks before subjecting them to advanced investigations. It is a therapeutic option for shoulder symptoms in patients who have already been diagnosed with CTS.

Conclusion and Recommendations

Despite those individual variations, clinicians should offer early decompression and assess potential resolution of shoulder symptoms for a few weeks before subjecting them to advanced investigations. It is a therapeutic option for shoulder symptoms in patients who have already been diagnosed with CTS.

Limitations

The recovery rates are only followed up to three weeks post decompression.

Declarations

Ethics: Ethical clearance was obtained from Ethical review committee, Teaching Hospital Kurunegala .

Availability of data and material: Electronic data is available on request

Consent for publication: All authors agreed.

Conflict of interest: None

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Authors' contribution: Ekanayake GNS and Manilgama SR are principal investigators. They equally contributed in developing the study concept, supervising the data collection, analyzing data and writing the manuscript.

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Presentation to healthcare and the prevalence of frailty among older adults to the outpatient department of a tertiary care hospital in Sri Lanka

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Abstract

Background: Sri Lanka is one of the fastest-ageing countries in the world, with the proportion of the population aged 60 years or older projected to increase from 12.5% in 2016 to 16.7% in 2021. By 2041, one out of every four individuals in Sri Lanka is expected to be an elderly person. In this study, the burden of geriatric presentation to a hospital's outpatient department (OPD) was assessed. These patients' frailty, along with comorbidities, the existing level of geriatric care by the healthcare team at the OPD, and the level of patient satisfaction were also studied.
Methods: A cross sectional study was conducted in March 2021.
Results: Of 406 recruits 58.4% were female and their mean (±SD) age was 72.25 (±5.63) years. Among them, 39.7% (95% CI 34.9% to 44.6%) were frail. There was a higher prevalence of frailty among men than women (p=.001). Hypertension was the most common comorbidity. The most common diagnosis was musculoskeletal pain followed by leg ulcers. The mean consultation time with waiting time was 56 (±54 SD) minutes. Most patients classified their overall feeling of satisfaction as "good" (80.3%) while 5% stated it was poor.
Conclusions: The prevalence of frailty among this sub-urban population is higher than previous studies. A majority of patients presented with non-life-threatening conditions and classified their overall satisfaction as relatively good.

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Key words: Older adults, outpatient department, frailty, comorbidity, Sri Lanka

Introduction

Sri Lanka is one of the fastest-ageing countries in the world, with the proportion of population aged 60 years or older projected to increase from 12.5% in 2016 to 16.7% in 2021. By 2041, one out of every four people in Sri Lanka is expected to be an elderly person (1-3). Categorical definitions of the old, elderly, aged and ageing are neither straightforward nor universally applicable (4). The United Nations considers an older person as a person who is over 60 years of age. But most countries of the developed world have accepted the chronological age of 65 years as a definition of 'elderly' or older persons. In this study, the elderly subjects considered are those above the age of 65 years. The population of older adults (>65 years) in Colombo district is 235,463 (5)

Frailty is an ageing - related syndrome of

physiological decline which increases the risk for developing negative health outcomes and the risk for hospitalisation (6). Clinical presentation in the elderly and the frail individuals can be very nonspecific.

Noncommunicable diseases have become one of the leading causes of hospitalisation among the elderly population (2). Although not specifically aimed at the elderly, a large proportion of curative healthcare services are consumed by them. Therefore, healthcare institutions should be equipped with both specialist multidisciplinary staff and assistive infrastructure to deliver targeted quality healthcare.

Patient satisfaction is an important and commonly used indicator for measuring the quality of healthcare. It is affected by timeliness, efficiency, and patient-centred care. It is thus a proxy but a very effective indicator to measure the overall performance of healthcare workers, and institutions.

To establish separate services for geriatric care, there is a need for identifying the number of geriatric admissions to the OPD and the type of their presentations. Hence our study assessed the proportion of the geriatric admissions to the OPD, presenting problems of older adults, any frailty and comorbidities among them, and their satisfaction levels.

Methods

A cross sectional study was conducted from 1st March 2021 to 31st March 2021 at the outpatient department (OPD) of University Hospital KDU. Most of the population was from a suburban area (Piliyandala-Colombo district).

Sample size was calculated using the formula ($n = Z^2p\ (1 - p)/m^2=400$) with a 95% confidence level, 50% population proportion and 5% margin of error. For the study, systematic random sampling was performed by selecting every fourth geriatric patient who presented to the outpatient department (OPD) over the period of one month, above the age of 65 years. Patients' overall satisfaction was assessed in terms of the waiting time at OPD, time taken for consultation, specimen collection, drug delivery , and their perception of overall care.

Patients brought by the community without a guardian (two patients for the study period) and critically ill patients were excluded from the study.

Study tool: An interviewer-administered questionnaire was utilised. The questionnaire consisted of sociodemographic data, a frailty assessment using Prisma 7 questionnaire, comorbidities, reason for OPD care, primary diagnosis based on International Classification of Primary Care (ICPC) and overall satisfaction of the patients. Prisma 7 questionnaire has been used in clinical practice for a long time in different countries and it is convenient for the OPD set up as it consumes less time . Face validity and content validity were obtained for Prisma 7 with three different clinicians. Patients' satisfaction was assessed using five responses (very good, good, fair, poor, very poor). The complete questionnaire underwent the same process of face and content validity with three different clinicians (two physicians, one with special interest in geriatric care and a clinical psychologist). Patients' identities were not disclosed, with each patient being assigned a code.

The interviewer administered questionnaire was delivered by co-investigators who were trained and supervised by the principal investigator throughout the study duration.

Data was analysed using SPSS version 24. Mean differences were compared using t test and proportions were compared using chi-squared test. One-way ANOVA was used to find the statistical significance in comorbidity among the study group.

Ethical clearance was obtained from the Ethical Review Committee of General Sir John Kotelawala Defence university and special permission was obtained from the executive director of UHKDU. Informed written consent was obtained from patients depending on their preference. When the patient was unable to give details, details were

taken from the carer.

Results

A total of 1932 elderly patients received OPD care during the study period and 406 (mean (±SD) age 72.25(±5.63) years] were recruited to the study. There were 237 (58.4%) females (mean (±SD) age of 71.8 (±5.8) years] and 169 (41.6%) males (mean (± SD) age of 72.9 (±5.7) years]. Out of them, 293(72%) were between 65-74 years of age, 97(24%) were between 75-84, and 16(4%) were older than 85 years of age. Among all, 340 (84%) of them were able to walk without assistance, while walking sticks were used by 37(9%) of the patients, walkers were used by 12(3%), and 17(4%) had to depend on a wheelchair. One hundred and sixty-one (39.6%) of them were frail while frailty was more prevalent among men than women (p=0.001) (Table 1). One hundred and twenty-nine (32%) patients claimed that they had some health issue which limited their activities.

The comorbidities among the study population were hypertension 201 (49.5%), dyslipidaemia 185(45.6%), diabetes mellitus 157(38.7%), arthritis 75 (18.5%), dementia 27(6.7%), cerebrovascular events 14 (3.4%), and Parkinson disease 8(2%). Hypertension is the proportionately higher comorbidity. Two hundred and ninety-four (72.4%) of them had more than three comorbidities which were hypertension, diabetes mellitus, and dyslipidaemia. Assistance with daily activities was required by 97(23.9%) patients. Three hundred and seventy-four (92%) of them stated that they had someone around to ask for help but 32 (7.9%) of them did not have anyone from whom to request support.

The main presenting complaints among the majority of subjects were body ache, chest pain, dizziness and arthralgia followed by leg ulcers. Musculoskeletal pain was the commonest primary diagnosis given on discharge at OPD, followed by leg ulcers. (Table 2). Forty-eight (11.8%) elderly patients were admitted to the hospital while one was transferred out. Mean duration of time (±SD) spent in the hospital for consultation was 56 minutes. Specimen collection time, time to receive investigation results, and duration spent in the pharmacy was <1 hour in 93.8%, 13.4% and 72.8% respectively. Most patients stated the overall satisfaction of OPD care as good (80.3%), 14,7% stated it was fair, and 5% stated it was poor.

Discussion

This study reflects the proportion of geriatric patients presenting to the outpatient department of university hospital KDU. . Though the study had

Table 1 - Frailty among elders

	Not frail (%) n=245	Frail (%) n=161	Total (%) n=406
Age (years)			
65-74	207(70.6)	86(29.3)	293(72)
75-84	32(33)	65(67)	97(24)
>85	6(37.5)	10(62.5)	16(4)
Gender			
Male	86(50.9)	83(49.1)	169(40.1)
Female	159(67.1)	78(32.9)	237(58.4)

Table 2 - Diagnoses at OPD

Diagnosis	Percentage (%) n=406	Admissions (%) n=48
Musculoskeletal pain	87 (21.4)	-
Leg ulcers	55(15)	-
Eye conditions	33(9)	-
Rheumatology problems	24(6)	-
Urinary tract infections	23(5.7)	6(12.5)
Cellulitis	19(4.7)	8(16.6)
Diabetes emergencies	11(2.7)	1(2)
Acute coronary syndrome	12(3)	12(25)
Hypertensive urgencies	10(2.5)	2(4.2)
Dizziness	9(2.2)	-
Stroke	5(1.2)	5(10.4)
Others (each category <1%)	119(30)	13(27)

a limited number of patients, a fairly large percentage of outpatient care was given to geriatric population at UHKDU. Out of the recruited patients, 39.7% (95% CI 34.9% to 44.6%) were frail. Frailty was more prevalent among men than women which is similar to findings in a comparable study performed in Colombo (7). These elderly individuals were between 65 and 101 years of age. Interestingly, 29.3% of a younger group (65-74 years) among them were frail to the point that they required serious consideration. The Colombo district study was performed with a newly-validated frailty validated instrument which differed from the one used in this study. The prevalence of frailty in the Colombo study was 14.9%, and higher in elders above the age of 75 years, which is comparable to the findings in this study (7). In a study done in rural Kegalle, Sri Lanka using "Fried phenotype", prevalence of frailty was 15.2%, out of which 47.5% were above the age of 80 years without any gender variation (8) . The population surveyed in this study largely consists of people seeking medical care from the hospital, which may explain the high prevalence of frailty in the study.

Presenting complaints were somewhat similar to a Singapore emergency unit study (9) which reported abnormalities of breathing (10.6%), falls (9.4%) and musculoskeletal pain (8.2%). This study is missing breathing difficulties and falls as they were diverted to COVID triage and accident service respectively. A South Indian study done in a geriatric outpatient department stated that their main presentations were hypertension, diabetes followed by musculoskeletal disorders (10) where this study had limited hypertensive and diabetes issues as presenting problems, but majority had hypertension as a comorbidity. But that study was conducted in a dedicated geriatric outpatient

department, not a common unit which was the case in this study. This study had more female population than the above studies. Mean age (72.2 years) of our study was compatible with the Singapore study (72.8 years) whereas the Indian study's mean age was 65 years (9, 10). In both the Singapore and Indian studies, the cut off age was taken as 60 years whereas our cut off was 65 years. Our study setting was a recently built spacious hospital which has a more pleasant environment than other surrounding hospitals where most of the patients had good overall satisfaction.

There are limited studies in outpatient departments of Asian countries in this field. The increasing demand on healthcare by geriatric patients will be a burden to the health sector. If there are community geriatric clinics, minor complaints could be directed there, and it would be much more convenient for them to get treatment than taking all the trouble to come to a busy hospital.

It is important that Sri Lanka should recognise the special need for elderly care due to the ageing population. Compiling the profile of geriatric cases presenting to the OPD and finding the prevalence of frailty among them will help to identify crucial areas of need and prepare the healthcare workers and healthcare system to confirm the challenges of delivering care for minor complaints and acute geriatric care.

Conclusion

The prevalence of frailty among this sub-urban population is higher than previous studies and frailty was more prevalent among men than women. A majority of patients presented with non-life-threatening conditions and musculoskeletal pain was the commonest diagnosis. Majority had more than three comorbidities while hypertension was the commonest. Many categorised their overall satisfaction as relatively good.

Recommendation

Implementation of community geriatric care led by geriatricians and specialists in internal medicine with special interest in geriatric care would focus on frail older adults and reduce the burden of the outpatient department. Then, the necessary admissions can be triaged to the curative sector. Training and retraining of doctors and supportive staff regarding geriatric care and improving the facilities in geriatric friendly manner at OPD and further studies with care given at OPD would help to further improve the overall care. Introducing simple elderly friendly care in any hospital would improve the services and help the older adults to a significant amount which can be adopted by any other state hospital without an additional cost. Performing similar studies in multiple centres would help us to get adequate information to initiate geriatric care in any state hospital.

Limitations

Throughout the study period, according to the guidelines issued by the Ministry of Health, OPD received patients after COVID triage at the gate. Therefore, most of the patients with respiratory symptoms and fever secondary to respiratory illness were directed to COVID screening and treatment unit. Further, as an active accident service is not running, falls were directed to a nearby tertiary care hospital. Both categories were not included in the audit. Prisma 7 frailty score is not validated in Sri Lanka but that was the most convenient and less time-consuming instrument which had face and content validity in this study. Patients brought by the community were not recruited due to high vulnerability and to avoid legal issues, but there were only two patients under that category over that period.

Declarations

Ethics: Ethical clearance was obtained from Ethical review committee of Faculty of Medicine, General Sir John Kotelawala Defence university.

Availability of data and material: Electronic data is available on request

Consent for publication: All authors agreed.

Conflicts of interest: None

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Authors contribution: Jayasekera MMPT, corresponding author and principal investigator, developed the study concept and was involved in the supervision of data collection, the verification of the accuracy of data, funding, and the preparation of the final document. Edirisinghe EMDT done the statistical analysis. Hulugalle CDK assist in development of the audit, data collection, verified the accuracy of data and entering, Ramawickrama SM, Merusinghe AP, Marasinghe TD, aided with data collection and verified the accuracy of the data.

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Additional information

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Perceived level of stress in patients with acute coronary syndrome in Sri Lanka: associations and short-term outcomes

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Abstract

Background: Chronic stress is a known risk factor for cardiovascular disease. This study sought to determine the association between the 'perceived level of stress' in patients with acute coronary syndrome (ACS) and its short-term outcome. This is the first study done on the perceived level of stress in patients with ACS in Sri Lanka.

Methods: A total of 313 ACS patients from the Professorial Unit of the Colombo South Teaching Hospital completed the Perceived Stress Scale-10. The scale assesses the stress perceived by the patient based on ten questions. The sum of scores ranges from 0-40. High stress was defined as scores of 20 or above.

Results: High-stress levels were found in 238 (76%) patients and low stress in 75 (24%). There was no difference in the level of stress perceived by males and females (p=.5). Stress levels did not change the nature of the presenting complaint: typical chest pain versus another complaint (p=.09). Patients with high-stress levels presented early (within 12 hours) to the hospital (p<.05). There was no difference in the stress levels of patients presenting with different types of ACS: ST-Elevation Myocardial Infarction (STEMI), non-ST-elevation myocardial infarction (NSTEMI), or unstable angina (UA) (p=.147).

Conclusions: High-stress levels were seen in most patients with ACS and steps need to be taken to reduce stress. The stress levels did not influence the severity or the type of ACS. Patients with high-stress levels were likely to present early to the hospital.

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Key words: Stress, acute coronary syndrome, Perceived stress

Introduction

Cardiovascular disease (CVD) is the leading cause of death worldwide. It has a significant toll on the health system of developed as well as developing countries. Acute Coronary Syndrome (ACS) is now one of the leading causes of mortality in the Asia-Pacific region. With the current demographic transition and increase in life expectancy, the incidence of non-communicable diseases (NCD), including ACS is on the rise. In a report by the WHO, NCDs account for approximately 85 percent of the forgone disability-adjusted life years (DALY) in Sri Lanka (1).

In Sri Lanka, 34 % of proportional mortality is due to CVD (2) . Well-known risk factors for CVD include dyslipidemia, diabetes, hypertension, obesity, sedentary lifestyle, smoking, family history, menopause, and advanced age. Prevention

is a key public health strategy in controlling any NCD. The modification of risk factors significantly reduces morbidity and mortality from heart disease.

Psychological stress is becoming an important preventable established risk factor for cardiovascular disease (3) However, compared with many other CVD risk factors, stress is difficult to measure as there is no consensus on the measurement which is very objective . Exposures to psychological stress may influence health through neuroendocrine mechanisms or their association with unhealthy behavior (4,5).

In a meta-analysis by Richardson, high perceived stress was implicated with a 27% increase in CVD risk (6). It has been found that myocardial ischemia induced by mental stress increases the risk of fatal and nonfatal cardiac events (7,8). It is established that structured mental stress tests can provoke ischemia in 40-70% of patients with CHD (coronary heart disease) to a similar or greater severity than that due to exercise (7-9). Similar to ACS, perceived stress levels were higher in Takotsubo cardiomyopathy , a condition characterized by acute reversible severe left ventricular dysfunction.

Assessing the level of perceived stress among patients with ACS would help in understanding the relationship between stress and ACS and would also help to formulate approaches to reduce stress. Much of the evidence supporting the relationship between ACS and stress comes from studies relating self-reported psychosocial parameters , such as perceived stress. We explored the relationship between self-perceived stress among patients admitted with ACS to the professorial medical unit of Colombo South teaching hospital. There are no previously published studies in Sri Lanka assessing the level of perceived stress among patients with ACS.

Methods

All patients with ACS treated at the Professorial Unit of the Colombo South Teaching Hospital , who could read and write and gave consent were invited to participate in the study. The patients were administered the Perceived Stress Scale-10 (PSS 10). The PSS was translated to Sinhala and back translated to English. The PSS-10 was administered during the first 48 hours after the admission. The scale assessed the level of stress perceived by the patient based on ten questions. The sum of scores ranges from 0-40. High stress was defined as scores of 20 or above.

Cohen and colleagues developed the original 14-item English version of the Perceived Stress Scale (PSS-14) (10) . We used the PSS-10 which was developed later (11).The PSS is one of the most frequently used tools to measure stress in chronic conditions and situations often not listed on other life-event scales. The PSS is a brief scale that can be administered in a few minutes. PSS-10 scores are obtained by reversing the scores on the four positive items, e.g., 0=4, 1=3, 2=2, etc., and then summing across all 10 items. Items 4,5, 7, and 8 are the positively stated items.

Normally distributed continuous variables (age, PSS-10) are given as mean ± standard deviation and categorical variables as frequencies. Summary statistics of mean, median, standard deviation, and percentiles were used for quantitative measurements. The association between qualitative measures was assessed using the chi-square test, ANOVA, and Kruskal Wallis. The results were evaluated with a confidence interval of 95%, and the statistical significance was established at $p<.05$. Descriptive statistics frequencies were used for qualitative measurements. SPSS 18.0 software (SPSS Inc., Chicago, Il, USA) was used.

Results

Demography

A total of 313 patients were recruited out of which 221(70.6%) were males. . Multimorbidity, defined as having two or more of the following illnesses;diabetes mellitus, hypertension, CVD, dyslipidemia, stroke/transient Ischaemic attack was present in 168 patients. The presence of chronic illnesses were as follows: IHD 46.6%), DM (41.2%), HPT (53.4%), Dyslipidaemia (26.5%), Stroke/TIA (7.4%)

Level of stress

High-stress levels were found in (76%) patients and low stress in 24%). The level of stress was not affected by the presence of diabetes (p=.824), hypertension (p=.05), IHD (.268), dyslipidemia (p=.296).

Gender

In our study sample no difference was observed between the genders in terms of perceived stress.

Stress effect of presentation and MI

Stress levels had no association with the nature of the presenting complaint: typical chest pain versus another complaint (p=.09). Patients with high-stress levels presented early (within 12 hours) to the hospital (p<.05).

Stress level and ACS

There was no difference in the stress levels of patients presenting with different types of ACS: ST-Elevation Myocardial Infarction (STEMI), non-ST-elevation myocardial infarction (NSTEMI), or unstable angina (UA) (p=0.147).

Discussion

Stress is difficult to define objectively and measuring stress is complex as perceived stress may be different for individuals in different countries. In the present study it was revealed that 76% of the study population had higher levels of stress. Though we are unable to prove causation as it was not a case-control study, most participants being under stress could indicate that it is an important risk factor for ACS. Stress and psychosocial factors have been established as important risk factors for MI in the INTERHEART study (12). In one of the studies on pre-acute MI stress in India, it was found that 11.5% of females and 4.1% of males have stress (13) . Prevalence of stress was much lower than in our study. Since only a few studies are done on assessing stress levels before acute MI there is no prevalence data from other countries in the region to compare. The impact of stress on an individual is devastating.

Studies have found individuals with high levels of stress compared to those with low levels of stress were less likely to quit smoking, more likely to become physically inactive, less likely to stop drinking, and stressed women were more likely to become overweight during follow-up (3) It has also been shown moderate to high perceived stress over the month before an AMI was associated with increased long-term mortality, even though patients with increased perceived stress levels were younger, had fewer STEMIs, and had lower risk scores (14)

In the INTERHEART study the effect of stress was independent of socioeconomic status, smoking, age, and gender (12). This study assessed the level of stress in a patient before developing ACS. In one study done in India males were found to have more stress compared to females (15). But several studies done to evaluate stress post-MI have found that stress was more common in females than males (16).

Patients with high-stress levels presented early (within 12 hours) to the hospital. In a study done in Korea, it was revealed that younger patients who were more stressed presented to the hospital early < 5 hours from symptom onset (1) It is possible that patients with high-stress levels had health-seeking behavior and that would explain the early presentation to the hospital.

There are no studies done in Sri Lanka to assess mental stress in patients with CHD or ACS. However an indirect insight into this aspect may be obtained from studies done to assess quality of life (QOL) since mental health is an essential part of it. In one of the few studies done in Sri Lanka to assess the QOL pre-ACS using SF-36, there was a significant reduction of QOL at day 28 after discharge from hospital compared to the pre-event QOL (18).In the same study, pre-event QOL of patients with NSTEMI was significantly lower in seven domains compared to that of patients with STEMIThere was no difference in the level of stress perceived between patients who had STEMI and NSTEMI in our study.

With the rise of NCDs, if a health system in Lower and middle-income countries (LMIC) such as Sri

Lanka is to provide comprehensive healthcare effective steps should be taken to mitigate and control the risk factors of NCDs. As we aim to provide holistic care which includes psychosocial health, stress is an important risk factor that needs to be addressed.

Conclusion

The identification of perceived stress as a psychosocial risk factor for ACS has important clinical implications, especially in terms of public health. Early recognition, identification, and management of perceived stress may lead to a reduction in cardiovascular risk. Further exploration and research are needed to determine the mechanisms of these stress levels in Sri Lankan patients and the methods which can be used to manage them and the association of stress with long-term outcomes.

Limitations

The findings of the study should be interpreted in the context of the following potential limitations. The retrospective nature of our study is the biggest limitation as it does not allow for causal inferences. To minimize the recall bias participants were asked to fill in the details within the first two days of the acute MI. The assessment of perceived stress at the time of the acute MI (AMI) was done with the PSS-10, a psychometrically appropriate instrument with a recall period of 1 month, but it is not clear whether the acute stress of the MI can affect their recall of pre-AMI stress levels. Studies done previously using PSS have found it doesn't affect recall (14).

This study did not involve following up with patients to see if outcomes are affected by stress levels. The study did not assess anxiety or depressive symptoms which also contribute to stress levels.

Since study participants were recruited using convenient sampling, the distribution of stress levels and coronary events in terms of gender cannot be generalized.

Declarations

Ethical approval and consent to participate: Ethical approval was from the Ethics review Committee of the Colombo South Teaching Hospital. There were no ethical issues. Informed verbal consent was taken from the participants and this was approved by the ethics review committee.

Consent for publication : Not applicable

Competing interests: The authors declare that they have no competing interests.

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Audit on lipid screening, management and target achievement in prevention of cardiovascular disease in patients attending a medical clinic in National Hospital Kandy: Are we on par with the guidelines?

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Abstract

Background: Cardiovascular disease (CVD) remains a major cause of morbidity and mortality in Sri Lanka. 2019 European Society of Cardiology (ESC) guidelines recommend risk stratification based on co- morbidities, lipid profiles, standardized scoring and prescription of statins to achieve set lipid targets, to reduce CVD. Nevertheless implementation of guidance remains variable. The objective of this study was to identify the gaps in clinical practice and adherence to ESC guidelines in the management of dyslipidaemia.

Methods: AAll patients attending a routine internal medical clinic were assessed retrospectively. Their comorbidities, level of risk, current therapy, cholesterol monitoring, and response to LDL-C targets were noted and compared with guideline based audit standards.

Results: Out of 114 patients (69 female) with a mean age (±SD) of 63.98 (±11.5) years, 39 (34.2%) had CVD, 18 (15.8%) strokes, 70 (61.4%) hypertension and 63 (43.8 %) type 2 diabetes mellitus. Only 55.3% of patients had a single lipid profile and 39.7% a subsequent measurement. While 56.4% of CVD and 38.8% of stroke patients were on moderate intensity statins, 38.4% of CVD and 44.4% of stroke patients were on high intensity statins. Despite lack of contraindications 5.1% of CVD and 16.6% of stroke patients were not on satins. Of the patients with diabetes, 22% were not on statins and 68% were on low or moderate intensity statins. Lipid targets were achieved in 23.8% of the patients with diabetes. Targets were not checked in the majority. Of the 56% who didn't achieve targets only 41.1% received drug optimisation.

Conclusions: Lipid screening and treatment targets remain suboptimal despite set guideline standards. Dissemination of guideline recommendations and motivation to reduce physician inertia is mandatory in preventing cardiovascular disease.

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Key words: dyslipidaemia, lipids, atherosclerotic cardiovascular disease (ASCVD), statin, LDL-C

Introduction

Dyslipidaemia remains one of the major causes of mortality and morbidity in Sri Lanka and worldwide. While 77.4% of Sri Lankans have some abnormality in lipids, the mortality due to cardiovascular disease is estimated to be 34% (1). The South Asian population has a higher incidence of premature coronary artery disease with a morbidity and mortality that is 3-5 times higher than that of the rest of the world (1,2). The higher rate of atherosclerotic cardiovascular disease (ASCVD) can be explained by the higher prevalence of traditional risk factors in this population such as diabetes, dyslipidaemia, tobacco use, obesity and hypertension (2). Furthermore the SHARE study concluded that metabolic syndrome is evident at an early age in South Asians as total cholesterol, low density lipoprotein cholesterol (LDL-C), lipoprotein (a) [Lp (a)], triglycerides and prevalence of impaired glucose tolerance were notably higher amongst the South Asians compared to Europeans and the Chinese (2–4).

Since dyslipidaemia is one of the major modifiable risk factors of cardiovascular disease (CVD), its proper management can reduce major CVD events (5). Evidence suggests that for every 1 mmol/L reduction in LDL-C the cardiovascular mortality is reduced by 19% whereas the overall mortality is reduced by 12% (5)There are many international consensus and guidelines on the ideal management of dyslipidaemia. Although these mostly cater to a western population they provide the best available standards for management of lipids for South Asians as well (4). Current European society of cardiology (ESC) guidelines in 2019 defines risk scores to identify individual risks and stratify patients based on their risk to commence statin therapy. Furthermore the guidelines have set LDL-C targets based on the risk levels for cardiovascular disease prevention (6,7). There are four major risk categories namely low, moderate, high and very high risk. Patients with ASCVD invariably fall into the very high risk category, so do the diabetics with target organ involvement and patients with severe CKD (eGFR <30 mL/ min/ 1.73 m²). All diabetic patients without organ damage and diabetes for more than 10 years , CKD patients and patients with markedly high single risk factor (Total cholesterol> 310 mg/dL, LDL-C >190 mg/dL, BP>180/110 mmHg) fall under high risk category while young diabetics (DM1<35 years, DM2 <50 years) with a duration of less than 10 years come under moderate risk category. ESC guidelines have recommended LDL-C targets depending on the risk category with more stringent control for higher risk strata (7). Lipid management includes lifestyle modifications and pharmacotherapy where statins play a major role. If targets are not achieved ezetimibe and PCSK9 inhibitors should be used as “add on therapy” to statins consecutively (1,7). High intensity statins are recommended for high and very high risk patients as first line therapy regardless of their cholesterol levels (7). The average dose of statin that reduces LDL-C by >50% is defined as high intensity while the dose expected to reduce LDL-C by 30-50% is defined as moderate intensity. The dose required to reach the same intensity differs according to the type of statin used. For example, widely available atorvastatin is considered high intensity at a dose of 40- 80 mg while 10-20 mg is considered moderate intensity (8). Due to the considerable inter-individual variation in LDL-C reduction with the same dose of the drug, monitoring of response to statin is warranted (7).

As demonstrated by numerous available audits, implementation of these guidelines remains subjective not only in Sri Lanka but also in the West (1,6). There were no substantial audits carried out in the medical clinics of National hospital Kandy, a tertiary care facility in Sri Lanka in this regard. Considering the growing burden of cardiovascular disease in the South Asian population and the role of lipid management in prevention of CVD, the aim of our study was to assess the gap between clinical practice and set guidance in lipid management in a clinic setup of a tertiary care facility in Sri Lanka. Our intention was to determine the percentage of patients who underwent lipid screening, had indications for statin therapy according to risk factors, percentage of patients on optimal doses of statin and if they had targets checked and achieved according to ESC guidelines.

Methods

This audit was carried out at National Hospital Kandy (NHK), Sri Lanka. It was carried out on long term follow-up patients in the medical clinic attached to one of the three units in NHK. It was a single-site retrospective audit carried out on patients attending the medical clinic on the two clinic days of first week in the month of august 2022. All patients who gave informed written consent were included in the study. Those who were unable to give informed consent, and were not of sound mind were excluded. Patient records were retrospectively analyzed. Each patient's risk factors and co-morbidities were noted. High- and very-high- risk individuals were identified on the basis of documented CVD, DM, moderate-to-severe renal disease, or very high levels of individual risk factors. Details regarding their lipid profiles including dates on which lipid profiles were conducted and repeated were noted. Total cholesterol, LDL-C, HDL-C, Triglyceride levels were noted down. Their medications were reviewed and statin status including drug doses and changes were recorded. The physician responses to LDL-C targets were also taken into account.

All data were collected in a common database and patient identifiable data was not stored. The data was analyzed against three audit standards according to the ESC guidelines summarized below:

1. Patients with CVD or cerebrovascular disease are at high risk and thus warrant high intensity statins.

2. All type 2 diabetics are at a risk category of moderate and above and therefore warrant routine statins.

3. LDL-C targets for very high, high and moderate risk categories are <55 mg/dL, <70 mg/dL, <100 mg/dL respectively and a 50% reduction of LDL-C was recommended from the initial value.

Continuous variables are expressed as mean ± SD and categorical variables as proportions. Percentages were calculated on the basis of total number of responses. Excel software was used for data storage and statistical analysis.

Results

A total of 114 patients were included in the study (69 female, 45 male) with mean age (±SD) of 63.98 (±11.5) years, (range 23-83 years). General characteristics of the cohort are displayed in Table 1.The average laboratory parameters of the cohort include total Cholesterol of 207.56 ± 56.48 mg/dL, LDL-C of 128.88 ± 55.02 mg/dL, Triglycerides 136.34 ± 60.0 mg/dL and HDL-C 50.41 ± 10.49 mg/dL.

Out of 114, 39 (34.2%) had CVD, 18(15.8%) had strokes, 70(61.4%) had hypertension (HTN) and 50 (43.8 %) had diabetes mellitus (DM2).While 56.4% of CVD, and 39% of stroke patients were on moderate intensity statin therapy, 38.4% of CVD and 44.4% of stroke patients were on high intensity statins. Despite lack of contraindications 5.1% of CVD and 16.6% of stroke patients were not on statins. Of the patients with diabetes 22% were not on statins and 68% were on low or moderate intensity statins (Figure1). All patients with CKD were on statin therapy, one patient was on low intensity statin while others were on high intensity (83.3%).

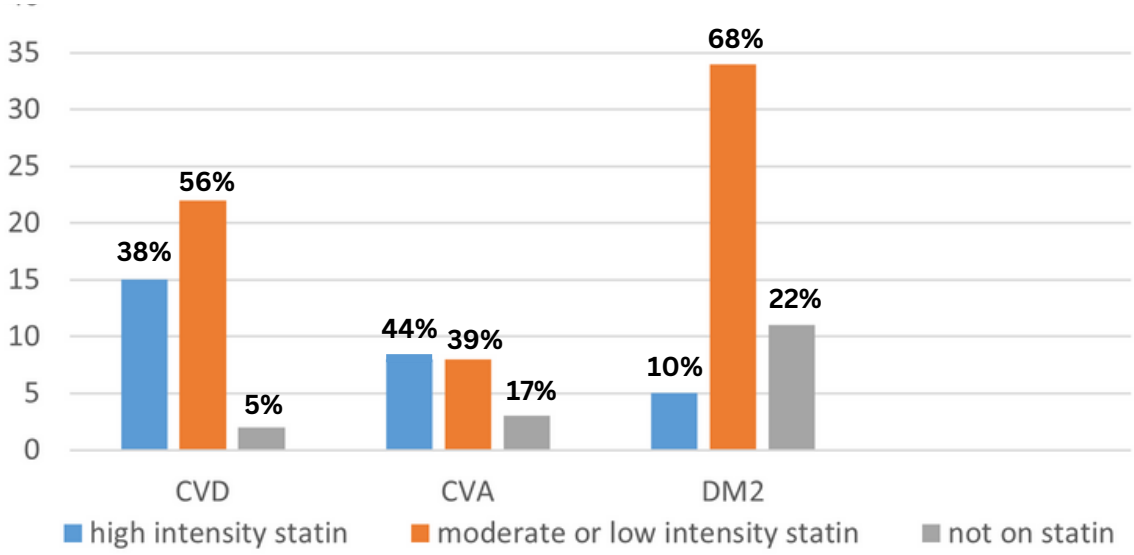
Number of patients who had at least one lipid profile was 63 (55.3%), while 25 patients had follow up lipid profiles (21.9% of all, 39.7% of those with initial lipid profile). Only one patient's lipid profile was rechecked at 8 weeks. The mean duration of repetition was 2.1 years.

Lipid targets were achieved in 15 (23.8% of those checked and 13% of all patients).Targets were not checked in the majority. Of the 25 patients who had subsequent lipid measurements 14 (56%) did not achieve targets, but only 7 patients (41% of patients considered for drug alteration) received drug optimization. The rest were continued on their routine statin dose. Three patients were on LDL-C targets for very high risk and in view of CVD and stroke they warranted high intensity statins but were on suboptimal doses.

Table 1 - General characteristics of the cohort

Characteristic	Number (percentage)
Number of patients	114
Male patients	45 (39.47)
Female patients	69 (60.53)
Number of patients with Diabetes	63 (43.8)
Number of patients with hypertension	70(61.4)
Number of patients with CVA	18(15.8)
Number of patients with CVD	39 (34.2)
Number of patients with CKD	6 (5.2)
Mean age (SD) years	**63.98 (±11.5)**

Figure 1 - Comparison of Statin status according to individual risk profiles. (Percentages given as a proportion of total number of patients with a specific comorbidity)



Discussion

This audit was carried out to assess the lipid screening and management for primary and secondary prevention of cardiovascular disease in a tertiary care facility in Sri Lanka.

This study is a demonstration of suboptimal management of lipids in patients attending long term medical care. Lipid guidelines keep updating, but the implementation of these remains questionable. Furthermore physician inertia curtails optimization of medication to obtain the ideal LDL-C targets. We noted that many patients were not on high intensity statins despite having strong indications such as stroke and CVD. As most patients followed up in the government sector are on atorvastatin, they should be at least on 40 mg or more, But majority of these patients were on suboptimal doses despite the absence of contraindications. None of the patients attending the clinic were on 80 mg of atorvastatin. Although many had not reached the LDL-C targets physicians may be reluctant to prescribe the maximal dose of statin. Ezetimibe and PCSK9 inhibitors are financially demanding and also not freely available in Sri Lanka. We could not elicit whether the patients were candidates for ezetimibe and PCSK9 inhibitor therapy because targets were not checked and statin doses were not optimized in some.

Many patients attending the clinic did not have at least a single lipid profile. This may be due to financial constraints as lipid profile is available only periodically at NH Kandy. Nevertheless physicians should be aware that mandatory early lipid profiles should be ordered for these patients and repeated ideally in 4-6 weeks or at the earliest availability and annually or more frequently if needed (1,7). Although obtaining these tests might be financially challenging for the patients initially, it is by far less financially demanding than actual treatment cost of ASCVD. A study done in London in 1996 on lipid management for secondary CVD prevention, in patients referred for coronary angiography, noted that patients reviewed in primary and secondary centers with documented coronary artery disease had lipid profiles recorded only in 22% (9). Although the study is not a demonstration of recent practices, it showcases how ordering lipid profiles may be suboptimal even in the developed world. In fact the more recent guidelines have set greater importance to lipid management in primary and secondary prevention of CVD (7). This may explain why our numbers mismanaged out of long term follow up patients are greater than recent similar audits conducted in acute medical wards (1).

Dyslipidaemia guidelines may be confusing and guideline non adherence is seen even in developed countries (5,6). Nevertheless in countries with limited resources service providers assume that LDL-C targets will be reached when high intensity statins are prescribed. This is untrue in many occasions where high intensity statins have not managed to lower LDL-C to target (10). In the dyslipidaemia International study 61.8% of all patients did not achieve their LDL-C targets in the Middle East while 63% of all patients in the UK achieved targets (5,11,12). Although comparing these results with our audit is not justifiable as most of our patients did not undergo a single or subsequent lipid profile, out of those who did receive lipid profiles only 23.8% achieved targets, which is suboptimal in all standards. A study conducted in Macau to analyze the effectiveness of an audit for dyslipidaemia concluded that management was significantly improved reaching western standards following feedback and dissemination of results(5),justifying the need for regular audits such as ours.

A study conducted in Italy showing lack of target achievement, discussed less aggressive lipid treatment related to poor knowledge on guidance of family doctors, poor patient compliance and statins not being freely available (6).This emphasizes the need for specialists in the field to have one to one discussion with the attending doctors when guideline changes are published.(5) All patients in a medical clinic may need to be reviewed by either trainees or specialists at least periodically to ensure that their management is up to date.

The audit results were made available to the staff and problems in management were discussed to

bridge the knowledge and practice gap. The importance of CME (continuous medical education) was emphasized.

Conclusions

Lipid screening and treatment to target remains suboptimal despite set guideline standards. This study is an eye opener on the degree of non-adherence to guidelines. Further audits and re-audits are necessary for quality control and may assist in changing the routine practices to be on par with guideline recommendations. Furthermore dissemination of guideline recommendations and motivation to reduce physician inertia is mandatory in preventive cardiology.

Limitations

The limitations of our study were that data collection was based on patient records and we were unable to calculate risk scores due to lack of certain information such as smoking history. The scope of our study was quite wide which included lipid screening and management for secondary as well as primary prevention that mainly included diabetic and dyslipidaemia patients. Thus calculating risk scores was beyond the scope of our study. The risk estimation and lipid estimations were based on retrospective data rather than prospective analysis. Nevertheless this is a representation of real world practice. The patients selected were those who attended a clinic on a particular week but may not be a representation of all the patients attending the medical clinics at NH Kandy. Nevertheless this study gives a sneak peek as to what to expect in the general population that attends a medical clinic. The lipid profile data was obtained from different laboratories, but all used quality assured standardized methods.

Declarations

Ethical approval and consent to participate: Ethical clearance was obtained from the Ethical Review committee at NH Kandy. Informed consent was obtained from all patients participating in the study to obtain details from clinic records.

Competing interests: The authors declare that they have no competing interests.

Availability of data and materials: Data generated during this study are available from the corresponding author on reasonable request.

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Authors' contributions: All authors read and approved the final manuscript. FNN conceptualized the study, collected the data and drafted the manuscript. MJ and FF helped in data collection and analysis. SB and KK revised the article critically. All authors read and approved the final manuscript.

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To be or not to be content is the question

Emotional intelligence and leadership training to stem brain drain of medical doctors

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Contentment means to be happy with what you have, who you are and where you are. It involves simply coming to terms with the reality of the present. Words used to describe a content person include fulfilment, comfort, peace, equanimity, serenity, tranquillity, gratification, ease, happiness, pleasure, and cheerfulness, amongst others.

At the beginning of the year 2019, I would like to think that like many Sri Lankans, medical professionals who either lived here or had moved back, were content in life. However, stemming from the Easter attacks in April 2019, followed by the COVID-19 pandemic and lockdowns, and the eruption of the current economic crisis that had been simmering for a while, the country found itself in a situation akin to the RMS Titanic. Simply, about to sink.

When the Titanic began to sink, many escaped via 'lifeboats', some could not escape as there were not enough lifeboats and some chose not to abandon ship. Of those who remained, many perished and yet there was a significant number who were rescued.

At the time of writing this article, Sri Lanka is still bankrupt and a lower middle-income country. There seems to be a tiny light at the end of the tunnel, as the country has started moving towards a slight recovery. Tourists have started to trickle in. Though foreign investments are still at an all-time low and debt is not sustainable, debt restructuring is going on. Foreign exchange reserves are low. Though basic needs shortages have minimised, and power outages are less, they are unpredictable, and more work must be done. Expenses have trebled and taxes have increased. There are ripples of civilian protests, which have the potential to erupt.

Like the unfortunate people on the Titanic, when the economic crisis erupted, many Sri Lankans too rushed away. A massive 'brain drain' ensued, including migration of a large number of medical doctors. Those who did not have the means to or chose to, remained behind. Unlike those onboard the Titanic, if we as a nation rally round, be innovative and make the best use of our resources, we will not perish. Yet we would most certainly experience a disruption to the contentment that we once enjoyed.

Those who left, left in search of greener pastures. They left to escape a set of 'severe' problems in this country and will live better lives elsewhere, amidst a different set of problems. They would argue that they left because of their children, for a better system and peace of mind, and better remuneration and quality of life.

Those who couldn't escape, live with the hope of an opportunity to take flight. Those who chose to remain, live with the hope that things will get better. They argue that it is better to live in one's own country than be a second-class citizen in another.

There are no rights or wrongs in these decisions.

We cannot blame anyone for seeking greener pastures elsewhere. However, the state invests a great deal to train specialists, and in the event of brain drain this is a tremendous waste of resources, time, and commitment. Retaining these specialists who return within the country should be

a major agenda, as it indirectly improves health care and quality of life by means of quality patient care, research and teaching. The reality is that they are offered very little perks in terms of remuneration and other benefits; most are often posted to distant stations and as a result their families are divided. This often induces them to migrate. To compare, a specialist in Sri Lanka would receive a monthly salary of around 600 sterling pounds. A colleague in the same grade in the west would earn approximately 10 times more, health care would be free, schooling, transport and cost of living would be manageable. Conscience and a sense of loyalty and patriotism keep some of us serving our country, yet not everyone is strong enough to resist the lure of more benefits.

Those who leave should not be deemed unpatriotic. Those who remain are not all patriots. Some are probably those who did not have a lifeboat to escape in or a place or opportunity to escape to.

The possibility of a dearth of doctors is a frightening prospect of mass migration. Though those who migrate could through large earnings generate large remittance inflows, driving economic growth and boosting recovery and supporting long-term growth, brain drain of health professionals coupled with lack of medicines and essential items would surely cripple the health system.

It seems important then to halt or minimise this mass migration. The question is how? Though waving a carrot stick of increased remuneration and perks with reassurance of a quality lifestyle would be a good solution, a better solution would be to inculcate a sense of purpose, to plan, innovate and implement strategies to uplift the lives of fellow countrymen.

It is interesting to try and understand why doctors would 'desert the ship' in difficult times.

After all, why does one become a doctor? The medical profession is not actually a profession, but a vocation. A vocation is a strong feeling of suitability for a particular career or occupation, sometimes called a 'calling' or 'mission'. It is also described as a person's main employment or occupation especially regarded as worthy and requiring dedication. So again, why does one become a doctor? Because it is their vocation? Because they want to serve the people? Or is it the glory, prestige, and the perks? Or because their parents and family insisted? Or just because?

If the reason is anything other than to serve patients or that it is their vocation, it can be assumed that one becomes a doctor for personal gain. Hence, when the environment ceases to be conducive for personal growth, or for their families' well-being, it is time to leave.

It is of deep concern that today a vast majority of newly passed out doctors are looking towards leaving as soon as they finish their internship, so much so that recently, when a medical student came to me to discuss his anxiety issues and was greatly concerned that he would not be assured of employment when he graduated, sadly, I was able to reassure him that his fears are unfounded and that he would possibly be able to have more than one job at this rate of migration of health professionals.

It can be argued that doctors are also human beings with basic needs and expectations and that they have a right to stability and remuneration. But if the medical profession is a vocation, why is that only a few have the inclination to stay on board and help patch up the holes and right this sinking ship?

Having served as a medical teacher for over two decades, I ponder whether we have failed at inculcating soft skills in our students, to instil in them a sense of selflessness, to take responsibility to try and right the system and make the most of what is available. If one became a doctor to serve people, isn't it better to serve where it is needed most?

Should such traits lay root even earlier, such as during school days?

Looking at the 'race to nowhere' that took precedence after the dawn of the new millennium, one wonders whether that is even a remote

possibility. From a small age, children are thrust into a race to achieve at whatever cost. Children are expected to excel in everything. High achievement at academics, sports, extracurricular activities is expected. Standardised testing is imposed on everyone. They are taught that happiness is proportionate to academic and extracurricular achievements. Parents run a rat race vying to outdo each other through their children. Burnout and stress are commonly seen in most, as even fun and voluntary extra-curricular and community service activities become competitive and for personal gain. There is no time for anything else, let alone inculcation of soft skills and patriotism. Though there are leadership programmes in some schools, do they really inspire students to be entrepreneurs and forward-thinkers in their own country?

Some of these high achievers enter medical schools. Most do so of their own volition. Others respect their parents' wishes. Even in those who came with great expectations, the cramming of facts in the curriculum overwhelms and disturbs rest. Nowadays many students suffer from anxiety and burnout, more so than ever. As a student counsellor of the medical faculty, I have observed that the number of students seeking help has increased tremendously, especially in the newer batches who mostly suffered and continue to suffer from the effects of the pandemic, lockdowns, and economic instability. In general, medical students suffer from anxiety, depression, and suicide at much higher rates than the general population. They face unreasonable demands on their time, with frequent high-pressure exams followed by long hours during clinical rotations. This leaves students with insufficient time for adequate sleep, healthy eating, and regular exercise. On top of that, many students are far from home with small or nonexistent support systems and dealing with uniquely stressful situations like witnessing death for the first time. It all adds up to extreme mental health challenges, and the erosion of the exact social emotional skills doctors need to provide top quality care with love and compassion for patients.

Though medical humanities are incorporated into the curricula, the heavy burden of academics make it difficult to appreciate the gist of the activities and the possible life lessons learnt, and it appears that for a considerable proportion of students this is an additional burden. Therefore, even if medical students have some inclination of emotional intelligence and leadership skills when they enter, it is often seen that there is a decline of such knowledge and skills as they wade through the curricula. It is observed that the anxiety and stress related negative impact, results in less emotional intelligence in the students than when they arrived. Along with this, there is a decline in the ability to exercise optimism, evaluate the costs and benefits of choices, and practice empathy.

Are we failing as medical educators?

Emotional intelligence and leadership is not a trait that is commonly addressed in medical school. We are more intent on delivering knowledge and skills. Yet, influence on attitude and behaviour is as important, and sometimes more. Our emotions most often drive our behaviours, and our behaviours determine our success or failure. Doctors who can manage their own emotions and react to the emotions of others, demonstrate better clinical outcomes, greater professional satisfaction, increased empathy, and improved teamwork within health care organisations. This is what emotional intelligence teaches.

Low emotional intelligence often results in being overly defensive, resolving conflicts poorly and not connecting well with ones' team. Unfortunately, medical schools and clinical programs traditionally give little attention to the soft skills needed for effective leadership. We fail to detect when the erosion of emotional intelligence begins or have no insight as to whether medical students lack high emotional intelligence at the point of entering medical school. Development of leadership qualities among health professionals is often neglected, with young professionals having to learn leadership skills by trial and error. It is important to incorporate leadership training programmed into the medical curriculum.

Doctors like everyone else must have a balanced life and be able to care for themselves and their families as well as for others. Yet one of the

biggest challenges for modern day Sri Lankan doctors is working in a highly complex, emotionally demanding environment. The ability to manage oneself and relationships with others is an invaluable skill that must be inculcated to be successful. Consequently, doctors may be challenged to succeed in leadership roles. Whether one is leading a team in the operating room, managing staff in a clinic, or running an executive board meeting, these soft skills are essential.

Like nearly any other skill, emotional intelligence improves with continuous practice. An important starting point to developing emotional intelligence is to simply learn to pause and reflect on how one is feeling. This commonly known as 'getting on to the balcony' provides space to perceive and understand emotional responses, acknowledge them, and understand the drivers of one's behaviour. The outcome of this exercise is greater self-awareness and learning how to respond better in stressful and tense situations, rather than being controlled by impulse. Over time, triggers will be noticed, and one would learn how to control them. Practising mindfulness and meditation is also one such way to strengthen mental capacity to manage oneself and others.

One of the important things that needs to be realised is that success will not be enough, but significance and being content may be. Rushing down the road to nowhere, pursuing what we want, we may end up sacrificing what we need to live a fulfilling or meaningful life. It is important to teach children and adults to prioritise their lives, or someone else will. Success shouldn't dictate how one spends their time or life. Goals and actions that support one's purpose should come to the forefront. Unfortunately, financial success is a powerful motivator and controls the lives of many. It chooses occupations. It dictates how time, energy, and resources are spent. It influences relationships, schedules, and families, and it influences whether we stay or run away, in a crisis such as ours.

As a young lecturer in my 30s, I had the privilege of attending the Young Physician Leader (YPL) programme, a novel concept of nurturing young leadership among health professionals, an initiative of the interacademy medical panel in partnership with the WHS and the M8 alliance. It was based on the opinion that effective healthcare institutions need effective leaders. I learnt many aspects of leadership and emotional intelligence in a very practical manner, many of which I was able to put into practice.

On my return, I teamed up with other Sri Lankan alumni of this programme and we conducted a similar programme in 2015 funded by the Sri Lanka Medical Association. Fifteen young health professionals under the age of forty were selected using comprehensive selection criteria by a team of independent reviewers. All of them had excelled academically, professionally, had exceptional extracurricular performances and had carried out a leadership role at some point in their school years and careers. Though selected randomly we found that there was a good mix in the selection in terms of career, gender, research interests and there were a few non-medical participants too. The programme was conducted in such a manner that they were introduced to leadership theory by means of interactive discussions with alumni and eminent leaders. Some highlights of the workshop were where they looked at themselves, at their strengths and weaknesses and developed a personal leadership plan. There was also a dedicated session on working with non-medical health professionals and the allied health sciences. Reflecting on oneself and pondering one ones' leadership roles in their day to day lives, helped to 'build the next generation of Health Professional Leaders"

It is interesting to note that almost all of these Young Physician Leaders are still in Sri Lanka, despite the ongoing and current crises. They are leading teams of their own in their diverse fields with a sense of purpose. This is a first-hand experience of how emotional intelligence and leadership was able to shape the future career paths of young medical professionals. It appears that they are content in their careers and the paths they have taken, excelling in the niches they have carved out for themselves. They chose to be big fish in a little pond.

It is becoming evident that it is time to incorporate emotional intelligence and inculcate leadership into schools and medical curricula in a more effective way than it is being done at present, with the hope that the next generation of health professional leaders would remain content, and though it may seem like wishful thinking at this point, hopefully help rebuild our motherland. Though the utmost solution to right this country economically would include removal or rehabilitation of corrupt policy makers and politicians or election of new ones, our control of such solutions is sadly limited. Until such time there is always a role for each of us to play. A major attitude change is the need of the hour. Such attitudes would stem from knowledge and practice of emotional intelligence and leadership. For one thing is certain. Our country is too poor to train medical doctors for other countries!

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This article is the personal opinion of the author

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Epidemic of COVID-Associated Mucormycosis in India and a road ahead

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Abstract

COVID-associated Mucormycosis (CAM) was a peak-hour crisis in India. The situation arose from an unprecedented ICU workload of critical COVID-19 cases, insufficient resources and the impaired immune status of the patient. We recommend strong preventive measures, chemoprophylaxis and Amphotericin-B nebulisation for the effective management of CAM.

Key words: COVID-19, Mucormycosis, Rhino- orbito cerebral mucormycosis, Nebulized Amphotericin-B

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Introduction

In April 2021, a major second wave of SARS-CoV-2 infection, predominantly caused by the delta variant, swept across India. In 2021, the country also witnessed the first COVID-19-associated mucormycosis (CAM) epidemic in several states (1). The states worst affected by COVID-19, also suffered most from invasive fungal diseases. The data indicates that the estimated prevalence of mucormycosis in India is nearly 70 - 80 times higher than the global data before the onset of the COVID-19 epidemic (2). The spread of mucormycosis was nosocomial and iatrogenic in the hospital setups. A previous single-centre study reported mucormycosis in up to 12% of its ICU patients (3). A study from north India noted that 9% of the mucormycosis cases were nosocomial in origin. Contaminated intramuscular injections; surgery, adhesive tapes, and endo-bronchial tubes were considered the sources of infection in nosocomial mucormycosis (4). Recently mucorales were isolated from 11.1% air-conditioning vents and 1.7% of patients' used masks in samples collected from eleven hospitals (5).

COVID-associated Mucormycosis (CAM)

Rhizopus and Mucor species are broad ribbon-like, thin-walled, primarily aseptate or pauci septate hyphae with irregular diameters and non-dichotomous irregular branching. Humans acquire infection by inhalation of sporangio spores (1). The rhino-orbital mucormycosis starts with a unilateral disease process involving nasal space. Disease spreads to maxillary sinus through middle meatus and to ethmoidal sinus through superior meatus and finally floor or medial wall of orbit is broken leading to invasion of orbit. Spread to the central nervous compartment is through cavernous sinus in majority of the cases and also through cribriform plate and pterygopalatine fossa. Sphenopalatine fossa serves as a reservoir. CNS invasion may be by direct, hematogenous or transneuronal spread (6). Apart from rhino-orbital-cerebral mucormycosis (ROCM) and pulmonary involvement, cutaneous and gastrointestinal manifestations are also known. Rarely this disease

is seen disseminated.

The cases started appearing before the upsurge of the second wave of COVID-19 reached its peak in April-May and started declining by July-August 2021 (7,8). Overall, about 40% of patients with severe COVID-19 reported CAM. Most of the studies showed male predominance, and most suffered from Rhino-orbital-cerebral mucormycosis (ROCM). Association with diabetes was observed in 76.6 -90.2% of cases with CAM. Mortality was high and so was morbidity, leaving many more with facial disfigurement and blindness (9,10,11).

The factors that favoured the occurrence of CAM were highly variable. Impaired host defence, increased virulence and environmental factors played a crucial role in the precipitation of CAM. Important variables included uncontrolled diabetes, acidosis, hypoxia, immune suppression with monoclonal antibodies, steroids, antibiotics, immunomodulation with zinc and other vitamins, and high ferritin levels.

The use of non-humidified oxygen, reuse of masks and other medical essentials and lack of sterile water were correlated with the spread of CAM. The industrial supply of oxygen, makeshift delivery systems, and unhygienic cylinders, hot and humid weather were also linked to the occurrence of CAM (12,13,14). Surprisingly, shreds of quality evidence in the scientific literature are lacking for the use of industrial oxygen, unhygienic oxygen cylinders and the makeshift oxygen delivery system in the causation of CAM.

Prevention

The prevention of invasive mould diseases caused by filamentous fungi included strict environmental preventive measures and adequate control measures for hospital infections (15). On routine microbiological surveillance colony forming unit (CFU) counts above 25 CFU/m³ suggest a significant presence of invasive fungus. Continuous air-conditioning through absolute high-efficiency particulate air (HEPA) filters with at least 12 complete air changes per hour reduces the number of CFU/m³ to near zero concentrations (16, 17, 18). In several cases, the causative strains of filamentous fungi were isolated from the hospital water supply (19). Single-use of disposable commodities and use of sterile water in intensive care units are necessary for prevention of infection (20).

Management

Management of mucormycosis is truly a multidisciplinary task that involves both surgical and medical arms. Radical surgeries are often more effective in achieving disease-free status. Currently, chemoprophylaxis against CAM is not recommended (21). We strongly feel a need for prophylactic medicines in COVID-19 patients with high risk such as uncontrolled diabetes mellitus and other associated conditions (Table 1). This fact is justified by the observation made by several authors that 40% of patients reported mucormycosis after active COVID-19 infections. The optimum duration of antifungal prophylaxis for mucormycosis is not clear. During this disaster, wide-spectrum azoles (Isavuconazole and Posaconazole) were used for the treatment of mucormycosis. Posaconazole (oral solution) was found superior to other antifungal azoles in randomized controlled studies for the prophylaxis of invasive fungal infection in high-risk patients (22). However, Posaconazole has poor CNS penetration (23). One of the strategies is to use a higher dosage (10 mg/Kg) of amphotericin-B in invasive intracranial mucormycosis by intravenous route of administration (24). Anecdotal reports suggest adjuvant use of intraocular topical instillation of amphotericin in sino-orbital mucormycosis to achieve disease-free status in a post-surgical group after exenteration of orbit (25, 26). This finding may be extrapolated for use of topical nasal drops after an ENT surgery. Drug penetration is easy in view of extensive soft tissue and bony damage. A nebulised form of amphotericin-B is an attractive option for the primary treatment and prophylaxis of pulmonary and most prevalent ROCM forms, depositing drug in maximum concentration at the sinus region.

On nebulization only 10-20 % of the delivered dose will reach the lung tissue and the rest gets deposited into the epithelial lining and upper

respiratory airway. The distribution depends on the diameter of fine particulate size. Most of the systemic side effects of amphotericin- B therapy is avoided by using the drug in a nebulised form lipid formulation that seems to nebulize better and tolerated well (27). Side effects encountered in post-lung transplant present include cough, mild bronchospasm, nausea, dizziness, and chest tightness (28). A randomized placebo-controlled study with inhaled liposomal amphotericin-B noted reduced incidence of pulmonary invasive aspergillosis. In patients with allergic bronchopulmonary aspergillosis with cystic fibrosis amphotericin-B deoxycholate, 20 mg was administered in a 1 mg/mL concentration for 10-15 minutes. If tolerated well, therapy was continued three times a week or Amphotericin-B lipid complex 50 mg was administered at 5 mg/mL for 10-15 minutes (29).

Liposomal amphotericin-B is also found effective for prophylaxis against invasive fungus in lung transplant patients. Prophylactic liposomal amphotericin-B 25 mg or lipid complex 50 mg in nebulized form was administered every 2 days for the first 3 weeks and once weekly thereafter. In another regimen, Liposomal amphotericin-B 25 mg was administered in nebulized form, on alternate days until resolution of bronchial suture followed by once a week from the second to the sixth month and once a fortnight from the sixth month (30, 31).

Conclusions

Though the CAM epidemic left a negative impact on the society no clear guidelines emerged yet to manage the disease. Strategies to combat CAM produced highly variable results with high mortality. Standardization of drug regimens followed by meticulous research is the need of the hour in a country where a major risk factor, viz. diabetes mellitus is rampant.

Table 1 - Factors which increase susceptibility to invasive fungal disease when combined with moderate to severe COVID-19 infection*

1	Uncontrolled diabetes and diabetic ketoacidosis
2	Other associated conditions**
3	Use of Steroid (cumulative dose above 97 mg of dexamethasone)
4	Neutropenia (count below 1000/micL)
5	Mechanical ventilation above 14 days
6	Prolonged hospital stays above one month

***Moderate to severe COVID -19**
Pneumonia with or without respiratory failure
Pneumonia with respiratory failure with septic shock with MODS

****Other associated conditions**
Malignancy, Post organ-transplant, Chronic kidney failure on maintenance dialysis, Chronic liver disease, Tuberculosis, People living with HIV, Intravenous drug abusers, Smokers and ethanol abusers, Disorders requiring regular immunosuppression therapies apart from steroids.

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Are low-and-middle-income countries using scarce resources effectively to tackle noncommunicable diseases in the pandemic era?

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Abstract

The noncommunicable disease (NCD) burden continues to grow and is a major threat to socioeconomic development, particularly in low-and-middle-income countries. The COVID-19 pandemic has had a significant negative impact on the prevention and control of NCDs. Pre-existing challenges to the prevention and control of NCDs, including financial and health workforce limitations, have been further intensified by the COVID - pandemic. Despite these barriers, accelerating action to address NCDs is imperative to reduce premature mortality and escalating healthcare costs. In the post-pandemic context, a strong focus on cost and sustainability considerations is essential for making progress on reducing premature mortality by one-third by 2030: Sustainable Development Goal target 3.4. Low and middle income countries (LMIC) can succeed only by prioritizing the implementation and national scale-up of at least 16 very cost-effective NCD interventions. Among them are population-wide policy interventions which address tobacco, harmful use of alcohol, physical inactivity and unhealthy diet. The only health system intervention affordable to all LMICs embraces the total risk approach to tackle hypertension, diabetes, hypercholesterolemia, smoking and overweight in an integrated manner in a primary health care pathway. The burden of sustainability calls for the inclusion of best buy interventions as integral components of the basic benefits package of Universal Health Coverage initiatives.

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Noncommunicable diseases: a global health challenge

Major noncommunicable diseases (NCD) - cardiovascular disease, diabetes, cancer and chronic respiratory diseases, killed approximately 33.2 million people worldwide in 2019, a 28% increase compared to 2000 (1). More than 20 million of these deaths were in middle-income countries. NCDs continued to be leading causes of ill health worldwide and were responsible for 7 of 10 premature deaths in 2019. The COVID-19 pandemic threatens to worsen that trend. Globally, age-standardized death rates for all ages combined have declined between 2000 and 2019 for chronic respiratory diseases (37%), cardiovascular disease (27%) and cancer (16%). However, deaths due to diabetes increased by 3% in the same period. The age-standardized rate of mortality due to diabetes increased by 5% in upper- middle- income countries and by 13% in lower- middle- income countries (LMIC).

Progress in addressing NCDs has been slow, even

prior to the COVID-19 pandemic. Based on 2010–2016 trends, women in only 17 of 176 (9·7%) countries and men in only 15 of 176 (8·5%) countries were expected to achieve the Sustainable Development Goal target 3.4: one-third reduction relative to 2015 in premature mortality due to NCDs (2).

No country can address the prevention and control of NCDs using piecemeal efforts to target single risk factors/diseases, particularly in the post-pandemic era. There are three essential, complementary and synergistic strategies for tackling the burden of NCDs in a viable fashion (3). They are; **1.** Implementation of healthy public policies that reduce exposure of the population to behavioural and environmental risk factors (population-wide primary prevention through control of tobacco, harmful use of alcohol, unhealthy diet, physical inactivity and air pollution), **2.** Early detection and management of behavioural and biological risk factors using integrated interventions in primary health care and vaccinations for cancer - primary prevention at the individual level, **3.** Prevention of recurrent heart attacks and strokes in individuals with established cardiovascular disease (CVD) - secondary prevention, and early diagnosis and treatment of cancer.

Behavioural risk factors that drive the NCD burden

Major NCDs are driven by aging and exposure to behavioural and environmental risk factors: tobacco, harmful use of alcohol, unhealthy diet, physical inactivity and air pollution. In 2020, an estimated 22.3% of the global population aged 15 years and older were current users of some form of tobacco, down from approximately one-third (32.7%) in 2000. About one-half of men (49.3%) and one sixth of women (16.2%) aged 15 years and older in 2000 were current users of some form of tobacco. By 2020, the proportion of men using tobacco had declined to slightly over one in three (36.7%), while that of women had declined to one in thirteen (7.8%) (4). Analysis of data from demographic and health surveys conducted from 2010 to 2019 in 49 LMICs showed that tobacco smoking among men aged 15–49 years tended to be higher among the poorest and least educated subgroups. Countries continued to adopt tobacco control measures during 2019 and 2020, with approximately 5.3 billion people in 146 countries protected by at least one demand-reduction measure at best practice level. This is an improvement from 2018 (5).

The average level of alcohol consumption worldwide in 2019 was 5.8 litres [uncertainty interval (UI) 5.5 to 6.2] of pure alcohol per capita (person aged 15 years or older), a slight decline from 6.1 litres (UI 5.8 to 6.5) per capita in 2010. On average, men consumed over three times more alcohol than women (6).

Worldwide, 1 in 4 adults, and 3 in 4 adolescents (aged 11–17 years), do not currently meet the global recommendations for physical activity, set by the World Health Organization (7). High level of physical inactivity is a major contributing factor to the rising trends of obesity and diabetes.

Metabolic risk factors of NCDs

The age-standardized prevalence of obesity among adults aged 18 years and older increased between 2000 and 2016. Prevalence was estimated at 13.1% (UI 12.4 to 13.9) globally in 2016 and ranged from 4.7% (UI 3.9 to 5.6) in the South-East Asia Region to 28.6% (UI 26.6 to 30.5) in the Region of the Americas (8). According to the latest estimates, 6.8% (UI 6.1 to 7.6) of children and adolescents aged 5–19 years worldwide were obese in 2016, up from 2.9% (UI 2.6 to 3.2) in 2000 and 4.9% (UI 4.6 to 5.3) in 2010.

The global prevalence of raised blood pressure (defined as systolic and/or diastolic blood pressure ≥140/90 mmHg) in adults aged 18 years and over is around 22% (3). The global prevalence of diabetes (defined as a fasting plasma glucose value ≥7.0 mmol/L] is estimated to be 9%. The global prevalence of raised total cholesterol (defined as total cholesterol ≥ 5.0 mmol/L) in adults aged 18 years and over is estimated to be 39% (9).

Notably, the prevalence of hypertension, diabetes and dyslipidemia increases with age. For example,

the prevalence of hypertension rises to 70% in adults ≥65 years (10). As populations age in LMICs, numbers requiring treatment for metabolic risk factors will continue to increase the demands for care. Hence the critical need to move away from costly approaches targeting single risk factors in isolation based on risk factor cut-offs to more cost-effective interventions such as treatment based on total risk assessment (WHO best buy).

The impact of the COVID-19 pandemic

The COVID-19 pandemic has upended the global health, socioeconomic and political landscape (11, 12). As of 3rd November 2022, 628 million cases and 6.5 million deaths have been reported (13). Many countries have limited testing capacity and lack functioning vital statistics systems to provide accurate mortality data and causes of death. WHO excess mortality estimates show that the actual death toll associated with the COVID-19 pandemic between 1st January 2020 and 31st December 2021 was approximately 14.9 million worldwide. People in many LMICs remain critically underserved by vaccination programmes (14). Globally, there is a downward trend in newly reported weekly cases. The SARS-CoV-2 virus continues to mutate. The Omicron variant of concern accounted for 99.9% of sequences reported to the World Health Organization (WHO) in October 2022 (15).

The impact of the pandemic has widened health inequities worldwide. Moreover, it has aggravated pre-pandemic resource constraints and health workforce shortages in countries of all levels of development. However, LMICs are less well-placed to cope with these adverse effects. Hence progress made towards tackling NCDs and sustainable development might be reversed.

Abundant evidence shows that people with NCDs are more vulnerable to contracting COVID-19 and becoming seriously ill with the SARS-CoV-2 virus (16). The long-term impact of COVID-19 on cardiovascular health and mortality is an emerging concern. Post-acute sequelae of COVID-19) a condition characterized by the persistence of COVID-19 symptoms beyond three months, is anticipated to affect many people. Cardiovascular symptoms, including chest pain, shortness of breath, fatigue, and autonomic manifestations are common. In addition, a range of cardiovascular abnormalities has been reported among patients beyond the acute phase and include myocardial inflammation, myocardial infarction, right ventricular dysfunction, and arrhythmias (17).

The COVID-19 pandemic has significantly disrupted the prevention and control of NCDs, particularly in LMICs (18). The provision of essential health services was adversely affected for cardiovascular disease, diabetes, cancer, kidney disease and other NCDs. Pandemic mitigation measures such as travel bans and national lockdowns restricted access to inpatient and outpatient services. Patients were reluctant to seek care for fear of being exposed to infection. The main reasons for disruptions were intentional service delivery modifications (40% of countries), such as temporary closures or postponement of services, and shortages of staff, medicines, diagnostics, and health facility infrastructure (19). These disruptions will result in delayed diagnosis, suboptimal treatment and postponement of rehabilitation services and surgery (20). The downstream effects will likely include more advanced disease and non-fatal and fatal complications.

In terms of disruption of activities, out of 163 countries surveyed, 77% reported some disruption to the Ministry of Health NCD activities (18). There was disruption in public screening programmes for NCDs and NCD Surveys (39%) and suspension of mass communication campaigns (37%). The WHO Package for Essential NCDs (PEN) training and implementation in primary health was disrupted in 65% of low-income countries (LICs) and 49% of LMICs. A quarter (26%) of countries indicated that other ministry of health NCD activities were also impacted, including policy and guideline development and training of health personnel.

Further, government funding initially allocated for NCDs had been reassigned to non-NCD services in 20% of countries due to COVID-19 response efforts, with just seven countries (4%) reporting a

loss of more than 50% of funds.

Injustice and inequalities in global health: a reality

Timely access to physical and mental health care services is a fundamental human right that should not be affected by social determinants of health (21). Yet, as of 25th April 2022, 74% of persons in high-income and upper-middle-income countries were vaccinated compared to 51% in LMICs and only 12% of persons in LICs. In LICs, only 30% of healthcare workers had been fully vaccinated against COVID-19 by April 2022, compared to a global average of 80%. In African countries, only one-fourth of adults aged over 60 years and only 11% of people with comorbidities were fully vaccinated. Tackling the pandemic and its aftermath requires global cooperation and solidarity in the form of development assistance. Yet, support for development assistance is likely to be dampened by domestic economic and political concerns of high-income countries.

The pandemic has also aggravated the disparities in health workforce distribution that existed before the pandemic (22). In 2016, WHO had projected a global shortfall of 18 million health care workers by 2030, particularly in the WHO Africa and South-East Asia region . Africa, which bears almost one quarter of the world's disease burden, has only 3% of the world's healthcare workers (23).

The growing burden of NCDs will continue to be a major threat to the socioeconomic development of LMICs. Delays in addressing NCDs will worsen the negative impact of the pandemic in LMIC economies due to the high healthcare costs of NCDs and loss of productivity. Further, established risk factors of NCDs (obesity, hypertension and diabetes) and end-organ damage of the heart, brain, lung and kidney are both accelerators and consequences of severe COVID-19 (24), and might also adversely influence the efficacy of COVID-19 vaccines (25). In addition, NCDs may also increase the vulnerability of populations to emerging and re-emerging viral infections that emerge in the future (26). Thus, regardless of the new challenges to NCD prevention and control that have arisen due to the COVID-19 pandemic, LMICs need to prioritize action to address them. In order to do so, now more than ever, NCD interventions have to be selected based on cost considerations, scalability and long-term sustainability.

Cost, scalability and sustainability of NCD interventions: WHO best-buy interventions

Healthcare expenditure in LMIC, even before the negative impact of the COVID-19 pandemic on economies, was inadequate to sustain comprehensive national NCD programmes (27). The share of health in government spending is two and a half times greater in high-income countries (14%) compared to LICs (5.4%) (28). The share of health in government spending in high-income countries grew steadily from 2000 to 2019 while it stagnated and later declined in LMIC. In addition, out-of-pocket spending on health accounts for 44% of health expenditure on average and continues to be the largest source of health expenditure in LICs (1).

Prioritized implementation of 16 very cost-effective NCD interventions with a high return (best buys) is the strategic response recommended by WHO to address the critical resource limitations in LMICs (29) (Table 1). Thirteen best-buys are policy interventions that address tobacco (5), harmful use of alcohol (4), unhealthy diet (3) and physical inactivity (1). Two interventions target cancer. Health system interventions are more costly than population wide policy interventions. They need to be implemented in such a way as to target limited financial and workforce resources at individuals at medium to high risk (30). Only an integrated health system intervention can tackle established cardiovascular disease, hypertension and diabetes using a total-risk approach. These 16 interventions are affordable to all LMIC, and their implementation can help reduce premature mortality from heart attacks, strokes, end-stage renal disease and cancer.

Seventy-two other NCD interventions that are less cost effective are also available, which can be implemented after the national scale-up of best buy interventions if the government is prepared to increase health care spending. However, introducing them early will result in opportunity

costs, particularly in countries with competing public health priorities such as maternal and child health and communicable diseases.

How to improve the outcomes of hypertension and diabetes despite growing resource challenges and competing health priorities

The metabolic risk factors of NCDs-obesity, diabetes, hypertension and hyperlipidemia are intertwined and often coexist as comorbidities. For example, up to 75% of adults with diabetes also have hypertension, and patients with hypertension alone have features of insulin resistance (31) . Further, detection, treatment and control of hypertension, diabetes, hyperlipidemia , smoking and overweight must be improved. However, the long-term nature of these highly prevalent risk factors means that sustainability and affordability of detection, treatment, and control programmes need to be ensured (32). Vertical national programmes targeting single risk factors may be appropriate for high-income countries (33) but they significantly reduce cost effectiveness of programme implementation and service delivery (34). Further, they also aggravate out-of-pocket spending on health, negatively impacting poverty alleviation (35). Thus, they are unsustainable and unaffordable to LMICs unless public spending on health is increased substantially (30).

The very cost effective total risk approach intervention (a WHO best- buy), estimates the overall risk of hypertension, diabetes, hyperlipidemia, tobacco smoking and overweight for treatment and referral decisions. Tools (36) and simplified protocols (37) available for implementing this intervention in primary health care also identify individuals with previous heart attacks and strokes to ensure the continuation of drug treatment (secondary prevention). The total risk approach is being implemented in many LMICs (38-51) and already included in the basic benefit packages in some universal health coverage initiatives (3).

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The cost of medicines is a major component of health system expenditure. Notably, the treatment of low-risk stage 1 hypertensives comes at a high cost and limited added benefit unless treatment costs can be minimised (52). The four very cost-effective interventions to reduce population salt consumption can help to reduce expenditure on antihypertensive medicines. Providing access to an affordable set of essential medicines (aspirin, statin, angiotensin-converting enzyme inhibitor, beta blocker, calcium channel blocker, metformin and insulin), at all levels of the health system should be one of the targets of multisectoral national NCD plans (3). New drug treatment guidelines recommend combination therapy, with a single-pill combination, as the initial treatment of hypertension (53). However, most single-pill combinations used for treatment of hypertension contain an angiotensin converting enzyme inhibitor or an angiotensin receptor blocker. Whatever the advantages, they should not be prescribed to women of child bearing age in LMICs because they may cause harm due to delays in pregnancy detection and low health literacy. These drugs have been reported to cause miscarriage, oligohydramnios, foetal growth retardation, foetal malformations, neonatal renal failure, hypotension and death (54).

Overcoming challenges to NCD prevention and control

The financing needs for tackling NCDs in LMICs have been estimated and translated into health and economic return. Every dollar invested in NCD best buys gives returns of USD 7 (55). However, there are other challenges besides resource limitations that need to be overcome for NCD prevention and control in LMICs. A range of policy

Table 1 - Very cost-effective NCD interventions (source: World Health Organization (29))

Risk factor/disease	'Best buys': effective interventions with cost effectiveness analysis (CEA) ≤ I$100 per DALY averted in LMICs
Reduce tobacco use	Increase excise taxes and prices on tobacco products. Implement plain/standardized packaging and/or large graphic health warnings on all tobacco packages. Enact and enforce comprehensive bans on tobacco advertising, promotion and sponsorship. Eliminate exposure to second-hand tobacco smoke in all indoor workplaces, public places, public transport. Implement effective mass media campaigns that educate the public about the harms of smoking/tobacco use and second-hand smoke.
Reduce the harmful use of alcohol	Increase excise taxes on alcoholic beverages. Enact and enforce bans or comprehensive restrictions on exposure to alcohol advertising (across multiple types of media)Enact and enforce restrictions on the physical availability of retailed alcohol (via reduced hours of sale).
Reduce unhealthy diet	Reduce salt intake through the reformulation of food products to contain less salt and the setting of target levels for the amount of salt in foods and meals. Reduce salt intake through the establishment of a supportive environment in public institutions such as hospitals, schools, workplaces and nursing homes, to enable lower sodium options to be provided. Reduce salt intake through a behaviour change communication and mass media campaign. Reduce salt intake through the implementation of front-of-pack labelling.
Reduce physical inactivity	Implement community wide public education and awareness campaign for physical activity which includes a mass media campaign combined with other community based education, motivational and environmental programmes aimed at supporting behavioural change of physical activity levels.
Manage cardiovascular disease and diabetes	Drug therapy (including glycaemic control for diabetes mellitus and control of hypertension using a total risk approach) and counselling to individuals who have had a heart attack or stroke and to persons with high risk (≥ 30%) of a fatal and non-fatal cardiovascular event in the next 10 years (feasible in all resource settings including by non-physician health workers). Drug therapy (including glycaemic control for diabetes mellitus and control of hypertension using a total risk approach) and counselling to individuals who have had a heart attack or stroke and to persons with moderate to high risk (≥ 20%) of a fatal and non-fatal cardiovascular event in the next 10 years (Applying lower risk threshold increases health gain but also increases implementation cost).
Manage cancer	Vaccination against human papillomavirus (2 doses) of 9–13 year old girls. Prevention of cervical cancer by screening women aged 30–49, either through: Visual inspection with acetic acid linked with timely treatment of precancerous lesions, Pap smear (cervical cytology) every 3–5 years linked with timely treatment of precancerous lesions, Human papillomavirus test every 5 years linked with timely treatment of precancerous lesions.

options to overcome them are outlined in the global NCD action plan 2013-2030 (56). Further, in 2022, the 75th World Health Assembly adopted several resolutions and action plans to accelerate the global progress needed for addressing NCD. These include; a) a roadmap to guide countries to reorient and accelerate their domestic action plans to place themselves on a sustainable path to meet the nine global NCD targets and SDG target 3.4 (57), b) an acceleration plan for prevention and management of obesity (58), and c) an action plan to effectively implement the global strategy to reduce the harmful use of alcohol as a public health priority (59).

Conclusion

Before the COVID 19- pandemic, only a few countries in the world were on track to reduce premature mortality due to NCDs by one-third by 2030: SDG target 3.4. Given the substantial negative impact of the COVID-19 pandemic on financial and health workforce resources, actions taken to accelerate national NCD responses in the pandemic era need to accord the highest priority to very cost-effective NCD interventions. They can be implemented and adequately scaled-up with limited resources. Failure to do so will result in LMICs falling further behind in the pursuit to attain the SDG target 3.4 by 2030.

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SLCIM PICTURE QUIZ

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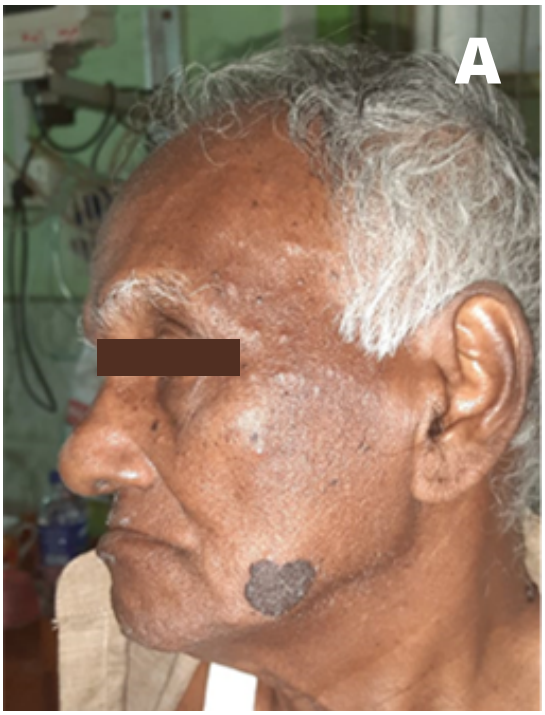
(1) A 78-year-old man presents with a slow growing, asymptomatic skin lesion over his face for 4 years. (See A)

What is the diagnosis?

(A) Actinic keratosis
(B) Basal cell Carcinoma
(C) Seborrheic keratosis
(D) Viral wart



(2) A 48-year-old woman with Type 1 diabetes mellitus has the following appearance. (See B)

What is the diagnosis?

(A) Telogen effluvium
(B) Alopecia totalis
(C) Trichotillomania
(D) Alopecia universalis

(3)

A 68-year-old man presents with fever, malaise, headache and right sided eye pain for two days. (See C)

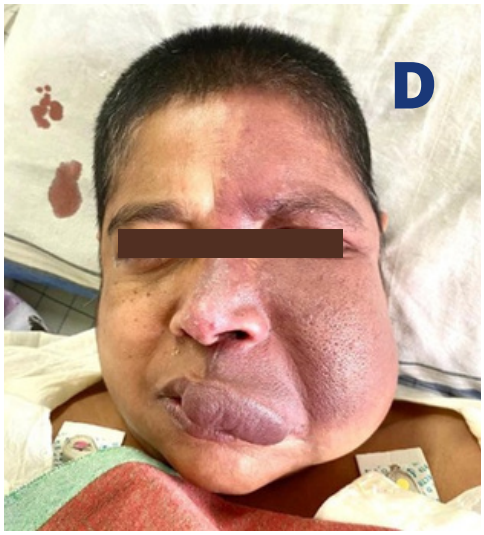
What is the diagnosis?

(A) Viral conjunctivitis
(B) Herpes zoster ophthalmicus
(C) Blister beetle dermatitis
(D) Periorbital cellulitis

(4) A 45-year-old diagnosed patient with epilepsy presents with an overdose of antiepileptic drugs. Her facial appearance is shown in the picture. (See D)

What is the diagnosis?

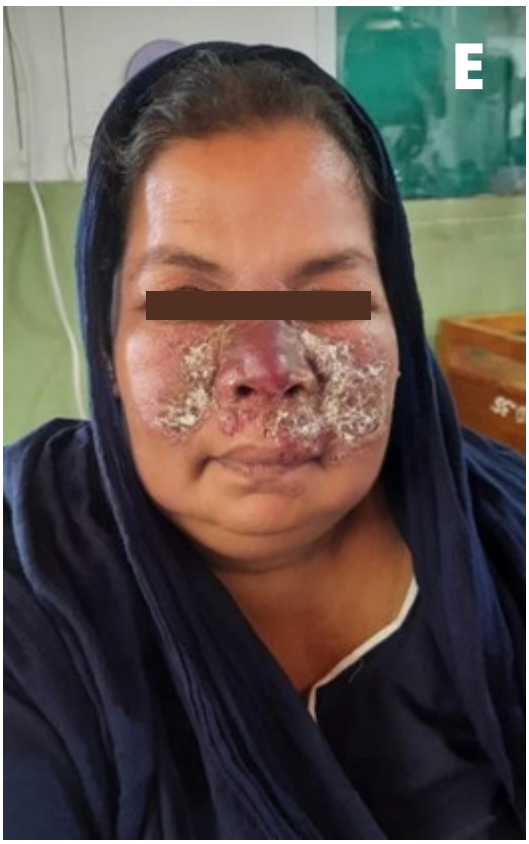
(A) Osler-Weber-Rendu syndrome
(B) Noonan syndrome
(C) Sturge-Weber syndrome
(D) Ramsay Hunt syndrome



(5) A 46-year-old woman presents with fever, headache, rapid facial swelling and discoloration of nose for 4 days. (See E)

What is the diagnosis?

(A) Facial erysipelas
(B) Rosacea
(C) Necrotizing fasciitis of the face
(D) Systemic lupus erythematosus



N.B.: The above photographs were published with consent from the respective patients.

*Refer Appendix on page 86 for answers and explanatioins.

Docetaxel- induced organising pneumonia in a patient with advanced breast cancer: case report

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Abstract

Pulmonary toxicity is a rare complication of taxanes, which are used in chemotherapy regimes in advanced breast carcinoma. We report a case of a 47- year- old woman with locally advanced breast carcinoma who developed organizing pneumonia following docetaxel based neoadjuvant chemotherapy. Following exclusion of infective causes, she was treated with prednisolone, resulting in a remarkable clinical and radiological resolution on high resolution computed tomography. Early identification and judicious steroid therapy can provide excellent outcomes in patients with docetaxel induced interstitial lung disease despite reported high morbidity and mortality.

Key words: organising pneumonia, docetaxel, advanced breast carcinoma

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Introduction

Docetaxel, which belongs to the class of Taxanes, is a chemically semi-synthesized analogue of paclitaxel and is mainly used in advanced or metastatic breast cancer and non-small cell lung carcinoma. Its chief adverse effect is cytopaenia. Pneumotoxicity, though recognised, is a rare adverse effect with an incidence of 1-5%. Early recognition and prompt treatment are essential since the prognosis could vary from remarkable recovery to rapid fatality. Here we present a case of a patient who developed organising pneumonia following neoadjuvant chemotherapy with a docetaxel-based regime and responded successfully to steroid therapy.

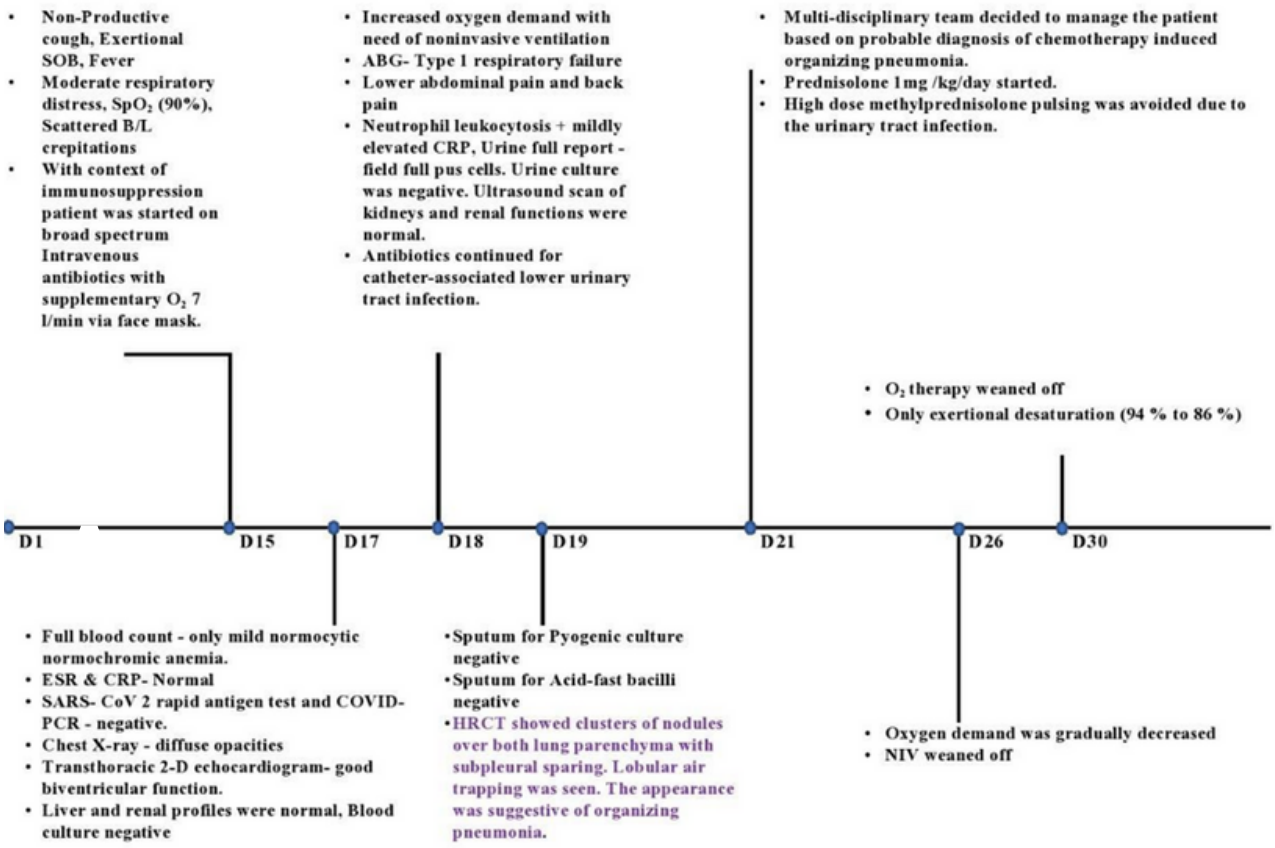
Case presentation

Our patient was a 47-year-old woman with left-side locally advanced T3N1M0, oestrogen receptor positive, progesterone receptor positive and HER 2-receptor negative breast carcinoma. She was treated with neoadjuvant chemotherapy with doxorubicin and cyclophosphamide followed by four three weekly cycles of standard dose docetaxel. Two weeks following the last docetaxel dose she developed a non-productive cough, exertional shortness of breath and low-grade fever which progressively worsened over the next three weeks.

On presenting to us, she was febrile and had moderate respiratory distress with a few scattered crepitations in both lung fields. Saturation of oxygen was 90% on room air and arterial blood gas analysis showed type 1 respiratory failure. The left breast had a firm mass measuring 2 cm × 3 cm, with no palpable regional lymph nodes. She had alopecia and the rest of the systemic examination was unremarkable. Figure 1 shows her clinical course following hospital admission.

Bronchoalveolar lavage (BAL) was performed on

Figure 1 - Timeline of events (D = Day of the illness, D1 – onset of the disease, D15 – presentation to the hospital)



day 30 of the illness which did not reveal any evidence of pyogenic infection, Pneumocystis jirovecii pneumonia or tuberculosis. Lung function tests revealed a restrictive pattern of lung disease with low carbon monoxide diffusion capacity. She continued to improve clinically and was stable by the third week of starting prednisolone. It was planned to taper off steroids over three months.

Repeat high resolution computed tomography (HRCT) in eight weeks showed marked resolution of the organising pneumonia pattern except for a patch of residual fibrosis in the apex of the right lung.

Discussion

Organising pneumonia (OP) is a type of interstitial lung disease that is characterised by inflammation and destruction of distal bronchioles, respiratory bronchioles, alveolar ducts, and alveolar wall (1). The majority is idiopathic but OP secondary to infections, connective tissue disorders, malignancy and a variety of drugs is well known (2,3). Clinical and radiological features closely resemble infection, therefore greater degree of suspicion and thorough assessment is crucial for early diagnosis.

Docetaxel can induce lung injury through various mechanisms; interstitial pneumonitis and capillary leakage syndrome which are well described and OP which is rare. The underlying pathophysiology is believed to involve type 1 and type 4 hypersensitivity (4).

The most common form is interstitial pneumonitis which can develop within days to weeks following receiving docetaxel and paclitaxel or it can arise in the later course of the therapy (4). The largest case series described 18 cases of interstitial pneumonitis which developed following docetaxel

therapy given to 392 metastatic non-small- cell lung cancer patients. It showed that time from the last docetaxel administration to finding evidence of toxicity on chest x-ray was approximately 10-20 days (median time: 18 days) (5). The capillary leakage syndrome can present as pulmonary oedema or pleural effusion.

OP pattern in docetaxel-induced pneumotoxicity is yet to be defined in terms of the time of onset and major contributing risk factors. Based on current literature, patients with underlying chronic lung disease, lung malignancy and those who have had radiotherapy are known to be at high risk of developing lung injury (6). Paclitaxel is more pneumotoxic than docetaxel. When considering docetaxel, a three weekly regime is safer than the conventional weekly dose (6). OP may recover spontaneously with some residual fibrosis or can even lead to diffuse lung injury which carries high morbidity and mortality (3).

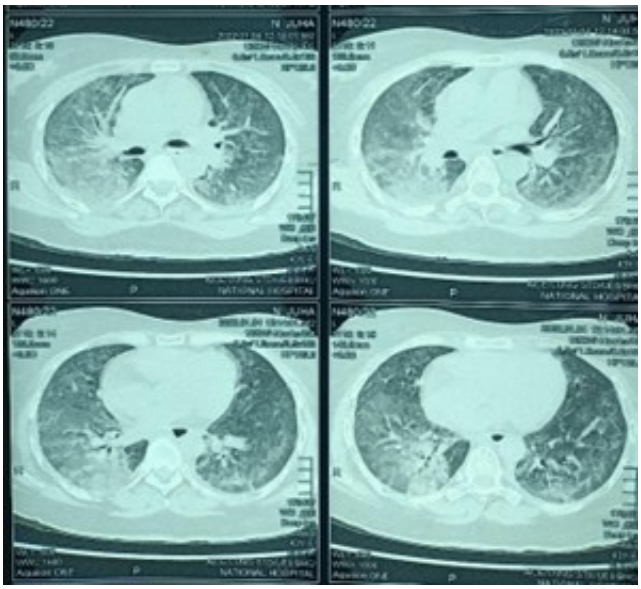
Pneumotoxicity would be more when combined with other drugs which can cause lung injury. Our patient was treated with cyclophosphamide and doxorubicin. Cyclophosphamide induced pulmonary injury is rare. The frequency is < 1% (7). Usually in early onset disease HRCT images would show bilateral reticular or nodular patterns or ground glass opacities predominantly in the periphery of upper lungs (6). Doxorubicin can very rarely cause OP, but direct co- relation is not proven (1).

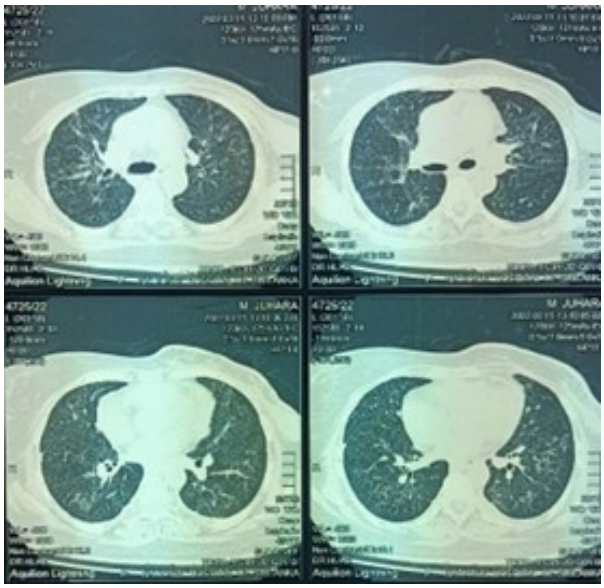
Treatment of docetaxel induced pneumonitis consists of cessation of the drug, oxygen therapy with ventilatory support and immunosuppression with steroids. There is no established steroid schedule, and its use is reserved for severe pneumonitis after exclusion of any infectious pathology. Rationale of using steroids is based on immunologic mechanisms and benefits observed in case reports (1,7,8). But still if not recognised promptly mortality would be high (9).

Our patient had developed respiratory symptoms approximately 14 days following the last dose of docetaxel. Though she was concurrently treated with cyclophosphamide and doxorubicin, considering her clinical presentation, investigation results and the response to immunosuppression, her lung disease could be attributed to docetaxel. She showed excellent response to steroids combined with oxygen and supportive therapy.

Figure 2 - High resolution computed tomography (HRCT) images before and after steroid therapy

HRCT images on diagnosis	HRCT images 8 weeks after steroid therapy





Conclusion

Docetaxel induced diffuse parenchymal injury though rare has significant morbidity and mortality. Early identification and judicious use of steroids can provide excellent outcomes. Therefore, clinicians should be aware of this potentially life-threatening complication of docetaxel therapy.

Declarations

Conflict of interest: None

Funding: None

Ethical approval: Not required

Consent: Informed written consent was obtained from the patient

Additional information

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A case report of remitting seronegative symmetrical synovitis with pitting oedema

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Abstract

Syndrome of Remitting Seronegative Symmetrical Synovitis with Pitting oedema (RS3PE) is a rare condition which is easily missed because of lack of clinical vigilance and presence of other relatively common rheumatological conditions that mimic RS3PE. We discuss a case which presented with acute onset synovitis and pitting oedema of the extremities. The patient did not have any other systemic causes for pitting oedema. He had elevated inflammatory markers and negative rheumatoid factors. There was no radiological evidence of bony erosion. Ultrasound scan of hands showed evidence of extensor tenosynovitis. He had a significant response to low dose steroids. RS3PE may be associated with malignancy and it was excluded during our evaluation.

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Key words: RS3PE, paraneoplastic syndrome, polysynovitis

Introduction

Syndrome of Remitting Seronegative Symmetrical Synovitis with Pitting oedema (RS3PE) is an acute presentation of polysynovitis with pitting oedema of bilateral extremities. Other characteristic features include negative rheumatoid factor (RF), absence of bony erosion, and favourable outcome with low dose steroids. Other rheumatic diseases, such as rheumatoid arthritis, spondyloarthropathies and, polymyalgia rheumatica, which are relatively common than RS3PE, may also present with pain and swelling. Clinical, radiological, and biochemical evaluation may distinguish these conditions from RS3PE. In this case, we describe a patient whose initial presentation was bilateral pitting oedema of the extremities and pain without any other systemic cause for oedema.

Case presentation

A 52-year-old man with hypertension and asthma presented with bilateral swelling of hands and legs for 10 days which was associated with pain in the wrist joint, small joints in hand and ankle joints. The joint pain was of acute onset, worsened with movements, and was associated with morning stiffness lasting for half an hour. He did not have fever or other constitutional symptoms. There was no history of urinary symptoms or altered bowel habits. He was a non smoker and a social drinker. On clinical examination, there was pitting oedema of both hands mainly on the dorsal surface and legs (Figure 1). The joints including the wrist, small joints in the hand and ankle joints were tender and warm. Other joints including sacroiliac joints were normal. Rest of the examination was unremarkable.

Figure 1 - Symmetrical distribution of pitting oedema in bilateral hands and legs

His laboratory investigations showed neutrophilic leucocytosis (white blood cell 13,900/µL; N:71%, L:24.5%, haemoglobin 11.9 g/dL, platelet count 430,000/µL) and elevated inflammatory markers (ESR 108 mm/1st hour, CRP 59 mg/L). His liver profile revealed an alanine transaminase of 95 U/L, aspartate aminotransferase of 43 U/L, alkaline phosphatase of 197 U/L, total bilirubin of 5.6 µmol/L, albumin of 37 g/L, globulin of 43 g/L and an INR of 1.2. The TSH, serum creatinine, electrolytes and urine analysis were within normal limits. Chest X-ray and echocardiography were normal. Ultrasound scan of the abdomen was normal except for the fatty liver. Thus systemic causes for oedema were excluded.

Subsequent investigations were focused on identifying the cause of arthritis . X-rays of both hands and ankle joint did not reveal any deformities or erosions. Ultrasound scan of the hands showed extensor tenosynovitis. Serum uric acid level was normal (257 µmol/L). Autoimmune serology including antinuclear antibody, RF and anti-cyclic citrullinated peptide antibody were negative. Antistreptolysin O titre was <200 IU/ml. Thus the diagnosis of RS3PE was established. He was administered celecoxib 200 mg twice daily and oral prednisolone 20 mg daily. A dramatic improvement was observed in oedema and joint pain during the follow up visit after two weeks. The course prednisolone was tailed off over one month. The patient remained in remission 8th months into follow up. As RS3PE may manifest as a paraneoplastic syndrome, he was screened for possible malignancies by testing for tumour markers (prostate specific antigen, carcinoembryonic antigen, and alpha-fetoprotein), and performing contrast enhanced computed tomography of chest, abdomen and pelvis, findings of which were unremarkable.

Discussion

RS3PE was first described by McCarty et.al in 1985 with a case series of 10 elderly patients who presented with acute onset of symmetrical synovitis with pitting oedema of extremities (1). A retrospective study done by Olive et.al in patients with RS3PE described diagnostic criteria for RS3PE as follows: 1. pitting oedema of bilateral extremities, 2. acute onset of synovitis, 3. age more than 50 years, 4. negative RF (2). Our patient

fulfilled the above criteria. RS3PE is considered as a distinctive condition. However, in clinical practice, it is not an easy task to diagnose RS3PE, because the mimics (rheumatoid arthritis, spondyloarthropathy, polymyalgia rheumatica) are substantially more common. Our diagnosis of RS3PE was further supported by absence of bony erosions and improvement with low dose steroids with complete remission.

Even though symmetrical involvement had been classically reported as in our case, unilateral presentation has also been described (3). Most of the reported cases were in the elderly but rarely young cases have also been recognised (4). Bony erosions are not a recognised feature of RS3PE (5). A study done by Agarwal et.al showed that tenosynovitis is more common in the extensor than the flexor aspect as in our case (6). USS with colour doppler is a cost-effective investigation modality to evaluate tenosynovitis.

Etiopathogenesis of RS3PE is still unsettled. Some studies proposed that vascular endothelial growth factor (VEGF) may play a role in oedema formation (7). HLA-B7 was found to be associated in some reported cases (1). Infective agents such as Streptobacillus moniliformis, Mycoplasma pneumoniae, and Parvovirus have been suspected as triggering factors (8).

A review article by Yao et.al suggested that RS3PE may be associated with malignancy and present as a paraneoplastic syndrome (8). It has been reported in association with solid organ malignancies such as ovary, endometrium, lung, gastrointestinal tract, liver, breast, and prostrate and haematological malignancies such as leukaemia and non-Hodgkin's lymphoma. Thus, all the cases of RS3PE should be screened for neoplasms.

RS3PE usually responds to small doses of prednisolone (5-20 mg) and has an excellent prognosis. Hydroxychloroquine and nonsteroidal anti-inflammatory drugs (NSAIDS) may have some beneficial effects. Most of the cases achieve full remission with a course of steroids. If they relapse or fail to respond, an underlying malignancy or an alternative diagnosis must be considered. There are case reports highlighting steroid resistant RS3PE in the absence of malignancy. A patient who presented with RS3PE associated with gout has been successfully treated with TNF inhibitor, etanercept (9). Tocilizumab has been used as a successful choice in a patient who has had a relapse while tailing off steroids (10).

Conclusion

RS3PE is characterised by rapid onset of synovitis with pitting oedema, negative serology of rheumatoid factor, absence of bony erosions, and a remarkable outcome to low-dose steroids, with a sustained remission. It may be a paraneoplastic syndrome especially in those who show poor response to steroids. Thus, evaluation for underlying malignancy is indicated.

Article information

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Systemic lupus erythematosus presenting as acquired factor XIII deficiency and spontaneous subdural haemorrhage

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Abstract

Factor XIII deficiency is a rare, potentially life-threatening bleeding disorder. While congenital disease is inherited in an autosomal recessive manner, acquired factor deficiency can be associated with autoimmune disease or malignancy. Clinical spectrum may range from mucocutaneous bleeding to intracerebral bleeding.

This case describes a 21-year-old woman who initially presented with low grade fever and cervical lymphadenopathy. In two weeks' time she developed bilateral spontaneous subdural haemorrhages along with bilateral small and large joint arthritis. Investigations revealed an acquired factor XIII deficiency, positive antinuclear antibodies (ANA) titer and Coomb's positive autoimmune hemolytic anaemia and was subsequently diagnosed to have systemic lupus erythematosus.

Intracerebral bleeding due to acquired factor XIII deficiency is a rare initial presentation of systemic lupus erythematosus in literature.

Key words: Factor XIII deficiency, Acquired factor deficiency, SLE, subdural haemorrhage

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Introduction

Coagulation factor XIII is a tetramer, involved in the common pathway of coagulation cascade, activated by thrombin and calcium. It is essential for hemostasis in catalysing the covalent bond between the fibrin molecules and increasing the tensile strength of fibrin polymer which protects it from the fibrinolysis. Factor XIII also contributes in the maintenance of pregnancy, bone and cartilage growth and wound healing. Its deficiency can present with bleeding episodes of varying severity depending on the factor XIII levels (1). Congenital factor deficiency is a rare autosomal recessive disorder which can present as spontaneous and provoked bleeding including umbilical and intracranial bleeding and heavy menstrual bleeding. Patients can also have recurrent pregnancy loss and impaired wound healing (2). Acquired factor XIII deficiency can occur due to the presence of autoantibodies against factor XIII subunits and can present with mucocutaneous as well as intracranial bleeding. Both congenital and acquired conditions have normal screening coagulation tests and can easily be missed. Failure to recognize this rare condition may lead to catastrophic outcomes (3).

Case presentation

A twenty-one-year-old girl presented with multiple painful neck lumps for 1 month. She also had low grade intermittent fever for 2 weeks with night sweats, loss of appetite and weight loss. In 2016, she was diagnosed with pulmonary tuberculosis and treatment was completed. She denied any respiratory symptoms. There was no history of blood transfusions, intravenous drug abuse or high-risk sexual behaviour. She denied raw milk or meat consumption.

On examination her body mass index was 20 kg/m² and she was pale. Her bilateral posterior cervical and a few axillary lymph nodes were enlarged. They were firm, tender and discrete.

On investigation her full blood count revealed marginal pancytopenia (white blood cell count (WBC) 3.25 $\times 10^9$/ L, haemoglobin 10.7 g/dL and platelets of 130×10^9/L). Erythrocyte sedimentation rate (ESR) was 40 mm/ first hour while c-reactive protein (CRP) level was 15 mg/L. Serum transaminases were elevated with AST of 306 U/L and ALT of 186 U/L but subsequent reports became normal. Lactate dehydrogenase was high (435 U/L) with marginally high serum ferritin (402 µg/L). Hepatitis B surface antigen, Hepatitis C IgM antibodies and human immunodeficiency virus 1 & 2 antibodies were negative. SARS-CoV-2 Rapid Antigen Test was also negative. Ultrasound scan of the neck confirmed multiple bilateral posterior cervical lymphadenopathy with no suspicious features. Ultrasound scan of the abdomen did not show any intra abdominal lymphadenopathy or hepatosplenomegaly. We went ahead with lymph node biopsy which showed necrotizing lymphadenitis favouring Kikuchi - Fujimoto disease.

She was diagnosed with Kikuchi- Fujimoto disease and managed symptomatically. As she was clinically improving, she was discharged from the ward and was planned to be reviewed in two weeks.

Two weeks following the discharge she presented again with a persistent throbbing headache which worsens with coughing and sneezing for 1 week. It was associated with vomiting but no features of meningism, fever or any neurological deficit were present. During this admission she also complained of bilateral symmetrical small and large joint pain with early morning stiffness for more than 30 minutes. No photosensitive rash, oral ulcers, alopecia, Raynaud's phenomenon or any personal or family history of bleeding disorders were found. She denied the use of any over the counter medication.

On examination she was pale with stable vitals. Previously noted cervical lymphadenopathy was there with evidence of active arthritis. Her Glasgow Coma Scale was 15/15 and there was no focal neurological deficit. No papilledema on fundoscopic examination.

Now her full blood count showed normal WBC (10 × 10³/µL) and platelets (294 ×10³/µL). However haemoglobin had dropped to 7.5 g/dL (MCV – 89.5fL, MCH – 30.1 pg, RDW – 47.4 fL). ESR was further elevated to 110mm/1st hour and CRP remained normal. As she had a severe headache with features suggestive of increased intracranial pressure, a non contrast computed tomography (NCCT) of the brain was performed. It revealed bilateral acute on chronic subdural haemorrhage with no cerebral oedema or midline shift.

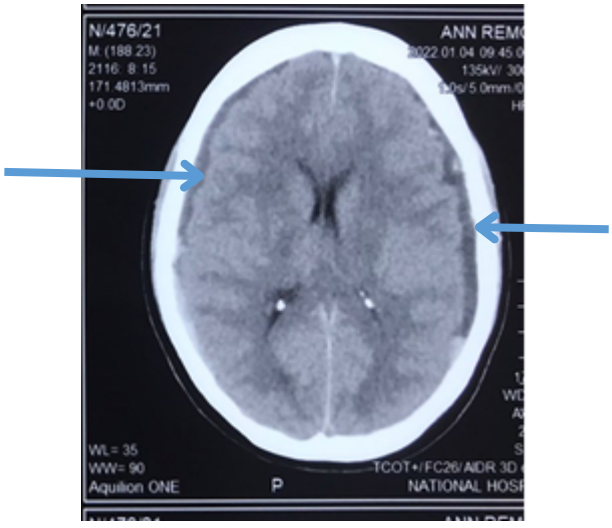

Figure 1 - Initial NCCT brain showing bilateral acute on chronic subdural haemorrhage (black arrows).

Considering the clinical picture possible local and systemic causes such as arteriovenous malformation, cerebral vasculitis, and an acquired bleeding disorder were suspected.

Coagulation screening including Clauss fibrinogen assay which was 346 mg/dL (150-450) and the rotational thromboelastometry (ROTEM) were normal. A contrast enhanced CT Brain and venogram done to identify any structural causes were negative. Magnetic resonance imaging (MRI), MR angiography and MR venography brain were also normal.

When investigating for an acquired bleeding disorder, both clot solubility test and clot solubility after 50:50 mixing with normal plasma were positive. The Factor XIII assay was 59.5% (75.2%-154.8%) which was low. Hence, she was diagnosed with acquired Factor XIII deficiency.

Considering the overall clinical features SLE was suspected. The ANA nuclear pattern was positive with a titer of 1:640. Both complement 3 level [76 mg/dL (90-180)] and complement 4 level [9.5 mg/dL (10-40)] were low. Both Anti-Ds DNA and Anti-smith antibody were negative. A direct antiglobulin (DAT) profile which was positive with anti IgG specificity.

According to the EULAR classification criteria for SLE our patient scored 16 points. The diagnosis of SLE complicated with acquired factor XIII deficiency and warm autoimmune hemolytic anaemia was made.

As the bleeding was life-threatening, she was transfused 5 units of cryoprecipitate and started on oral prednisolone 1mg/kg/day. Subsequently her clinical condition improved and the SDH was without any neurosurgical intervention.

The clot solubility test repeated two months following her presentation was negative and Factor XIII level was 101.6% (75.2%- 154.8%). She was asymptomatic. She was continued on prednisolone and HCQ 200 mg daily was started. Haematology and rheumatology clinic follow up were arranged.

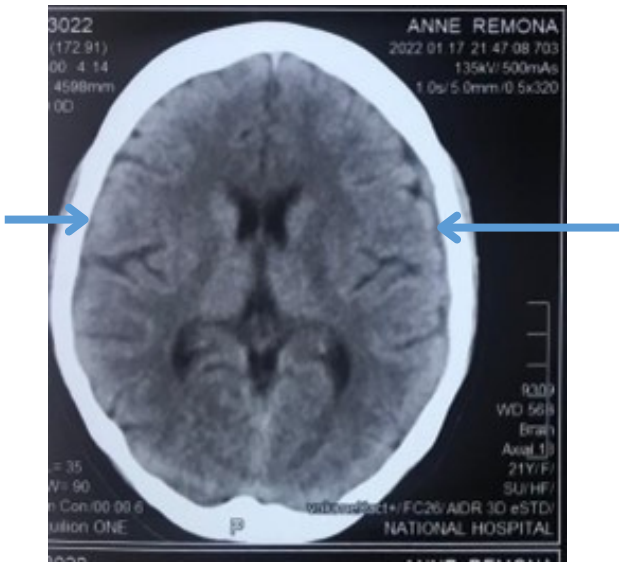

Figure 2 - NCCT brain two weeks after the initial image shows resolution of the subdural haemorrhage (black arrows)

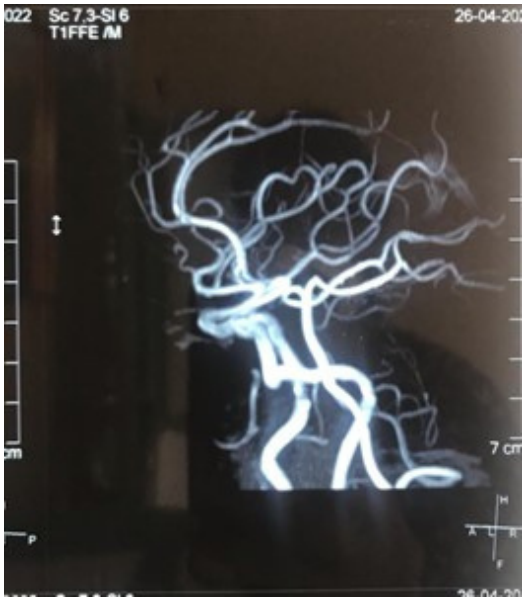

Figure 3 - A normal CT Venogram is observed

Discussion

Factor XIII is the final enzyme in the coagulation cascade and is involved in the fibrin clot stability. It comprises two A and two B subunits. While factor XIII-A is produced by hematopoietic cells, factor XIII-B is generated in the liver. Along with coagulation it is also involved in wound healing, maintenance of pregnancy and bone and cartilage growth.

Factor XIII deficiency can present with mucocutaneous bleeding (57%), delayed umbilical cord bleeding (56%), muscle hematoma (49%), haemorrhage after surgery (40%), hemarthrosis (36%) and intracerebral bleeding (34%). (1) Congenital factor XIII deficiency is a rare cause of lifelong bleeding disorder and can present with any of the above features. Development of autoantibodies against factor XIII subunits causes suppressed factor activity. This acquired factor XIII deficiency can be classified as immune mediated due to autoimmune diseases and non-immune mediated including increased consumption or reduced production like recent surgery, liver disease, malignancy, sepsis, or drug induced (Isoniazid, phenytoin, penicillin, ciprofloxacin and procainamide). Rarely it can occur due to inhibitor development against factor XIII in inherited deficiency patients receiving factor replacement therapy and can cause severe bleeding (2). Recently it was found that COVID – 19 is also associated with acquired factor XIII deficiency (4).

Clinical bleeding from any acquired immune mediated factor deficiency does not correlate with factor level or inhibitor titre and is usually more severe than in those with congenital disease (5).

This case also emphasises that in a patient with bleeding a normal PT/INR and APTT does not exclude a clinically relevant deficiency of a coagulation factor. In such cases platelet dysfunction, factor XIII deficiency or alpha-2-antiplasmin must be considered (6). Factor XIII deficiency is screened by clot solubility test (urea or monochloroacetic acid method) and confirmed by quantitative assays. The presence of inhibitors can be investigated by mixing studies. Quantification of the inhibitor can be done by Bethesda assay which is not available in the local setting.

Our patient, a young female with features of synovitis, warm autoimmune haemolytic anaemia, fever and low complement level with a positive ANA nuclear pattern, fulfils the 2019 EULAR/ACR classification criteria for SLE. Haematological abnormalities are common in patients with SLE. The prevalence is described as 47% in many studies (7). On review of literature there were very few case reports of intracerebral haemorrhage due to factor XIII deficiency, reported in already diagnosed patients with SLE. Usually acquired Factor XIII deficiency occurs a few years after the diagnosis of autoimmune disease (8). In our case it was the initial presentation of the diagnosis of SLE.

The management of acquired factor XIII deficiency aims at control of bleeding and eradication of inhibitors. Higher doses of plasma derived, or recombinant factor XIII concentrates (50-150 U/kg) are given in acquired deficiency to overcome inhibitors. Various forms of immunosuppressive treatments have been tried in several case reports. In cases of severe bleeding steroids with or without cyclophosphamide or rituximab can be tried as first line treatment. Cyclosporin, mycophenolate mofetil and other drugs can be given as second line treatment (9). It has been reported that a lupus patient with associated factor XIII deficiency who developed intracerebral haemorrhage was successfully treated with cyclophosphamide without any surgical evacuation as in the index case where the patient was successfully treated with glucocorticoids (8).

Conclusion

Acquired factor XIII deficiency is a rare life-threatening disease. As routine screening coagulation profile is normal it can easily be overlooked. Once diagnosed, extensive evaluation for the underlying aetiology must be undertaken. Early recognition and appropriate management are key in reducing patient's morbidity and mortality.

Article information

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Young girl with congenital hypo-dysfibrogenemia presenting with an acute subdural haemorrhage

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Abstract

Fibrinogen plays a pivotal role in the coagulation cascade. Inherited fibrinogen disorders are a heterogenous group that includes lack or reduced fibrinogen levels or a qualitative disorder of fibrinogen, dysfibrinogenemia. In fibrinogen disorders the clinical presentation is varied. Inherited dysfibrinogenemia is associated with a higher frequency of bleeding as well as thrombosis. We present a young girl with congenital hypo-dysfibrogenemia who suffered a significant intracerebral bleed. Herein we included a brief discussion on the diagnosis of fibrin disorders.

Key words: hypo-dysfibrinogenaemia, bleeding, fibrinogen disorders

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Introduction

Fibrinogen plays a pivotal role in the coagulation cascade. Inherited fibrinogen disorders are a heterogenous group that includes afibrinogenemia where circulating fibrinogen is absent (plasma level < 0.1 g/L) and hypofibrinogenemia which is a partial deficiency of fibrinogen (0.1–1.5 g/L). A qualitative disorder of fibrinogen, dysfibrinogenemia, is recognized when fibrinogen levels are normal with low functional activity. A small number of patients have both hypofibrinogenemia and dysfibrinogenemia, and this condition is described as hypo-dysfibrinogenemia. Fibrinogen disorders commonly present with oral, mucosal, gastro-intestinal tract and postoperative bleeding and rarely manifest as intracranial haemorrhage. We present a young patient with congenital hypo-dysfibrinogenemia who presented with a spontaneous subdural haemorrhage. This case highlights the importance of identifying the rare causes of bleeding tendency to avoid catastrophic consequences. A short description of diagnostic difficulties involved in functional bleeding disorders is included in the text.

Case presentation

A 16-year-old girl born to consanguineous parents with a past history of multiple bleeding episodes presented to the gynaecology ward with menorrhagia. Examination was unremarkable. Investigations revealed anaemia with normal platelet count and grossly prolonged prothrombin time (PT), partial thromboplastin time (APTT), Thrombin time (TT) and low fibrinogen. However the degree of prolongation of coagulation profile was disproportionate to the fibrinogen antigen level (0.7g/L). Thus Functional assay was indicated but could not be done due to unavailability of reagents. Prophylactic fibrinogen therapy was not considered for the patient as she did not have a personal or family history of severe bleeding episodes.

Few months later she was admitted with a

worsening headache without a history of trauma. Computed tomography (CT) of the brain revealed an acute subdural haemorrhage (Figure 1) and evacuation was done under cryoprecipitate cover. Subsequent functional fibrinogen assay by Clauss method failed to show any fibrinogen activity and the diagnosis of congenital hypo-dysfibrinogenaemia was made and she was started on regular prophylaxis with cryoprecipitate.

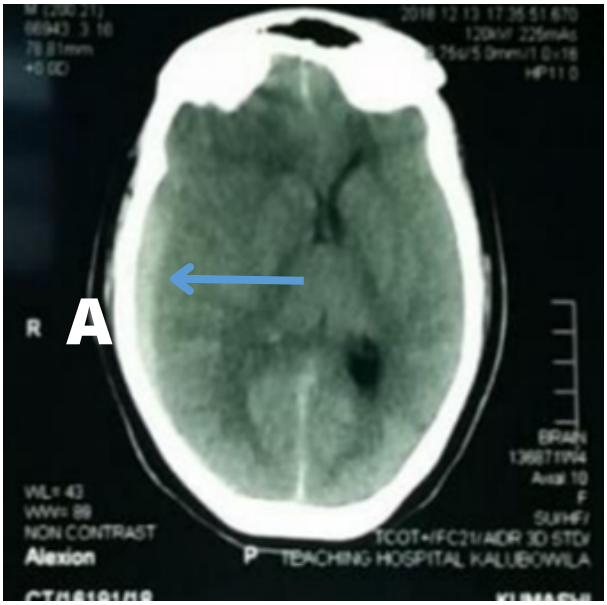

Figure 1 - NCCT brain showing subdural haemorrhage

Discussion

Inherited fibrinogen disorders are a rare form of coagulation disorders. The prevalence of afibrinogenemia is estimated to be 1:1,000,000. It is more frequent in countries where consanguineous marriages are common. The prevalence of other fibrinogen disorders is higher as heterozygosity for a causative mutation is sufficient to cause the phenotype, while complete fibrinogen deficiency in afibrinogenemia requires homozygosity or compound heterozygosity. Congenital fibrinogen disorders account for about 8% of the rare coagulation disorders (1).

In fibrinogen disorders the clinical presentation is heterogeneous. Patients with afibrinogenemia have a bleeding tendency that usually manifests in the neonatal period, with 85% of cases presenting with umbilical cord bleeding (2). Patients with hypofibrinogenemia are usually asymptomatic, but this depends on fibrinogen levels. The bleeding episodes in severe hypofibrinogenemic patients can be similar to afibrinogenemia. Spontaneous bleeding can be observed when the fibrinogen levels are lower than 0.5 g/L. Among bleeding episodes epistaxis, menorrhagia, hemarthrosis, as well as umbilical, skin, and muscular bleedings are common, while intracranial haemorrhage (ICH) is rare, but it is considered the most common cause of death. ICH has been reported in 5% of the patients with afibrinogenemia but it can also be observed in patients with hypofibrinogenemia (3,4,5).

In congenital dysfibrinogenemia the clinical presentation is varied. A review of more than 260 cases of dysfibrinogenemia revealed that 55% of the patients had no clinical complications while 25% presented with bleeding, and 20% had a tendency to thrombosis, mainly venous (6). In general, inherited dysfibrinogenemia with functional fibrinogen levels below 50 to 100 mg/dL are associated with a higher frequency of bleeding complications. Patients with dysfibrinogenemia bleed most often after trauma, surgery, or during the puerperium. In the largest published cohort of 101 patients with congenital dysfibrinogenemia, thrombosis was more common than bleeding manifestations (7).

The initial workup should include measurement of PT, APTT, TT, reptilase time (RT) and fibrinogen assays. Genetic analysis could be used to confirm the diagnosis (8). The sensitivity of PT, APTT, and TT varies according to the assay and laboratory-specific reagents. As a general rule, the TT and PT are more sensitive than the PTT in fibrinogen disorders (9).

Like TT the RT is sensitive to fibrinogen deficiency and dysfunction, but unlike TT, it is not prolonged by heparin or by fibrinopeptide B cleavage defects (10). When a mixing study is done on one or more of these tests, it may show correction in the setting of afibrinogenemia or hypofibrinogenemia but not in dysfibrinogenemia because a functionally abnormal fibrinogen may act as an inhibitor in a mixing study.

Factor antigen assay is an indirect way of measuring the levels of coagulation factors. This Immunologic assay measures all fibrinogen regardless of functionality and does not reflect the level of functional fibrinogen. Functionality should be measured using a separate functional assay. The functional fibrinogen activity is determined by Clauss method. Diagnosis of dysfibrogenemia is confirmed with the fibrinogen clotting activity-antigen ratio (2). Afibrinogenemia and hypofibrinogenemia, have absent or low plasma fibrinogen antigen levels and functional activity whereas in dysfibrinogenemia and hypo-dysfibrinogenemia, patients show normal or reduced antigen levels associated with disproportionately low functional activity (12). However, even in specialised laboratories, this diagnosis can be difficult because the sensitivity of the tests depends on the specific mutation, reagents, and techniques (2).

In the absence of a personal or family history of severe bleeding event or fibrinogen activity <0.1g/L, patients with fibrinogen disorders do not require routine primary prophylaxis. They are treated with "on-demand" fibrinogen replacement at the time of bleeding, surgery, or pregnancy. Mild bleeding episodes or minor surgery in afibrinogenemia, hypofibrinogenemia or haemorrhagic dysfibrinogenemia, can be managed with tranexamic acid alone. For severe bleeding or major surgery fibrinogen replacement with either fibrinogen concentrate or cryoprecipitate is required. For women with fibrinogen activity <0.5 g/L or with previous adverse pregnancy outcomes, prophylaxis throughout pregnancy should be considered (13).

As our patient did not have a significant history of a major bleed, prophylaxis treatment was not offered at the first presentation. Later regular prophylaxis was started as she presented with a significant bleed with very low functional fibrinogen level.

Article information

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Recurrent hypoglycaemia in a patient with thyrotoxicosis due to Insulin autoimmune syndrome

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Abstract

Insulin autoimmune syndrome (IAS) is an immune-mediated hyperinsulinaemic hypoglycemia in individuals previously unexposed to exogenous insulin. A 63-year-old woman developed recurrent hypoglycemic episodes despite being on optimal glycemic support. She was diagnosed with Graves' disease and was on carbimazole. Her insulin: C peptide ratio was suggestive of exogenous insulin administration or presence of insulin autoantibodies. Her insulin antibody level was elevated. IAS was probably secondary to her carbimazole therapy.

Key words: Hypoglycaemia, Insulin autoimmune syndrome, Hirata's disease, Insulin autoantibodies, Hyperinsulinism

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Introduction

Insulin autoimmune syndrome (IAS) is an immune-mediated hyperinsulinaemic hypoglycemia in individuals previously unexposed to exogenous insulin. It is also known as Hirata's disease (1). Prior viral illnesses or medications may trigger a de-novo antibody production against endogenously secreted insulin. These insulin-antibody complexes suddenly dissociate, precipitating steep hypoglycemic episodes caused by a surplus of unbound insulin in the system (2).

We report a patient with IAS in a 63-year-old woman, who was admitted to National Hospital of Sri Lanka with a Type 3 hypoglycemic episode which recurred throughout her stay, despite being on optimal glycemic support. Interestingly, she was initiated on carbimazole for Grave's disease just two months before. The diagnostic work-up of recurrent hypoglycemic episodes was challenging.

Case presentation

A 63-year-old woman was brought in a comatose state to the emergency unit. She was found to have a random capillary blood sugar of 19 mg/dL. On administration of a bolus of IV dextrose 50%, she regained consciousness. Thus, she fulfilled Whipple's triad for a major hypoglycemic episode. She reported to have had recurrent dizzy spells and palpitations over the 2 weeks preceding admission which improved with sugar containing food. She had regular meals and no undue exertion. She did not have any symptoms suggestive of renal disease, liver disease, gastrointestinal losses or Addison's Disease. Strikingly, she was not a diabetic and insulin-naïve. She had presented with symptoms of thyrotoxicosis and was diagnosed with Graves' Disease two months prior to this presentation. Carbimazole and propranolol were initiated. She denied taking any ayurvedic medication or any of

her family members' anti-diabetic medication even by mistake. She was treated for pulmonary tuberculosis in 2014 and it was complicated with post-TB bronchiectasis. She remained free of any features of re-activation.

She was thin built, rational, haemodynamically stable and clinically euthyroid. Except for a mild exophthalmos, she did not have a goitre, pretibial myxoedema or dysthyroid eye disease. She had no skin hyperpigmentation or postural hypotension. There were no signs of chronic liver cell disease, no rashes or abnormal lumps. Abdominal examination was unremarkable with no organomegaly. Respiratory examination revealed right sided lower zone coarse inspiratory crepitations compatible with her previous diagnosis of post-tuberculous bronchiectasis. Cardiovascular examination was normal. She did not have any focal neurological deficit.

During the ward stay she developed recurrent fasting and postprandial hypoglycemia (on an average of 4 hours after meals) despite being on a continuous 10% dextrose infusion. Her full blood count was normal. Her serum creatinine was 0.55 mg/dL. There was neither any renal impairment nor albumin-globulin reversal to suggest any liver impairment or monoclonal gammopathy. HbA1c was 5.7 %. She underwent a short Synacthen test with serum cortisol > 550 nmol/L at 30 and 60 minutes, excluding Addison's Disease. We proceeded with a supervised testing of insulin and C-peptide during a hypoglycemic episode.

insulin and C-peptide during a hypoglycemic episode

Serum RBS = 44 mg/dL	Test level	Normal
Insulin (mU/L)	>300	2-25
C-Peptide (ng/mL)	7.74	0.78-5.1

Ratio of insulin(pmol/L) : c-peptide (pmol/L) was > 8.1. Insulin was in excess of C-peptide, which suggested exogenous insulin administration or presence of insulin autoantibodies.

During the ward stay, she was closely observed and a drawer search was done to exclude any self-administration of exogenous insulin.

Next, she underwent a PEG (polyethylene glycol) precipitation test, a method to concentrate and capture large proteins. PEG is an inert solvent sponge which reduces solvent availability. As concentration of PEG increases, the solubility is exceeded and precipitation of the immune complexes occurs (3). Post PEG supernatant is tested for Insulin level.

insulin level of Post PEG supernatant

Pre-PEG supernatant insulin (mU/L)	> 3000
Post-PEG supernatant insulin (mU/L)	133
PEG precipitable activity (%)	< 4.4

Reduced recovery of insulin in the supernatant following addition of PEG was suggestive of the presence of insulin autoantibodies (3). Serum Insulin autoantibody levels were >300 U/mL (negative <12). These extremely high levels are associated with IAS.

Chest and abdomen imaging excluded any retroperitoneal sarcoma or tumours which may cause a paraneoplastic manifestation. Screening for a monoclonal gammopathy was negative.

After 3 weeks of recurrent episodes despite being on glycemic support, she developed hypoglycaemic unawareness as a homeostatic adaptation which added to the diagnostic challenge. She required 2 hourly CBS monitoring and increased nursing supervision. She was educated on taking small regular complex carbohydrate meals. Foods with low glycemic index have been advocated as they prevent postprandial hyperglycemia and hence insulin secretion. (8)

Once the diagnosis of IAS was made, carbimazole

and propranolol were omitted as drug induced autoimmunity was suspected. Lithium was commenced instead and a euthyroid status was maintained. (TSH 0.1 mU/L, FT4 1.07 ng/dL). She was booked for radioactive iodine therapy later. She was prescribed oral prednisolone 40 mg per day. She responded to it within a week. She has remained in remission to date after tapering down prednisolone. She would need a re-assessment of insulin autoantibody titres post-treatment to quantify the response.

Discussion

IAS was first reported in Japan in the 1970s and is also known as Hirata's disease. It is the third most common cause of hypoglycemia in Japan (4). However, it is relatively rare in other parts of the world probably due to an underestimated incidence as a result of insufficient diagnostic facilities and awareness of the disease.

Two types of immune mediated hypoglycemia are known to occur - IAS and Type B insulin resistance. In the former, the antibodies target the insulin molecule itself, while in the latter, the antibodies are against the insulin receptor. IAS is thought to be a type VII hypersensitivity reaction, the onset being in the 7th decades with an equal preponderance in both genders (5). Predisposing HLA alleles may play a major role, explaining an increased occurrence in those with Japanese ancestry.

IAS could also be a result of a generalised autoimmune tendency as in type 3A or 4 autoimmune polyendocrine syndrome. As in the index case, an increased risk of IAS was reported in patients with other autoimmune diseases such as Grave's Disease, systemic lupus erythematosus or rheumatoid arthritis (6). In Asians, IAS is considered an independent autoimmune condition and as a consequence of exposure to carbimazole (8). Medications like carbimazole and propranolol contain sulfhydryl groups which may induce auto-antibodies. These then bind to the di-sulphide bond of insulin as an example of molecular mimicry, hindering the action and clearance of insulin (7). In our patient omitting carbimazole and propranolol helped in resolving hypoglycemic episodes.

A secondary IAS has been reported in haematological malignancies such as multiple myeloma or monoclonal gammopathy of undetermined significance (4).

The pathophysiology centres around a mismatch between plasma glucose and insulin concentration due to insulin autoantibodies (5). Excess insulin is secreted to achieve normoglycemia and reduced clearance results in a state of hyperinsulinism. Once the blood glucose level drops the autoantibodies dissociate from insulin, resulting in increased amounts of free insulin, causing hypoglycemia. This results in hyperglycemia - hypoglycemia episodes. These episodes are a clue to the underlying IAS.

Although insulin and c-peptide are co-secreted by the pancreas in equimolar ratios, they have different half-lives, that of insulin being 5 to 10 minutes. C-peptide is more gradually excreted by the kidneys with a half-life of 30-35 minutes. Therefore, the normal insulin: C-peptide ratio is < 1. In IAS however, the half-life of insulin is prolonged due to the binding effect of antibodies. But the half-life of C-peptide is unchanged. This reverses the insulin: C-peptide ratio to > 1 (2). Hence, this ratio can be a useful screening tool in suspected IAS (4).

Differential diagnoses of spontaneous hypoglycemia include nesidioblastosis, insulinoma, sulfonylurea overdose and Type B insulin resistance. In contrast to IAS, the above conditions will have an Insulin: C-peptide ratio of < 1. PEG, an inert substance can be used to precipitate these autoantibodies (3). The diagnostic gold standard is demonstration of elevated serum insulin auto-antibodies, which was present in our patient in high titres.

IAS is generally a spontaneously remitting disease. It usually results in a mild hypoglycemia with intermittent hyperglycemic episodes, unlike in our patient who had severe episodes of hypoglycemia. In mild disease, withdrawal of the offending drug may be sufficient (8). Pharmacological intervention may be needed for patients with

severe IAS. Somatostatin analogues, diazoxide, immunosuppressive agents (glucocorticoids, azathioprine and rituximab), alpha-glucosidase inhibitors all have been used (4,5,9). Plasmapheresis has been used in extreme situations for a rapid lowering of insulin auto-antibodies (9).

The knowledge of IAS is still evolving and further research is needed to ascertain the long-term prognosis.

Declarations

Conflict of interest: The authors declare no conflicts of interest

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Splenic mycotic aneurysm complicating *Streptococcus salivarius* mitral valve endocarditis

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Abstract

A mycotic aneurysm is a serious, life-threatening complication occurring in 3-10% of patients with infective endocarditis. Splenic artery mycotic aneurysm is an extremely rare complication to occur, and it has not been previously reported with *Streptococcus salivarius* infective endocarditis. We are reporting a case of a 57-year-old woman with *Streptococcus salivarius* mitral valve endocarditis, complicated by a leaking splenic mycotic aneurysm which was successfully managed with embolisation. It is important to consider this rare complication in infective endocarditis patients with an acute abdomen.

Key words: Splenic mycotic aneurysm, *Streptococcus salivarius* infective endocarditis, coil embolisation

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Introduction

A mycotic aneurysm is a serious, life-threatening complication occurring in 3-10% of patients with infective endocarditis. A mycotic splenic artery aneurysm is extremely rare (1) and to the best of our knowledge, there are no previously reported cases in Sri Lanka. We are reporting a successfully treated case of a 57-year-old woman with *Streptococcus salivarius* mitral valve endocarditis, complicated by a leaking splenic mycotic aneurysm.

Case presentation

A 57-year-old Sri Lankan woman with diabetes and hypertension presented with acute onset shortness of breath and orthopnea for one day without chest pain or hemoptysis. She had three days of fever with no symptoms of a respiratory, genitourinary, or gastrointestinal infection. On examination, she was ill-looking, pale, and had multiple dental caries. There were no peripheral stigmata of infective endocarditis. Her pulse rate was 112 beats per minute (bpm) and her blood pressure was 100/70 mmHg. There was a grade 4 pansystolic murmur in the mitral area with normal heart sounds on auscultation. Her respiratory rate was 32/min, oxygen saturation was 86% on air with bi-basal fine end inspiratory crepitations in lung auscultation. Abdominal and neurological system examinations were unremarkable.

Her initial haematological and serological investigations are summarised in Table 1. Three peripheral blood cultures taken 12 hours apart were positive for *Streptococcus salivarius*. Chest radiograph had evidence of pulmonary oedema. Transthoracic echocardiogram showed a 15 mm large vegetation on the anterior mitral valve leaflet with a grade 3 mitral regurgitation (Figure 1). The ejection fraction was 45%. She was treated with intravenous penicillin G 4 million units six hourly for 42 days, and the echocardiogram showed a 4 mm vegetation after completion of antibiotics. Repeated blood cultures were negative.

Table 1 - Investigation summary

Investigation	Result	Reference Range
Total white cell count (per µL)	22000	4000-7000
Haemoglobin (g/dL)	8	11-16
Platelet (per µL)	327000	150000-450000
Serum creatinine (mg/dL)	1.6	0.5-1.1
Serum sodium (mmol/L)	136	135-145
Serum potassium (mmol/L)	4.3	3.5-4.5
Erythrocyte sedimentation rate (mm per 1st hour)	120	1-20
C-reactive protein (mg/dL)	134	<5
Aspartate aminotransferase (U/L)	26	8-33
Alanine transaminase (U/L)	31	4-36

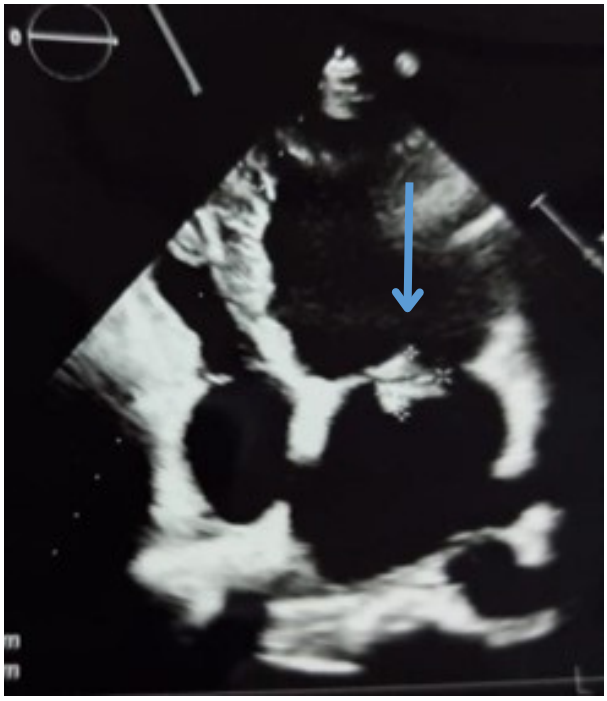

Figure 1 - Two-dimensional echocardiogram, apical four-chamber view of the mitral valve. Arrow showing the 15 mm vegetation on the anterior mitral valve.

Two days following completion of treatment, she developed sudden onset left hypochondrial pain with guarding and rigidity of the abdomen. She was pale. Her pulse rate was 120 bpm and her blood pressure was 90/60 mmHg. An ultrasound scan of the abdomen showed a mild amount of free fluid in the perisplenic and perihepatic regions with a vascular lesion in the spleen. Contrast-enhanced computed tomography (CECT) of the abdomen with the mesenteric angiogram showed a 2.9x 2.7 cm mycotic aneurysm in the distal part of the interpolar branch of the splenic artery. Haemoglobin dropped from 10 g/dL to 6 g/dL within 36 hours. Serum lactate was 1.4 mmol/L. After initial resuscitation and blood transfusion, she underwent urgent coil embolisation of the aneurysm. Post-embolisation angiogram confirmed complete occlusion of the arterial branch just proximal to the aneurysm (Figure 2). Post-procedure recovery was uneventful and mitral valve replacement was arranged.

Discussion

The prevalence of mycotic splenic artery

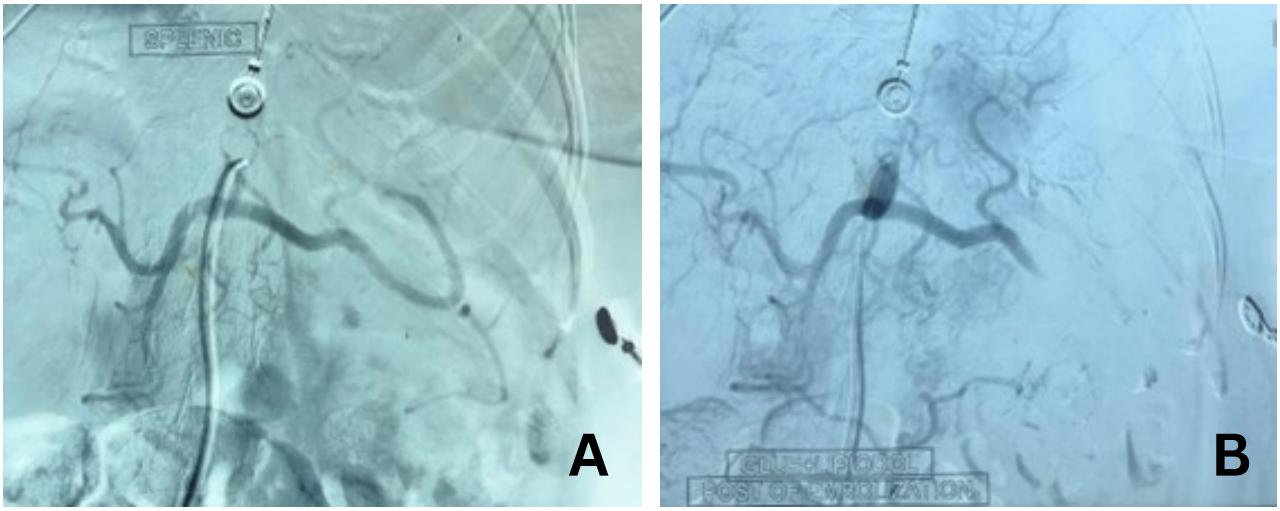

Figure 2 - Selective digital subtraction angiogram images of the splenic artery. (A) Pre-embolisation angiogram showing a 2.9x 2.7 cm aneurysm in the distal part of the inter-polar branch of the splenic artery. (B) Post embolisation angiogram showing complete occlusion of the arterial branch proximal to the aneurysm.

aneurysm is rare and to our knowledge, only a few cases have been reported to date (1). *Streptococcus salivarius*, the culprit organism in this case, is often disregarded as a contaminant. In one study out of 183 positive Viridans cultures in endocarditis patients, only 4 (2%) cultures were positive for *Streptococcus salivarius* (3). It was considered significant in this patient as three cultures taken 12 hours apart were positive, fulfilling Duke's criteria (4). There had been reported cases of *Streptococcus salivarius* causing cerebral mycotic aneurysms, but not splenic mycotic aneurysms (5). The occurrence of mycotic aneurysms after completion of treatment is also rare as the embolisation risk reduces after two weeks of antibiotics (6).

Infected splenic aneurysms have a high tendency to rupture and cause complications. In a case series by Dean et al. (1986), out of nine patients with splenic mycotic aneurysms, four resulted in rupture (7). Treatment options include surgical resection and trans-catheter embolisation which was the treatment of choice in this case (8). Endovascular treatment is preferred to open or laparoscopic surgery due to its safety, low mortality, and high success rates (8). The data is lacking on the role of coil embolisation in splenic mycotic aneurysms due to its rarity. This patient was successfully managed with endovascular treatment without post-procedure complications.

Conclusion

Streptococcus salivarius cannot always be disregarded as a contaminant in infective endocarditis and cultures should be repeated. It may cause splenic artery mycotic aneurysms leading to rupture. Therefore, early identification of this rare but treatable complication in infective endocarditis patients with an acute abdomen is vital.

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Inflammatory aorta in Giant Cell Arteritis disease: a case study of 5 patients

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Abstract

Introduction: Aortitis defined as the inflammation of the aortic wall can be due to various diseases including giant cell arteritis (GCA). Aortic involvement in GCA, reported since 1940, is rarely described. The main objective of this study was to analyse the epidemiological, clinical, radiological and evolutionary characteristics of patients with inflammatory aortitis in a cohort of patients diagnosed with GCA. We conducted a review of the literature to study the clinical and paraclinical aspects of this entity and to describe a diagnostic and therapeutic approach to inflammatory aortitis in GCA.

Methods: This is a retrospective descriptive study of 109 patients with giant cell arteritis fulfilling the diagnostic criteria established by the American College of Rheumatology (ACR), conducted over a period of 25 years (1996-2020) in the internal medicine department in Hedi Chaker University Hospital, Sfax, Tunisia. The diagnosis of inflammatory aortitis was made on the basis of aortic tomography.

Results: Five patients out of 109 (4.5%) had an aorta authenticated by aortic tomography. They were 2 men and 3 women with an average age of 64.2 years. The aortitis was revealed by non-specific systemic signs in all cases, namely fever, a biological inflammatory syndrome and abdominal pain in 1 patient. Clinical examination revealed a vascular murmur in one patient. A biological inflammatory syndrome (BIS) was present in all cases. Aortic involvement was discovered at the time of diagnosis of GCA in all cases. It was detected by thoracoabdominal aortic tomography in all cases and aortic MRI in one case. It involved the thoracoabdominal aorta in 4 cases and the abdominal aorta in one case. Treatment was based on high-dose corticosteroid therapy combined with an antiplatelet agent in the five patients. The evolution was marked by the achievement of apyrexia and regression of the BIS in all cases. A radiological check-up was carried out in only one patient, initially showing a stable appearance and then partial regression of the thoracoabdominal aorta at 6 and 18 months respectively.

Conclusion : Inflammatory involvement of the aorta in giant cell arteritis. remains a serious and potentially life-threatening complication in the case of aneurysm rupture or aortic dissection. Initially, the diagnosis may be difficult due to the non-specific clinical presentation. Systematic screening for this condition by aortic tomography is increasingly recommended. Prompt intensive drug treatment based mainly on corticosteroids may reduce short and long-term morbidity.

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Key words: Aortitis; giant cell arteritis; corticosteroids

Introduction

Giant cell arteritis (GCA), or Horton's disease (HD) is a systemic vasculitis of the large and medium-sized arteries of people over 50 years of age, with a preferential tropism for the branches arising from the external carotid artery (1,2).

Aortitis is the inflammation of the aortic wall characterised by a parietal cellular reaction that causes stenosis of the vascular lumen and sometimes thrombosis or ectasia with its risk of rupture. Aortic involvement in GCA, reported since 1940, is rarely described (3). Its clinical manifestations are not very specific depending on the vascular territory affected and its frequency seems to be underestimated.

It remains a serious complication, potentially fatal in case of aneurysm rupture or aortic dissection. The main objective of this study was to review the epidemiological, clinical, radiological and evolutionary characteristics of patients with inflammatory aortitis in a cohort of patients diagnosed with giant cell arteritis. A review of the literature described the clinical and pathological aspects of this entity and identified a diagnostic and therapeutic approach to inflammatory aortitis in GCA.

Methods

A retrospective descriptive study of 109 cases of GCA meeting the diagnostic criteria established by the American College of Rheumatology (ACR), conducted over a period of 25 years (1996-2020) in the Internal Medicine Department of the Hedi Chaker University Hospital in Sfax. The records were accessed from the department's archives. Informed written consent was taken from the patients at the point of recruitment to the study.

All patients had had a thoraco-abdominopelvic aortic tomography at diagnosis.

The diagnosis of inflammatory aortitis was made when the aortic tomography showed the presence of a circumferential, regular and homogeneous aortic parietal thickening greater than 3 mm in thickness on the aortic imaging data.

Results

It involved 2 men and 3 women (4.5% of cases in our series) with an average age of 64.2 years (with extremes ranging from 54 to 80 years). The reason for hospitalisation was fever in 4 cases associated with holocranial headaches in 2 cases and a biological inflammatory syndrome in all cases.

The aortitis was revealed by non-specific systemic signs in all cases, such as fever, a biological inflammatory syndrome and abdominal pain in 1 case. The clinical examination revealed: a vascular murmur in the left femoral artery associated with a right carotid and axillary murmur in one case, a cocoon-like skin lesion on the hands corresponding to Sweet's syndrome in one case.

In all cases, aortic involvement was discovered at the time of diagnosis of GCA.

Biologically, a biological inflammatory syndrome (BIS) was present in all cases, hepatic cholestasis in one case and moderate hypereosinophilia in one case. Infectious and neoplastic investigation was negative in all cases. Temporal artery biopsy showed giant cell arteritis in 4 cases. The diagnosis of giant cell arteritis was made on the basis of the ACR criteria in all five patients. Inflammatory aortitis was diagnosed by thoracoabdominal aortic tomography in all cases and aortic MRI in one case. It involved the thoracoabdominal aorta in 4 cases and the abdominal aorta in 1 case (Figures 1,2). The aortitis extended to the iliac arteries in 3 cases. Associated involvement of collateral branches of the aorta was present in 3 cases. It involved the supra-aortic trunks in two cases, the celiac trunk, the mesenteric and renal arteries in one case and the femoral arteries in another.

Treatment was based on high-dose corticosteroid therapy maintained for 4 to 6 weeks followed by a progressive degression until it was stopped after 2 years in 2 cases. Maintenance corticosteroid therapy with 10 mg prednisone equivalent was continued in 3 patients. An antiplatelet agent was administered to all 5 patients.

The evolution was marked by the achievement of apyrexia and regression of BIS in all cases. A radiological check-up was performed in only one patient, initially showing a stable appearance and then partial regression of the thoracoabdominal aorta at 6 and 18 months respectively. Table 1 summarises the clinico-biological and evolutionary characteristics of the 5 observations.

Discussion

Aortitis is mainly found in infections (syphilis, tuberculosis), inflammatory diseases such as Takayasu's arteritis, giant cell arteritis (GCA) or Behçet's disease, and more rarely in Cogan's syndrome, atrophic polychondritis, sarcoidosis, ankylosing spondylitis, IgG4-associated disease or

Table 1 - Clinical and radiological characteristics and therapeutic management of the 5 patients

	Observation 1	Observation2	Observation3	Observation 4	Observation 5
Gender	M	F	F	F	M
Age (years)	54	63	67	80	57
Revealing signs of aortitis	Fever + BIS²	Fever+BIS²	Fever+BIS² abdominal pain	Fever+BIS²	Femoral, carotid, axillary vascular murmur
Imaging technique	thoraco abdominal angio-CT	thoraco abdominal angio CT	Aortic angio-MRI	thoraco abdominal angio CT	*Arterial Echodoppler of the SAT *Aortic Angio-CT
Site of aortic involvement	Abdominal aorta and iliac arteries	Thoraco abdominal aorta, iliac arteries, SAT¹	Abdominal aorta	Thoraco abdominal aorta	Thoraco abdominal Aorta, iliac, mesenteric, celiac femoral arteries, SAT¹
Morphologic aspects of the aorta	Regular circumferential thickening	Regular circumferential thickening	T1 parietal thickening, T2 and Gadolinium contrastenhancement.	Regular circumferential thickening	Regular circumferential thickening
Treatment	1mg/kg/day Prednisone	1mg/kg/day Prednisone	1mg/kg/day Prednisone	1mg/kg/day de Prednisone	1mg/kg/day Prednisone
Evolution	*Regression of fever and BIS²*No radiological control	*Regression of fever and BIS²*No radiological control	*Regression of fever and BIS²*No radiological control	*Regression of fever and BIS²*No radiological control	* At 6 months: Stable appearance*At 18 months: regression of inflammatory aortitis

SAT¹ : Supra aortic trunks
BIS² : Biological inflammatory syndrome

rheumatoid arthritis. An idiopathic entity has also been described (4).

GCA is the most common cause of aortitis after the age of 60 (5). Retrospective clinical studies have estimated the prevalence of aortitis in giant cell arteritis to be between 3 and 18% (6,7). According to Deipolyi et al, two thirds (66%) of patients with giant cell arteritis develop aortitis, more than 10% develop large vessel stenosis and almost 20% develop aortic aneurysms (8). In our series, only 4.5% of patients had aortitis. This prevalence seems to vary from one study to another and to be underestimated due to diagnostic difficulties in front of its asymptomatic nature and the absence of systematic research into this condition. Aortitis was often revealed by a complication (symptomatic aneurysm, aortic dissection) which usually occurred several years after the diagnosis of GCA (9). Temporal involvement usually precedes aortic involvement. However, in our series, aortic involvement was concomitant with temporal involvement and was discovered at the time of diagnosis of Horton's disease in all cases.

The process may involve the entire aorta, but complications are usually related to thoracic involvement (10).

Pathophysiologically, aortitis is due to infiltration of the aortic wall by inflammatory cells and giant cells. The relationship between GCA and aortitis was established by pathological examination (surgical or autopsy specimen) which typically showed an inflammatory aortitis with the presence of giant cells. The development of an aortic aneurysm during GCA disease is due to two mechanisms. One is the development of the inflammatory aneurysm when GCA disease is in its active phase.The other is the development of the aneurysm on a thinned, dystrophic wall after the acute phase of the arteritis which has generated scarred and fragile aortic walls (11).

Aortitis in GCA is often insidious, pauci-symptomatic and nonspecific in its clinical presentation, which makes the diagnosis of this condition difficult. It is usually discovered during imaging. Nevertheless, the clinical examination remains crucial and should look for signs of

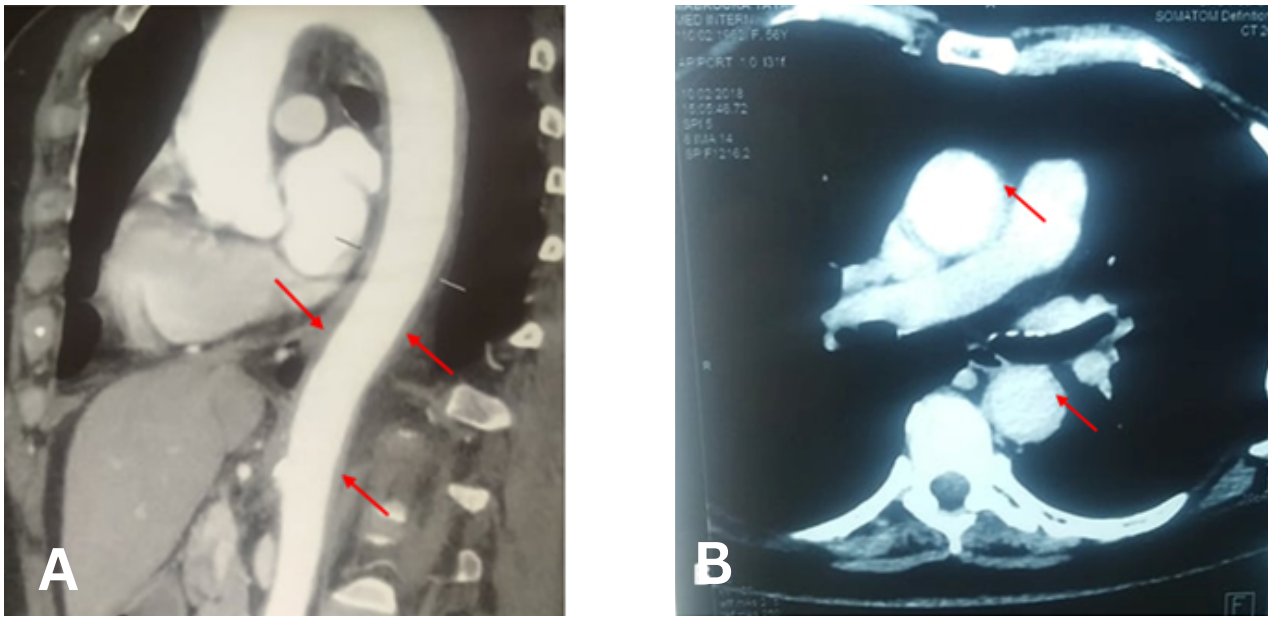

Figure 1 - Thoracoabdominal angio CT

A: Sagittal section: thickening of the wall of the thoracoabdominal aorta (Arrows)
B: Transverse section: circumferential wall thickening of the ascending and descending thoracic aorta (arrows)

damage to the aorta or its branches.

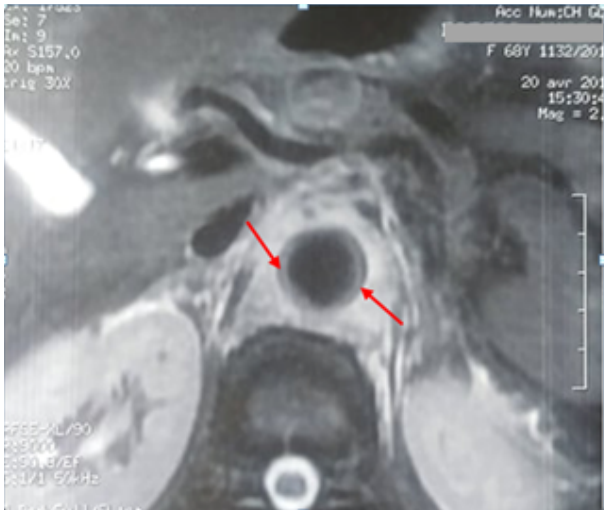

Figure 2 - Aortic MRI: T2 sequence: circumferential thickening of the abdominal aortic wall (Arrows)

The presence of chest pain, back pain or lumbago, abdominal pain, particularly inflammatory pain, and exertional dyspnoea are signs suggestive of aortitis during GCA. Signs of heart failure, aortic insufficiency murmur, abdominal flailing mass, abolition of a peripheral pulse, pulse or blood pressure asymmetry and signs of limb ischaemia are all clinical features that should raise suspicion of aortitis during GCA (7). In our series, aortitis was revealed by a femoral, carotid and axillary vascular murmur in one case and by abdominal pain in one case. Non-specific systemic signs were present in all patients. Inflammatory aortitis in GCA does not have a consensus definition. The diagnosis is often made on the basis of a range of imaging findings, without formal histological evidence of gigantocellular aortitis (12).

Aortitis is suspected when morphological abnormalities such as homogeneous circumferential thickening of the aorta greater than 3 mm or aortic ectasia/aneurysm are present, in the absence of atheroma and progressive infection. These abnormalities are most often visualised by aortic CT angiography or magnetic resonance imaging (MRI), or intense vascular fixation by fluorodeoxyglucose positron emission tomography (18F-FDG-PET) (13,14).

The differential diagnosis of aortitis is essentially atherosclerosis, given the advanced age of the patients. Imaging is essential to differentiate the two diseases. The recommendations of the French Large Vessel Arteritis Study Group (GEFA) in 2016, and those of the European League Against Rheumatism (EULAR) in 2018, recommend that aortic imaging should be performed as soon as GCA is diagnosed, to look for inflammatory aortitis and its complications (15,16). There is no consensus on which type of imaging should be performed. Doppler ultrasonography can help in the diagnosis of abdominal aortitis in GCA by demonstrating inflammatory involvement with 3 mm thickening, a "halo" sign and an aneurysm, but is of limited value in assessing overall aortic involvement. Aortic CT angiography allows a precise morphological exploration of the aorta. It is an excellent technique for diagnosing aortitis by demonstrating circumferential thickening of the aortic wall greater than or equal to 3 mm. It also allows the identification of complications such as stenosis, dissections, and especially ectasia and aneurysms (17). MRI is a non-irradiating examination that allows the simultaneous detection of structural lesions such as T1/T2 hypersignal vessel wall thickening, stenosis or luminal occlusion and arterial wall contrast reflecting active inflammation. However, MRI remains less efficient than angiography-CT due to a more limited analysis for thickenings below 3 mm (7). PET scans show parietal inflammation of the aorta by visualising continuous linear hypermetabolism of the aortic wall, but are less effective in characterising structural complications such as aneurysms. Its use remains limited by its non-specific, expensive, radiating nature and its sometimes difficult access (18,19).

In addition, radiological explorations allow the diagnosis of fatal complications, notably dissection, ectasia and aortic aneurysm, which are encountered in approximately 15 to 20% of patients, particularly in the thoracic aorta (7). These complications are responsible for the excess mortality of GCA patients compared to the general population.

Screening for aortic disease at the time of diagnosis of GCA is justified in the presence of clinical signs of aortic damage or in the case of

cardiovascular risk factors in order to detect complications in time, given the risk of potentially fatal vascular complications. The rhythm of imaging surveillance of aortic disease is not codified but imaging should be performed at least 5 years after diagnosis.

The results at 5 years should determine the subsequent timing of surveillance. Patients with hypertension and cardiovascular risk factors should be monitored more closely (20). A scannographic control was performed in a single patient with an initial stable appearance and partial regression of the thoracoabdominal aortitis at 6 and 18 months respectively.

Aortitis in GCA confers a particular profile and prognosis to the patient. Thus, GCA with large vessel involvement seems to be distinguished from those limited to cranial involvement by a younger average age at diagnosis and twice the frequency of joint involvement of the pseudopolyarthritis rhizomelia type. In addition, signs of cephalic involvement, ophthalmological complications and positive temporal artery biopsy are rarer than in the classical form, which results in a delay in diagnosis compared to the cephalic form.

Patients with aortitis also have more relapses, more cardiovascular complications and use a higher cumulative dose of glucocorticoids, which explains the more difficult control of the disease. Cardiovascular mortality is thus increased in the aortitis group (aortic dissection, arterial disease, coronary artery disease) (13,7,21).

According to the cohort study by Kermani et al, aortic disease complicated by aneurysms or dissection is associated with an increased risk of death (22).

Corticosteroid therapy presents the cornerstone of treatment for inflammatory aortitis in GCA. The 2016 GEFA recommendations do not suggest any specific intensification in uncomplicated aortitis. If strict disease control is not achieved, cortisone-sparing therapy (Methotrexate, Tocilizumab) may be necessary (15,16). All our patients were treated with high dose oral corticosteroids with good clinical and biological evolution in all cases and a favourable radiological evolution in 1 case.

Medical treatment of GCA aortitis also relies on optimising the management of cardiovascular risk factors. Statin therapy is not routinely prescribed and will be considered according to conventional LDL cholesterol intervention thresholds. Anti-platelet agents are recommended, but there is no clear evidence of benefit. Beta-blockers are justified when an aneurysm is found. (7,23).

Treatment is not codified for isolated aortic forms, but is generally modelled on that of GCA disease and modulated according to the clinical and biological activity of the disease. Aortic inflammation in GCA has a parallel course to that of other classically described conditions and regresses with corticosteroid therapy. It may relapse when treatment is stopped.

The surgical treatment of aortic aneurysms secondary to GCA is similar to that of the aneurysm related to atherosclerosis: any symptomatic aneurysm and any aneurysm equal to or larger than 5 cm in size for the ascending thoracic aorta, 6 cm for the descending thoracic aorta and 5.5 cm for the abdominal aorta, or if the diameter increases by more than 5 mm in 6 months, must be operated on (7,24).

Conclusion

Inflammatory involvement of the aorta in GCA remains a serious and potentially life-threatening complication in the case of aneurysm rupture or aortic dissection. Initially, the diagnosis may be difficult due to the non-specific clinical presentation. Systematic screening for this condition by aortic CT angiography is increasingly recommended. Prompt intensive drug treatment based mainly on corticosteroids may reduce short and long-term morbidity.

Our study has several limitations, mainly due to its retrospective nature and the small number of patients. In addition, our patients were not systematically screened for aortitis at the time of diagnosis of GCA. Another limitation is the lack of information regarding the follow-up of aortitis, as

80% of the patients with aortitis did not have a follow-up of the aortic involvement.

Declarations

The authors have no conflicts of interest to declare.

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Key to Picture Quiz

(1) Answer C – Seborrheic Keratosis

It is a common epidermal tumour mostly seen in middle aged rather than young individuals. It presents as a well demarcated, round or oval lesion with a stuck-on appearance and colour may vary from skin coloured to light brown, dark brown or black. Seborrheic keratosis is usually asymptomatic. The sign of Leser-Trelat (sudden appearance of multiple seborrheic keratosis with skin tags and acanthosis nigricans) is associated with several malignancies including those of the gastrointestinal system and lungs. As Seborrheic Keratosis is benign and a slow growing tumour, treatment is usually not needed. But lesions that are symptomatic can be removed by using cryotherapy, curettage/shaving, excision or electrodesiccation.

(2) Answer D – Alopecia universalis

Alopecia areata is a chronic, relapsing autoimmune mediated condition characterised by non-scarring hair loss. The course of alopecia areata is unpredictable. Most patients experience limited patchy hair loss which usually regrows within a year. A minority will experience total loss of scalp hair (alopecia totalis) or loss of all hair (alopecia universalis). There is an association between Alopecia areata and dermatological diseases like vitiligo, psoriasis, atopic dermatitis and some non-dermatological conditions like Type 1 diabetes mellitus, Down syndrome and polyglandular autoimmune syndrome type 1.

(3) Answer B – Herpes zoster ophthalmicus

This is a reactivation of the latent varicella-zoster viral infection involving the eye. Symptoms and signs of herpes zoster opthalmicus may be severe. It includes a unilateral dermatomal rash over the forehead and painful inflammation of all the tissues of the anterior and rarely posterior structures of the eye. The diagnosis is based on the characteristic appearance of the ipsilateral zoster dermatitis of the first branch of the trigeminal nerve (V1) and the anterior structures of the eye. Treatment mainly comprises oral antivirals, mydriatics and topical corticosteroids.

(4) Answer C – Sturge-Weber syndrome

Port-wine stain is a hallmark of Sturge-Weber syndrome, also called encephalotrigeminal angiomatosis. It is a neurocutaneous disorder with angiomas that involve the leptomeninges and the skin of the face, typically in the ophthalmic (V1) and maxillary (V2) distributions of the trigeminal nerve. It is also associated with ocular abnormalities. Neurological abnormalities include developmental delay, learning disability and seizures.

(5) Answer C – Necrotizing fasciitis of the face

Necrotizing fasciitis of the face is a life threatening rapidly progressive soft tissue infection. It has very high morbidity and mortality. It may end up with severe disfigurement of the face. It usually occurs due to infections of dental or pharyngeal origin. Early diagnosis and prompt initiation of broad-spectrum antibiotics are vital in preventing complications. Aggressive surgical debridement and reconstruction of the resultant soft tissue defects may be needed in severe infection.

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