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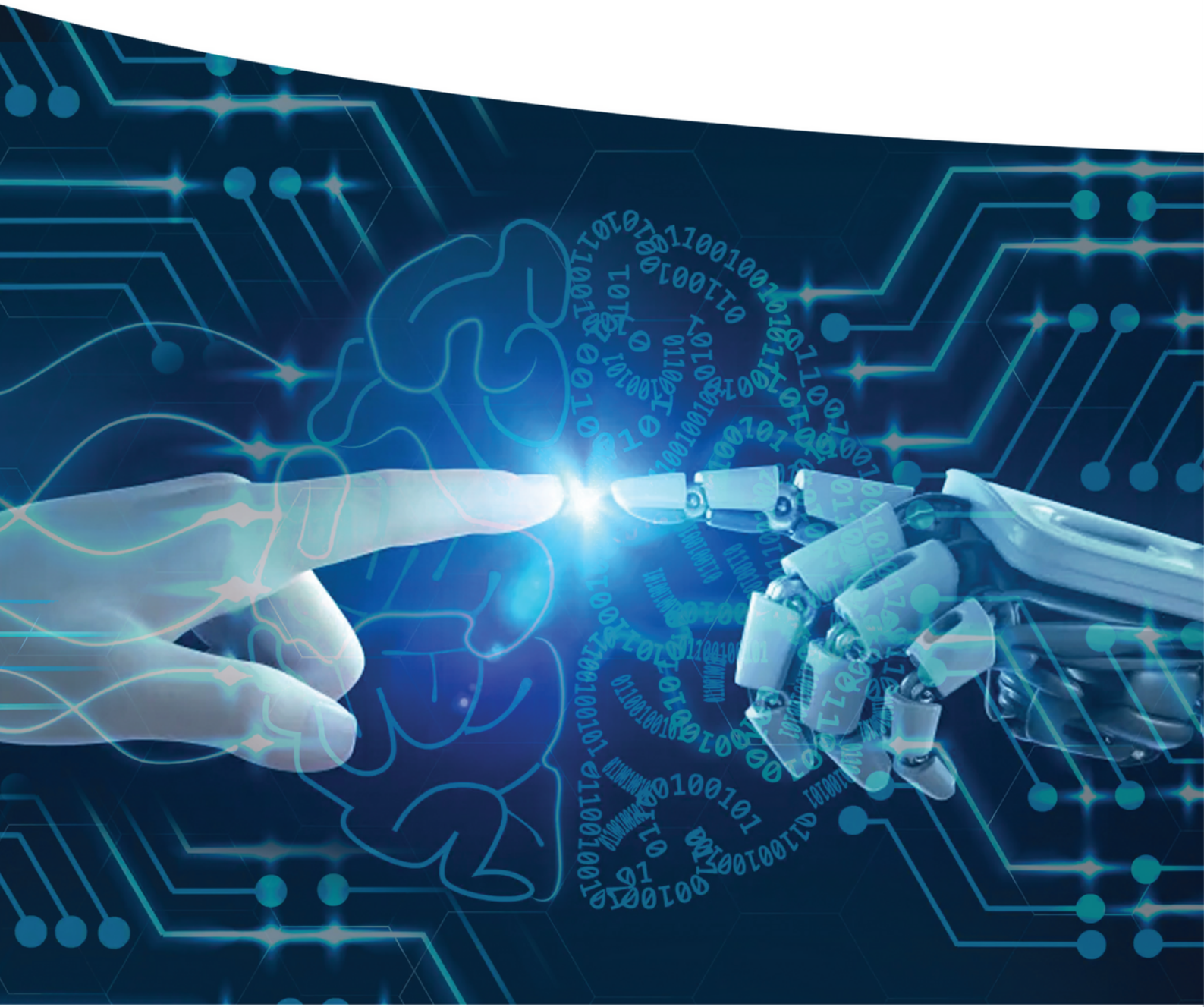

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Artificial intelligence in healthcare

Hettiarachchi NM[1], Manilgama SR[2], Liyanage ADMD[3]

Preamble

Artificial Intelligence (AI) has emerged as a transformative force in various fields, and its potential in medicine is particularly remarkable. The application of AI in healthcare holds immense promise, as it has the ability to revolutionise medical practice and the delivery of healthcare services. Over the past decade, AI has made significant strides in numerous medical specialties, presenting opportunities to enhance patient care, diagnostics, personalised treatment plans, and administrative processes within healthcare organisations. However, despite the tremendous opportunities presented by AI in medicine, there are also significant challenges to overcome.

Intelligence vs Artificial Intelligence

Exploring the concepts of intelligence and artificial intelligence (AI) is crucial for gaining a comprehensive understanding of their implications.

Intelligence is a fundamental aspect of human capability. It encompasses various abilities, including calculation, reasoning, perception of relationships, learning from experience, memory retrieval, problem-solving, comprehension of complex ideas, fluent use of natural language, classification, generalisation, and adaptability to new situations. These cognitive abilities collectively define intelligence.(1)

On the other hand, artificial intelligence (AI) refers to the simulation of intelligent behaviour and critical abstract thinking comparable to that of a human being using computers and technology.

History and background of AI

Coined by John McCarthy in 1956, AI represents the science and engineering behind creating intelligent machines capable of autonomously making decisions and performing actions on behalf of humans.(2) AI is not a singular technology but rather a collection of software and hardware components that support various areas such as machine learning, computer vision, natural language processing, and robotics.(3) In the book "Artificial Intelligence: A Modern Approach," Russel and Norvig classify AI into seven components: reasoning and problem-solving, knowledge representation, planning and social intelligence, perception, machine learning, robotics (motion and manipulation), and natural language processing, each of which can be further subdivided into subsets.(4)

The history of AI traces back to figures like Alan Turing, one of the pioneers of modern computers, who developed the Turing test in 1950. This test evaluates a computer's ability to exhibit human-level performance in cognitive tasks. The interest in AI surged during the 1980s and 1990s, and in recent years, there has been a growing focus on developing new healthcare models leveraging AI technology.(2)

Understanding the nuances of intelligence and AI is essential as these concepts shape our perception of human cognition and lay the foundation for the development of intelligent machines. By delving deeper into the history and classifications of AI, we can appreciate the progress made in this field and anticipate the potential impact of AI on various industries, including healthcare.

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Healthcare AI

The integration of AI into the healthcare industry, known as healthcare AI, consists of a range of technologies such as machine learning, natural language processing, and deep learning.(5) These cutting-edge tools have been employed to address various challenges and improve different aspects of healthcare.

Diagnostics and management

By leveraging AI, healthcare providers can derive meaningful insights, make accurate diagnoses, and develop tailored treatment strategies for individual patients. An AI system which was developed in China with the capability to diagnose paediatric diseases using available clinical data has shown similar proficiency to clinicians. Diagnosis of cardiac arrhythmias and epilepsy in real time were also made possible using wearable AI.(1) AI excels at analysing vast amounts of data, allowing medical professionals to identify disease markers and trends quickly and accurately. It also allows early disease detection by evaluation of radiological images and predicts patient outcomes. In North London, AI algorithms are used to prioritise emergencies for one million patients, surpassing the capabilities of a single physician.(3)

Administrative tasks

Furthermore, AI has the potential to streamline administrative processes within the medical field. Tasks like medical coding, billing, and patient scheduling can be automated, reducing the burden on healthcare professionals and enabling them to focus more on patient care. AI performs tasks such as digitising medical records and providing reminders for follow-up appointments or immunisations.(1,2) For example the new generation of chatbots can help with medical documentation. There are new programmes such as “Ambient Clinical Intelligence” that can analyse the conversation between a doctor and a patient and develop an electronic health record. Another programme called “Babylon”in the United States arranges patients’ appointments and routine tests.This increased efficiency in operations can lead to cost reductions and improved resource allocation within medical organisations.

Research, scientific writing and publishing

The advent of AI has empowered scientific publications by leaps and bounds. Those which once seemed to be laborious tasks are now made efficient, accurate and easy by AI powered tools. An AI tool is available to enhance efficiency in almost all aspects of scientific writing and publishing. From starting a literature search (eg: using Google Scholar), gathering relevant articles and organising (eg: Mendeley, Zotero), summarising and extracting information (eg: Scholarcy), analysing (eg: Tableau), citing and creating bibliography (eg: Zotero), running the grammar and language check (eg: Trinka) to the final plagiarism check (eg: Turnitin) are now made efficient by AI tools.

Drug development and innovation

Applications of AI in clinical development, manufacturing, patient surveillance, and post-market surveillance are already being utilised by healthcare providers, insurers, and life sciences companies to streamline processes and improve care. The field of surgery has achieved commendable reductions in postoperative complications by robotic surgeries which are minimally invasive and higher in precision than conventional procedures.

All in all , healthcare AI holds immense potential to revolutionise healthcare practices and improve patient outcomes. It enhances diagnostics, personalised treatment plans, and administrative processes, leading to cost reductions and improved resource allocation. With its wide-ranging applications, AI is transforming the healthcare industry and providing optimal care to millions worldwide.

Limitations and challenges

While AI technology in healthcare brings excitement and optimism, it is vital to address its limitations and concerns.

Data quality and quantity pose a significant challenge, as AI systems rely on robust and representative data for optimal performance. For example Machine Learning technology which is used in image recognition, speech recognition, etc. enables learning automatically from raw data to generate models that make accurate predictions.

Ethical implications surrounding AI in healthcare are multidimensional. These include **data privacy** and responsible use of patient information, potential biases in AI algorithms, accountability and transparency.

Security risks, such as data breaches and

unauthorised access, threaten patient privacy and trust in AI systems. Protecting patient data through robust cybersecurity measures and adhering to data protection regulations is crucial.

Failure to address **algorithmic biases** can exacerbate health disparities and inequitable outcomes. In addition to these, mistakes could be made by AI tools giving rise to the issue of **accountability** since it is difficult to establish accountability in such a situation.

Transparency in AI models is crucial for user trust and understanding but is equally challenging to manifest due to the complicated nature of the technology which the service provider might find difficult to explain and the recipient find difficult to understand.(6)

Certain human traits like critical thinking, communication, and empathy cannot be fully replicated by machines, raising concerns about patient-provider relationships and **care quality**. It is important to recognise that AI cannot entirely replace human healthcare professionals, as their expertise and judgement remain essential.

Ethical implications, particularly in critical medical decision-making, require careful consideration to strike the right balance between human expertise and AI algorithms.

AI in academic ***research and publication*** is a double edged sword. Despite its numerous positive applications that enhance efficiency and accuracy, various motives such as financial gains, career advancements and recognition in the competitive academic world could drive those conversant with new AI technologies to **misuse** them in producing fabricated research, encouraging fraud and contaminating the body of scientific research. The repercussions of such misuse maybe so grave as to impact new health policies and therapeutic interventions.(7)

Furthermore, using AI in research protocols raises concerns about **plagiarism**. Proper attribution and acknowledgment of AI contributions are necessary to maintain scientific integrity.

Another challenge faced in the Implementation of healthcare is the ***high investment costs***. The development and maintenance of AI systems require substantial financial resources, limiting accessibility, especially in resource-constrained settings.

By addressing these challenges, we can harness the potential of AI in healthcare while ensuring patient privacy, trust, ethical use, and equitable outcomes.

Future of AI

The future of AI in healthcare holds immense potential for revolutionising the industry and benefiting individuals worldwide. With advancements in AI, we can expect sophisticated applications that improve patient care, diagnostics, and healthcare processes. However, it is important to address challenges such as data privacy, ethics, and responsible AI use. By carefully implementing AI, we can transform healthcare and improve countless lives. While concerns exist about developing soft skills in AI systems, future advancements may enable the extraction of the best characteristics from both humans and machines, resulting in empathetic AI. Striking a balance between effective AI use and preserving the unique capabilities of the human brain is crucial.

Although there is apprehension about AI displacing human medical jobs, proactive management and oversight can harness the maximum benefits from AI systems. By embracing AI technology while preserving the human element in medicine, we can navigate this transformative era and leverage its full potential in healthcare.

It is important that all the medical professionals get well conversant with the application of AI since we are roaming in an unknown territory. It is high time that AI is incorporated into the curriculum of primary and secondary education in Sri Lanka as well as to the medical curriculum.

Conclusion

Advent of AI has revolutionised healthcare and holds great promise for further development. However certain challenges must be overcome for successful implementation. These challenges include data quality, transparency, ethics, biases, impact on human skills, high costs, security risks, and research protocol concerns. By overcoming these challenges, we can maximise benefits from AI while prioritising patient safety, privacy, and equitable healthcare outcomes. It is crucial to foster education and training that prepares healthcare professionals to effectively utilise AI in medicine and to continue exploring and developing practical applications.

There should be a fine balance between the effective use of AI without losing the automation of the human brain. This will ensure that AI technology is harnessed responsibly and effectively to revolutionise healthcare practices and improve patient outcomes.

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Basics of writing a scientific manuscript for publication in a peer-reviewed journal

Ekanayake L*

Preamble

Drafting a good research paper is a difficult and demanding exercise. For a manuscript to be accepted for publication in a peer-reviewed journal, researchers need to adhere to certain basic rules when drafting a research paper. This article discusses the basics of writing a good research paper for publication, common mistakes made by authors, how to avoid them, and matters related to authorship.

Introduction

Dissemination of research findings is the last step of the research process. To have an impact on one's discovery in the wider scientific community and to contribute to the advancement of knowledge, the findings need to be disseminated. The dissemination process involves writing up the findings, submission of the written manuscript to a journal for peer review, evaluation by the experts, following which it would be recommended for publication, revision, or even rejection. Of the different steps in the research process, writing the manuscript for publication could be the most daunting task, particularly for novice researchers. The phrase "Publish or Perish", first coined by Coolidge (1) in 1932, emphasizes the importance of publishing which has now become a reality, particularly for academia. However, in today's context conducting research and publishing are also relevant and necessary for clinicians for several reasons; it is a learning process, helps in clinical decision-making, provision of better care for patients, for career advancement,(2) and in the Sri Lankan setting for financial incentives in terms of the research allowance. Therefore, knowledge of the basic steps in drafting a research manuscript and adherence to these steps, will increase the likelihood that it will be accepted for publication in a peer-reviewed journal.

When conducting and publishing research, there are two essential factors that any researcher should bear in mind. First, even a piece of innovative research, if not written scientifically, will not be accepted for publication. Second, even a scientifically written manuscript will not be accepted, if there are methodological flaws. What makes a manuscript worthy of publication? A good research paper should address a specific research question (3) and FINER criteria (Feasible, Interesting, Novel, Ethical, and Relevant) developed by Cummings et al.(4) could be considered to formulate a good research question. If the research is based on a clearly defined research question and provides answers to the question, then writing will be easy.

Helpful tips to prepare for writing:

Scientific papers are read at various levels; some refer to the title only while others read the title and the abstract. If the title and the abstract are of interest to the reader, the full paper will be read for better understanding. Therefore, the ability to effectively communicate methodology , findings, and explanation for the findings according to readers' expectations is the primary skill required for scientific

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writing which necessitates considerable thought and planning. If a manuscript is to be accepted for publication, it should be a well-designed study, free of methodological flaws that convey a useful, and exciting scientific message, clearly written with a logical flow so that the reader can follow it easily.(5)

Structure of a research paper

The IMRAD format is widely followed in scientific medical writing.(6) The acronym IMRAD stands for Introduction, Methods, Results, And Discussion.

Introduction:

The purpose of the introduction is to inform about the background, basis, and relevance of the topic/problem. In other words, it should provide answers to the question "Why was the study done, why is it important?" Writing a good introduction is important because it sets the stage for the manuscript. It should convince the reader about the importance of the work and be strong to hold the attention of the reader. The introduction should include the following:

i) Importance of the research

ii) What is already known about the topic; (original and important work should be cited, including recent systematic reviews. Consideration should only be given to previous research that directly relates to the researcher's work)

iii) What is not known or gaps in the current knowledge related to the topic

iv) How is the new information useful?

The introduction should not be too long, limited to about 3-4 paragraphs and should conclude with a statement of the aim/hypothesis of the study. The aim/hypothesis should be related to the information gap associated with the topic mentioned in the introduction.

Method:

Of all parts of a research manuscript, the methods section is the easiest to write as this would involve merely stating what was done to answer the research question. In other words, "How was it done- when, where, and what was done?" It should give a clear, detailed description of the methods followed so that the reader could use it in future studies if needed, judge the scientific merits of the research, understand and interpret the results. This section should include the following; study design, study setting, study period, description of the study population , the formula used to calculate the sample size and the size of the sample calculated based on that formula, description of the sampling technique, inclusion/exclusion criteria, data collection instruments and procedures followed in data collection, description of an intervention where applicable, pilot test, investigator training, outcome measures, outline of the methods of data analysis including statistical tests and software used. It is also mandatory to mention ethical issues, for instance, whether informed consent was obtained from participants and other administrative requirements such as obtaining permission from relevant authorities. The research proposal should have been approved by an ethics review body and a statement to that effect should be made in the methods section.

Results:

The purpose of this section is to present the answers to the research questions. Tables and figures are used for this purpose. Data presented in a table should not be visualized again in a figure and vice versa. The findings should be reported in this section but do not try to interpret the results here. Tables and figures should be self-explanatory and have clear titles. They should indicate all salient details necessary for a reader to understand the findings without referring to the text.

The results section should begin by giving the number of participants in the sample based on the calculated sample size, the number participated (response rate) followed by the participant characteristics. Then a logical sequence should be followed based on the tables/figures to answer the research question. Even nonsignificant associations should be presented. Only the salient findings from a table/ figure should be mentioned in the text.

Discussion:

The discussion is the heart of the manuscript and the most difficult section to write. Its purpose is to interpret and explain the significance of the results. All relevant results should be discussed, not only the significant findings. Restating the results in detail in the discussion is a common mistake made by authors. The discussion should begin with a brief overview of the main findings. Explanations for the findings should be provided next, followed by whether the findings of the study are consistent with published research on the subject. If different, the possible reasons should be given. It is important to indicate the strengths/limitations of the study in the discussion. The discussion should end with conclusions based on the major findings. Do not extend the conclusions beyond what is supported by the results which is a common error found in many papers submitted for peer review. Also, indicate policy/practice implications of the results and

recommendations for future work.

Writing the main body of the manuscript based on IMRAD has been discussed so far. However, a manuscript should also include the list of references cited, title, abstract, and acknowledgments where necessary. The two commonly used referencing styles in medical journals are the Harvard and Vancouver systems. Yet the style of referencing depends on the journal to which the paper is submitted and therefore, it is necessary to refer to author guidelines when preparing the reference list and citing references within the text.

The title is an advertisement for the article, and as it is read first, it should attract the attention of the reader. It should be specific, informative, concise, and accurately reflect the research. The study population and study setting should be included in the title. Avoid using terms such as 'a study of,' 'investigations into', 'observations on' in titles and also abbreviations and jargon. In my view, an author should have an idea of the title at the commencement of writing the manuscript, but it could be modified and revised later.

After the title, the abstract is the most often read part of a research paper. It should give a summary of the paper and be clear, concise, and stand on its own. Many journals now request a structured abstract with a specific word count and distinctly labeled sections; aims, methods, results, and conclusions. The abstract should be written last, after drafting the full paper, and always written in the past tense.

The first step in drafting a paper is to prepare the tables and figures that are relevant to answer the research question. Many recommend writing the results followed by methods, introduction, discussion, and finally the abstract.(7)

Plagiarism

An author should be mindful of plagiarism when drafting a manuscript. According to the Oxford English Dictionary, plagiarism is the "action or practice of taking someone else's work, ideas, writings, thoughts, and passing it off as one's own". It is intellectual theft and a serious crime. The following are the most common types of plagiarism seen in medical and dental literature: use of ideas/ thoughts of others in their entirety and presenting as one's own without giving credit to the original authors, copying a portion of text from another source, failing to put quotation marks around that direct quote and not giving credit to its author, changing a few words here and there but copying the sentence structure of a source without giving credit, and self-plagiarism which involves submission of the same paper to more than one journal or reusing parts of a previously written text while authoring a new paper. (8) There are several ways to avoid plagiarism; always cite the source, have quotation marks around direct quotes, paraphrase -rewrite the idea in the researcher's own words, without changing its meaning, and cite the original source and plagiarism software could be used to check one's work prior to submission.

Publishing research is not easy even for experienced researchers and manuscript rejection by editors and peer reviewers is common in academic writing. Rejection could be due to editorial and technical flaws in the manuscript. According to the editors of the Australian and New Zealand Journal of Public Health, around 600 manuscripts are submitted to their journal annually, and nearly 50% are not sent for peer review by the editors and of the reviewed manuscripts 80% are rejected. In an editorial titled "The seven deadly sins of rejected papers" they have described the seven reasons. They include i) a topic not relevant to the scope of the journal ii) overall lack of focus iii) methodological flaws iv) poorly structured results v) inappropriate or insufficient interpretation of results in the discussion vi) inadequate attention to study implications vii) weak scientific writing or presentation style.(9) If due attention is paid to the above factors when drafting a manuscript, it will increase the chance of being sent for peer-review by the editors and even accepted for publication.

Authorship

A researcher should also be concerned about authorship as it is a contentious issue in research ethics. Authorship is important because it gives credit and carries responsibility and accountability to the published work.(10) According to the International Committee of Medical Journal Editors (ICMJE) authorship should be based on four criteria (10):

1. Made substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work; AND
2. Drafting the work or revising it critically for important intellectual content; AND
3. Final approval of the version to be published; AND
4. Agree to be accountable for all aspects of the work so that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Further, ICMJE has stated that all designated authors should meet all four criteria for authorship, and those who do not meet all these criteria should only be acknowledged. It is noteworthy that many journals now have an authorship policy.(11)

In conclusion, drafting a good research paper is a tedious and demanding exercise. A good manuscript cannot be produced at the first attempt. It is necessary to edit and revise the draft several times before the final product. Remember editors and reviewers are human. The presence of spelling, language, referencing, and formatting errors could put them off. Therefore, check and recheck for such errors prior to submission. Refer to "Author Guidelines" to confirm that all requirements of the journal are addressed. It is important to decide on **one** journal and do not submit the same manuscript to multiple journals concurrently as it is an unethical practice.

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Prevalence of obstructive sleep apnea risk and quality of sleep in chronic liver cell disease patients admitted to a tertiary care centre

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Abstract

Introduction: Cirrhosis and associated complications result in significant morbidity and mortality. In the absence of a liver transplant, the prognosis, and the quality of life of decompensated cirrhosis patients are dismal. Hepatic encephalopathy, a complication of cirrhosis; defined as potentially reversible neuropsychiatric abnormalities seen in patients with liver dysfunction, has sleep disturbances as an integral part. But cirrhosis patients also suffer from various other sleep disorders including obstructive sleep apnea (OSA) which are independent of hepatic encephalopathy manifestations. But diagnosing OSA is challenging in this patient population. But when diagnosed early OSA can be treated successfully preventing further complications and improving the quality of life of cirrhotic patients.
Methods: A cross-sectional study was conducted among cirrhosis patients admitted to Colombo South Teaching Hospital using investigator administered questionnaires to assess the risk of OSA. Internationally validated STOP-Bang and Pittsburgh Sleep Quality Index (PSQI) were used to screen for OSA and sleep quality respectively.
Results: Out of 42 participants, two-thirds were males, and the mean age of the study population was 58 years. Most of the patients were in Child-Pugh class C (76.2%) Of the study population, 38.1% were having high STOP-Bang scores (>5) and were in the high-risk group for obstructive sleep apnea. The percentage of poor sleepers with PSQI scores of more than 5 was as high as 85.7%. Higher severity of cirrhosis was associated with high PSQI scores and high-risk STOPBANG scores. Having ascites conferred a high risk for OSA.
Conclusions: Higher severity of cirrhosis is associated with poorer sleep quality as well as increased risk for OSA.

Key words: chronic liver cell disease, OSA, sleep quality

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Introduction

The global burden of liver cirrhosis has increased due to population growth and ageing. The number of deaths due to cirrhosis has increased from 1.9% in 1990 to 2.4% in 2017.(1) There is a rise in disability-adjusted life years (DALYs) due to cirrhosis.(1) Even though definite data is lacking, the prevalence of Chronic Liver Cell Disease (CLCD) in Sri Lanka is likely to be on the rise, keeping up with the trend of almost all non-communicable diseases in the world. Usually in clinical practice, the diagnosis of CLCD is made with the appearance of one or more of its complications. Complications such as hepatic encephalopathy (HE), variceal bleeding, ascites and spontaneous bacterial peritonitis, and hepatocellular carcinoma are often present simultaneously making the management of CLCD challenging.

HE, which is defined as potentially reversible neuropsychiatric abnormalities seen in patients with liver dysfunction, has sleep disturbances as an integral part. It includes sleep-wake disturbances, insomnia, fragmented night time sleep and excessive daytime sleepiness.(2) In addition to these, recent studies have found that CLCD patients also suffer from Obstructive Sleep Apnea (OSA). OSA is one of the most common and increasingly diagnosed sleep disorders which can be successfully treated once diagnosed. The prevalence of OSA is found to be very high (48% to 81%) in CLCD patients compared to the general population.(3)

To our knowledge, until now studies regarding sleep disorders in CLCD patients were not published in Sri Lanka. Thus, the purpose of this study is to assess both the risk of OSA and the quality of sleep in chronic liver disease patients admitted to a tertiary care hospital in Sri Lanka.

Methods

This was conducted as a cross-sectional study at Colombo South teaching hospital over a period of 4 months between August 2019 and November 2019. The Institutional Ethical Review Committee approved this study.

Data collection was done by MBBS-qualified doctors using an investigator-administered questionnaire and additional data was extracted using patient records, clinic records and diagnosis cards. Subjects who did not consent or were unable to communicate with the investigators to an extent enabling them to fill the questionnaire and those having severe HE (Grade 4) were excluded from the study.

Internationally validated STOP-Bang and Pittsburgh Sleep Quality Index (PSQI) were used to screen for OSA and sleep quality respectively. WHO-approved standard measurement techniques were used when taking anthropometric measurements. STOP-Bang had been used in Sri Lankan populations to predict the risk of OSA successfully.(4) PSQI, Sinhala version was validated in Sri Lanka and had been used successfully in previous studies as well.(5) West Haven Criteria (WHC) was used to define the severity of the hepatic encephalopathy as assessed by the investigator.

Clinic records or hospital records were used to confirm the diagnosis of CLCD. A trained interviewer interviewed the patients who consented and completed the questionnaire.

The sample size was calculated using the Kelsey method with the confidence level set at 95%, and power fixed at 80% for a prevalence of 48% for sleep disorders in cirrhosis patients.(6)

The demographic factors, comorbidities, severity of CLCD in the study population and presence of sleep disorders including OSA and quality of sleep and their relationship to the severity of the CLCD were analysed using SPSS statistical package.

Results

A total of 42 participants were recruited during the study period of four months. Their age ranged from 24 to 75 years and the mean age was 58 years. The population consisted of twice the number of males compared to females (males n=28,66.7%).

The severity of CLCD in the study population was determined by Child-Pugh class. There were none in class A. Class B and C had 23.8%(n=10) and 76.2% (n=32) respectively.

Of the study population, 38.1% had high STOP-Bang scores (>5) and were at high risk for OSA while 85.7% turned out to be poor sleepers with high PSQI scores. Even though it was not statistically significant, a higher number of poor sleepers with PSQI scores of >5 were noted in the Child-Pugh class C compared to class B (Figure 1).

Out of all the complications associated with CLCD ascites showed statistical significance with a p-value of 0.01 between high and low-risk OSA groups (Table 3). None of the other complications or the severity of CLCD between the two groups were statistically significant.

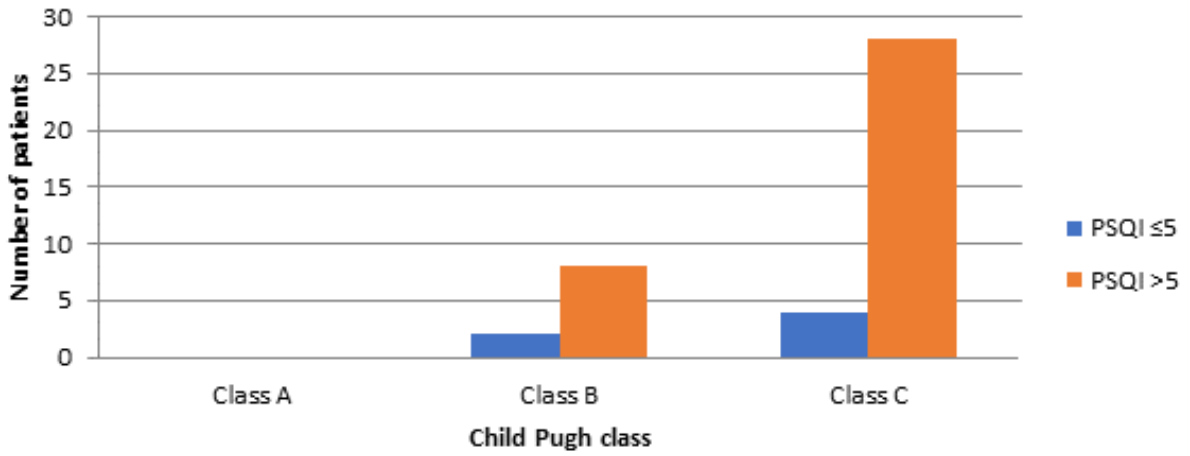

Figure 1 - Relationship between Child Pugh class and score

Fifty percent of the study population had type 2 diabetes mellitus (DM) and 30% had hypertension. These two comorbidities showed a statistically significant difference between high and low-risk groups of OSA (Table 1). In the study population, 28.6%,16.7% and 11.9% were suffering from ischemic heart disease, chronic obstructive pulmonary disease, and chronic kidney disease respectively.

West Haven Criteria for semi-quantitative grading of mental status; grades 0-4, assessed clinically, was used to determine the severity of HE. Grade 4 patients were excluded from the study due to communication difficulties. However, there was no statistically significant association between the severity of hepatic encephalopathy and the risk for OSA or poor-quality sleep in the current study (Table 2) despite HE being well-known to cause sleep disturbances in patients.

Discussion

In this study population, male to female ratio is 2:1, reflecting the possibility of males with CLCD secondary to alcohol abuse being overrepresented in the study population since in Sri Lanka female alcohol abuse is uncommon.(7) However, in Western countries as well as in Sri Lanka NAFLD is overtaking alcohol as the leading cause of cirrhosis (7–9), which can be true in our population as well considering the higher proportion of people suffering from DM and HTN as these are the commonest comorbidities associated with NAFLD.

A Sri Lankan study showed that 16.8% of the general population is at high risk for OSA.(10) In the current study, 38.1% are at high risk for OSA, implying more than twice a higher risk in the cirrhotic population compared to the general population. 85.7% of the study population suffered from poor sleep quality (PSQI score of > 5). However, between the severity of HE and poor-quality sleep, there was no statistical significance. A small sample size may have not detected the likely association as both covert and overt HE is known to be associated with sleep disturbances in other studies.(3,11) But the discrepancy between high risk for OSA and poor-quality sleep implies that OSA cannot be the sole reason for poor-quality sleep in CLCD but there may be various other disease-related factors affecting sleep quality. Similar findings were also seen in a study done in Saudi Arabia.(11) Furthermore, it has been shown that patients with cirrhosis have a high prevalence of other sleep disorders, mainly insomnia, and daytime sleepiness.(12)

Although it is not statistically significant, the study showed that the higher severity of CLCD was associated with poor quality of sleep and a high risk of OSA.(11) Similar findings have also been seen .in other studies.(9,11) Moreover, others are reporting a high prevalence of OSA and other sleep disorders in Child-Pugh class C compared to class A.(13,14)

There was a statistically significant association between ascites and the high risk for OSA. This may be because patients with ascites tend to have erroneously high body mass index (BMI) values due to the body weight increment secondary to water retention. BMI is used in calculating STOP-Bang which was used to predict high risk for OSA. Furthermore, ascites tends to reduce the effective lung volume giving the impression of shortness of breath which can lead to poor sleep quality.

Although it is not statistically significant, the study

Table 1 - Relationship of socio-demographic data, CLCD complications, Child-Pugh grade and comorbidities with STOP-Bang Score

Characteristics	STOP-Bang Score(low+intermediate)Total observations = 26n (%)	STOP-Bang ScoreHigh Total observations = 16n (%)	p-value**
Sex			
Male	19 (73.1)	9 (56.3)	.27
Female	7 (26.9)	7 (43.7)	
Presence of CLCD Complications*			
Ascites	26 (100.0)	12 (75.0)	.01
Varices	20 (76.9)	11 (68.8)	.57
Splenomegaly	20 (76.9)	11 (68.8)	.57
Upper GI bleeding	13 (50.0)	10 (62.5)	.44
Hepatorenal syndrome	6 (23.1)	1 (6.3)	.16
Spontaneous bacterial peritonitis	6 (23.1)	5 (31.3)	.57
Hepatocellular carcinoma	4 (15.4)	1 (6.3)	.39
PUGH Grade			
Class A	0 (0.0)	0 (0.0)	
Class B	8 (30.8)	2 (12.5)	.80
Class C	18 (69.2)	14 (87.5)	.86
Comorbidities			
T2DM	9 (42.9)	12 (57.1)	.01
Hypertension	4 (30.8)	9 (69.2)	.01
Ischemic heart disease	7 (58.3)	5 (41.7)	.76
Chronic obstructive pulmonary disease/Bronchial Asthma	5 (71.4)	2 (28.6)	.57
Chronic kidney disease	3 (60)	2 (40)	.93

*A patient may have one or more complications
**Correlation is significant at the 0.05 level

showed that the higher severity of CLCD was associated with poor quality of sleep and a high risk of OSA.(11) Similar findings have also been seen .in other studies.(9,11) Moreover, others are reporting a high prevalence of OSA and other sleep disorders in Child-Pugh class C compared to class A.(13,14)

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DM and hypertension were the most prevalent comorbidities in the study population. These conditions could be indirect contributing factors for CLCD due to associated non-alcoholic fatty liver disease which is the most prevalent cause for CLCD in Sri Lanka and worldwide.(7,9) Diabetes and hypertension are known to be independent risk factors for OSA as well.(15) In the current CLCD study population, a significantly higher prevalence of DM and hypertension is seen in the high-risk group for OSA. This observation further supports the fact that these two comorbidities are independent risk factors for the presence of OSA in the CLCD population. Furthermore, both diabetes and hypertension are part of the metabolic syndrome or syndrome 'X'. In metabolic syndrome the prevalence of OSA is high. (15) And since the underlying pathophysiology of both syndrome X and OSA are similar it is suggested that OSA should be ideally included in metabolic syndrome definition. Diabetes, hypertension, CLCD secondary to non-alcoholic fatty liver disease and OSA can be connected by the underlying aetiology of increased insulin resistance.(16)

Conclusion

CLCD patients have a high risk of OSA compared to the general population and poorer sleep quality. The high risk for OSA and the poor sleep quality are more prevalent in the severe CLCD category.

Recommendations

The establishment of the knowledge on sleep quality in CLCD patients may help in providing better nursing care for patients with cirrhosis in hospitals. It also paves the way for future studies for the improvement of sleep quality of CLCD patients and to address the OSA risk in CLCD to improve the quality of life in this patient cohort.

Limitations

STOP-Bang questionnaire is only a screening tool used to predict the risk of OSA. In the current study, it was the sole method of predicting OSA risk. It would have been more scientific if the presence of OSA was confirmed using sleep studies which were not freely available in the government health sector in the current setup.

Table 2 - Association between WHC grade and PSQI and STOP-Bang categories

Characteristics	WHC grade n (%)				Significance
Risk	0	1	2	3	
Low risk	5 (19.2)	9 (34.6)	9 (34.6)	3 (11.5)	X^2=.80 df=3 p=.85
High risk	2 (12.5)	6 (37.5)	7 (43.8)	1 (6.3)	
PSQI categories					
PSQI >5	7 (19.4)	12 (33.3)	13 (36.1)	4 (11.1)	X^2=.25 df=3 p=.48
PSQI ≤ 5	0 (0.0)	3 (50.0)	3 (50.0)	0 (0.0)	

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Authors' contribution
NSWP: Research planning, proposal writing, data analysis, manuscript writing, JI: Research planning, manuscript writing, TM: Research planning, manuscript writing, PP: Research planning, manuscript writing, SLW, BMACY, TABR: Data collection and data entering.

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Availability of data and materials
The data sets generated during current study are available from the corresponding author on request

Declarations

Ethics approval and consent to participate
Ethical approval for the current study was granted by the Institutional Ethical review committee of Colombo South Teaching Hospital Sri Lanka. Reference number for the study is 771 and ethical approval was granted on 22nd of May 2019. Informed written consent was obtained from the participants.

Consent for publication
Participants of the study were informed during the consent taking, regarding the possible future publications.

Competing interests
None

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Association of vitamin D levels with severity and outcome of COVID-19 infection among inward patients at a tertiary care unit in Sri Lanka

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Abstract

Introduction: A link between vitamin D and COVID-19 infection has been expressed by many experts. In this study, we aim to investigate the association of the prevalence of vitamin D deficiency with the severity and outcome of COVID-19 infection in patients who are admitted to Teaching Hospital Batticaloa, Sri Lanka.
Methods: A retrospective cross-sectional study was conducted among COVID-19 patients over a period of one month in May 2021. All patients who tested positive for COVID-19 were included. Patients with chronic kidney disease, known vitamin D deficiency, and patients on vitamin D supplements were excluded from the study. The vitamin D deficiency was defined according to the Oxford Academic Endocrine Society guidelines. The severity of the COVID-19 was defined according to the Provisional Clinical Practice Guidelines on COVID-19 suspected and confirmed patients. Primary endpoints of this study were 'recovered from COVID-19' or 'death'. Data was analysed to report the proportion of patients with different vitamin D levels and disease severity. Chi-squared and Fisher's exact tests were used to analyse the results. A p-value of <0.05 was considered as statistically significant.
Results: Out of 141, 58% were males. Mild, moderate, and severe COVID-19 were observed in 29.8%, 48.2%, and 22.0% of patients respectively. Only 30.5% of the population had normal vitamin D levels while the rest had some degree of vitamin D insufficiency. None of the patient population had severe vitamin D deficiency status. A 52.9% in the moderate category of COVID-19 severity had insufficient levels of vitamin D levels. Those that recovered from COVID-19 were 93.6%. No significant association was observed between the severity of COVID-19 and vitamin D deficiency (p=.1041). Interestingly hypoxia was significantly prevalent among those with normal vitamin D levels (p=.0005). vitamin D deficiency does not impact the mortality rate among COVID-19 patients (p=.6559).
Conclusions: The association of vitamin D levels with COVID-19 severity and mortality was not statistically significant.

Key words: COVID-19 severity, vitamin-D deficiency; COVID-19 mortality

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Introduction

The COVID-19 pandemic affected more than 100 million and caused nearly 3 million deaths globally.(1) COVID-19 is characterised by fever, fatigue, cough, shortness of breath, and loss of taste. It is associated with an inflammatory cytokine storm and immune dysregulation leading to life-threatening acute respiratory distress syndrome (ARDS). The COVID-19 ARDS mortality rate is more than 60%, and the major reason for mortality is respiratory failure.(2)

In the drive for potentially helpful pharmaceutical and nutraceutical therapies, studies have focused on the individual's intrinsic immune status, comorbidities, and nutritional status. Careful consideration of the pathological factors can help mitigate the cytokine storm and treat COVID-19 ARDS. vitamin D deficiency has been considered to be an important factor contributing to the severe manifestations and outcomes of COVID -19. It has been observed that vitamin D-deficient individuals have an increased COVID-19 risk and mortality.(3) vitamin D modulates both innate as well as adaptive immunity. It may potentially prevent or mitigate the complications associated with respiratory tract infections (RTIs) by inhibiting the production of pro-inflammatory cytokines and enhancing the production of anti-inflammatory cytokines. Only a few interventional studies have discovered the link between vitamin D and RTIs with conflicting evidence. There is a need for larger intervention trials.(4)

There are no studies that evaluate the association between vitamin D status and COVID-19 severity in Sri Lanka. In this study, we aim to investigate the association of vitamin D deficiency (VDD) with COVID-19 infection in patients who are admitted to teaching Hospital Batticaloa (THB), Sri Lanka.

Methods

A retrospective cross-sectional study was conducted among COVID-19 patients admitted to a tertiary care hospital during a period of one month in May 2021. All patients who tested positive for COVID-19 infection by rapid antigen test (RAT) or Polymerase chain reaction (PCR) were included. Patients with known chronic kidney disease (CKD) or vitamin D deficiency, or patients on vitamin D supplements were excluded from the study.

Sample size estimation: Sample size was calculated considering a prevalence rate of 50%. With a 10% margin of error, the minimum sample size was estimated to be 97.

Vitamin D deficiency was defined according to the Oxford Academic Endocrine Society guidelines as follows.(5)

- Normal: 30 – 100 ng/mL
- Insufficiency: 21-29 ng/mL
- Moderate deficiency: 11 – 20 ng/mL
- Severe deficiency: ≤ 10 ng/mL

The severity of the COVID-19 infection was defined according to the Provisional Clinical Practice Guidelines on COVID-19 suspected and confirmed patients in Sri Lanka (published in March 2020).(6)

Data were analysed using SPSS 24 statistical package. All the significant tests were performed at a 95% confidence interval. Chi-square and Fisher's exact tests were used to analyse the results.

Table 1 - Severity of COVID-19 infection

Parameter	Level of severity (one or more)		
	Mild	Moderate	Severe (Critical)
Respiratory Rate (RR/min)	12 - 20	21 – 30	≥ 31
Heart Rate (HR/min)	≤ 100	101 – 120	≥ 121
O_2 Saturation on room air (% by Pulse Oximeter)	≥ 94	90 – 93	≤ 89

Results

Total study population was 141. Among them, 58% (82) were males and 42% (59) were females. Mild, moderate, and severe COVID-19 were observed in 29.8% (42), 48.2% (68), and 22.0% (31) of patients respectively. vitamin D deficiency status is shown in table 2.

Table 2 - Vitamin D deficiency status

Vitamin D deficiency levels	Patient Population n (%)
Normal	43 (30.5)
Insufficiency	70 (49.6)
Moderate deficiency	28 (19.9)
Severe deficiency	0
Total	141(100)

Out of COVID-19 patients, 93.6% (132) recovered and 6.4% (9) died. The mean duration of hospital stay was nearly one month.

A higher proportion of female patients (32.2%) with COVID-19 infection had a moderate deficiency status of vitamin D compared to the male population (11%) (Figure 1).

Some degree of low vitamin D levels were found in 77.9% (53) and 51.6% (16) of moderately-severe and severe COVID-19 infection respectively. However, no significant association was found between the severity of COVID-19 and the status of vitamin D (p=0.1041). Hypoxia was found to be significantly more prevalent in patients with normal vitamin D levels (p=0.0005). vitamin D deficiency did not seem to have an impact on the mortality rate of COVID-19 patients (p=0.6599) (Table 3).

Discussion

Mild, moderate, and severe COVID-19 were observed in 29.8%, 48.2%, and 22.0% of patients respectively. In the study population, 30.5% had normal vitamin D levels while 69.5% had some degree of vitamin D insufficiency. The association between the severity of COVID-19 and vitamin D deficiency was not statistically significant.

Sri Lanka experienced a high number of COVID-19 cases during the period from 2020-2021. The limited vaccine coverage rate in the country has persuaded COVID-19 patients to switch to alternative products, including vitamin supplements that can enhance immunity.(7) Several studies conducted worldwide have shown heterogeneity in the results regarding the susceptibility to COVID-19 infection in vitamin D-deficient individuals.(8)

Studies based on the Sri Lankan population have reported vitamin D insufficiency in the range of 31.4%

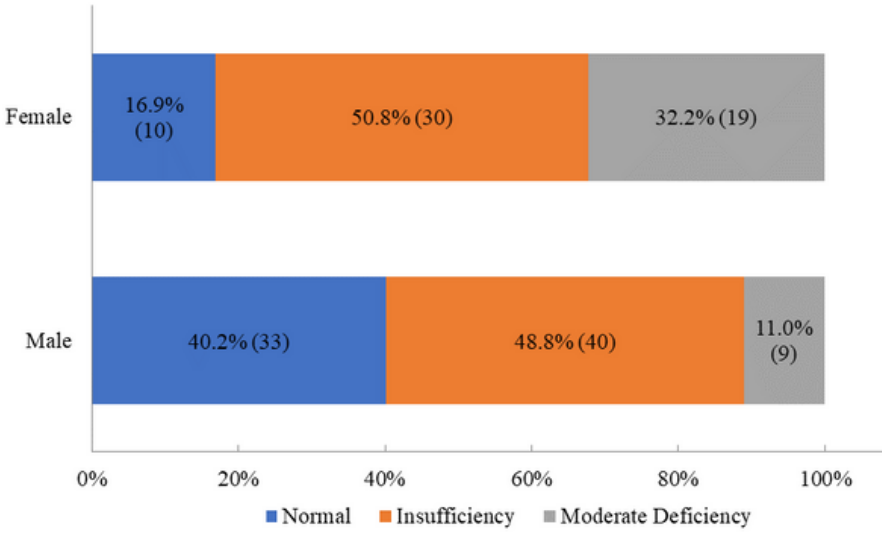

Figure 1 - Gender-wise distribution of vitamin D levels

Table 3 - Distribution of the study population based on vitamin D levels

		Status based on vitamin D levels			
		Normaln (%)	Insufficiency n(%)	Moderate Deficiency n(%)	p-value
The severity of COVID-19	Mild (n = 42)	13 (31.0)	22 (52.3)	7 (16.7)	0.1041
	Moderate (n = 68)	15 (22.1)	36 (52.9)	17 (25.0)	
	Severe (n = 31)	15 (48.4)	12 (38.7)	4 (12.9)	
Oxygen Concentration in room air	Normal (n = 120)	29 (24.2)	65 (54.1)	26 (21.7)	0.0005#
	Mild to severe hypoxia (n = 21)	14 (66.7)	5 (23.8)	2 (9.5)	
Outcome/Primary end points	Recovered (132)	39 (29.5)	66 (50.0)	27 (20.5)	0.6599
	Dead (9)	4 (44.4)	4 (44.4)	1 (11.1)	

The mild to severe hypoxia group was merged to have a non-zero value. This is to avoid having a 100% probability that is statistically deemed irrelevant and practically impossible to measure.

- 45.6% and vitamin D deficiency in the range of 13.2% - 58.8% among different age groups.(9,10) Several reasons have been postulated for high vitamin D deficiency levels, including lack of proper education, lower income, lack of milk in the diet, and insufficient outdoor activity.(9) Corresponding to the enormity of the vitamin D deficiency among the Sri Lankan population, we also observed that 70% of the study population with COVID-19 had insufficient or deficient vitamin D status. However, our study findings did not observe a significant association between the severity of COVID-19 and vitamin D deficiency which is in concordance with other studies. (11,12)

Although studies have associated the status of vitamin D insufficiency and deficiency with hypoxia (13), severity (14), and mortality of COVID-19 infection (15,16), a meta-analysis study after analysing 31 observational studies, found no correlation between the status of vitamin D and the severity of COVID-19. (17) Another meta-analysis conducted with 76 studies found no associations between vitamin D deficiency/insufficiency and mortality in COVID-19, when studies with a high risk of bias or studies reporting unadjusted effect estimates were excluded. (8) In concordance with the above meta-analyses, our study found no significant association between the status of vitamin D and the severity of COVID-19, and between the status of vitamin D and COVID-19 mortality. Although a significant association was found between the prevalence of hypoxia and the status of vitamin D levels, a significantly higher prevalence of hypoxia was observed in patients with normal vitamin D status as opposed to those with vitamin D insufficiency or deficiency. Vitamin D deficiency did not seem to have an impact on the mortality rate of COVID-19 patients. However, a recent study has suggested that vitamin D deficiency may be considered as a predictor of COVID-19 mortality rather than a side effect.(15)

Studies regarding the correlation between vitamin D and COVID-19 are scanty, and the status of the relationship still remains unclear and needs further studies.(18) Larger, population-size retrospective studies can be conducted using data previously collected during outbreaks to further explore the relation between COVID-19 severity and vitamin D.

Conclusion

Despite the high prevalence of low vitamin D levels (69.5%) among COVID-19 patients, we found no significant association between vitamin D deficiency and COVID-19 severity or outcome of COVID-19 infection.

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Knowledge and adherence to National Institute of Clinical Excellence 2020, dyslipidaemia management guidelines and its associations among medical officers in Gampaha district, Sri Lanka: a descriptive study

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Abstract

Introduction: Dyslipidaemia is an important risk factor for cardiovascular diseases(CVD) and optimal management helps prevent CVD burden in a country. Knowledge of medical officers(MOs) on dyslipidaemia management is critical in this regard. We assessed knowledge and adherence of MOs of Gampaha district to the National Institute of Clinical Excellence (NICE) guideline 2020 on management of dyslipidaemia.
Methods: We conducted a cross-sectional study at five secondary/tertiary-care hospitals in Gampaha District in January 2022. Knowledge and adherence were studied using a self-administered questionnaire consisting of 25 multiple-choice questions. Each question was scored "1" and the cumulative score was converted to 100. A score >80 was considered "good knowledge and adherence" and its associations were studied using logistic regression.
Results: A total of 413 MOs (63.4% females, mean age 45±7.6 years) participated in the study . Of them, 73.1% had worked in a medical ward previously. The mean knowledge and adherence score was 77±9.3. Only 30% had a score >80. Good knowledge and adherence was significantly associated with being <45 years(p .004) in age, having work experience in a medical ward(p<.001), having post-graduate training(p<.001), working in a tertiary care hospital(p=.007), and involved in private practice(p=.002). There was no significant association with attendance at continuing medical education programmes (p=.320) or the duration of service(p=.120).
Conclusions: Only a third of MOs of Gampaha district had good Knowledge and adherence to NICE-2020 dyslipidaemia guidelines. Knowledge and adherence to the guideline was better in MOs who are young, in postgraduate training, with previous experience in medical wards, working in tertiary care hospitals or engaged in private practice.

Key words: Statins, dyslipidaemia, cardiovascular disease, NICE guidelines, lipid-lowering medication

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Introduction

Dyslipidaemia is an important modifiable risk factor for atherosclerotic cardiovascular diseases (CVD) including coronary heart disease, stroke, and peripheral vascular disease. Reduction of LDL cholesterol by 1 mmol/L is associated with a 22% reduction of major adverse cardiovascular events.(1,2) Ischemic heart disease is the commonest cause of hospital deaths in Sri Lanka accounting for 22% (37 per 100,000 population) deaths in 2019.(3) Around 77% of Sri Lankan adults have some form of dyslipidaemia.(4) Therefore, control of dyslipidaemia is paramount in reducing the CVD burden of the country which will cut down healthcare costs.

There is an unmet need for the control of dyslipidaemia in the world. The underutilization of lipid-lowering therapies in general, and in particular the relatively low usage of high-intensity statins among patients with uncontrolled LDL-C is reported in the United States of America.(5) Lipid control among patients with previous CVD is reported to be low in the United Kingdom.(6) There is no data on the state of lipid goal achievement of Sri Lankans.

Dyslipidaemia management guidelines are frequently updated with different authorities worldwide releasing different guidelines but with minimal changes across guidelines.(6–8) The latest national dyslipidaemia guideline was released in 2023 (9) and the one before was in 2005.(10)

Dyslipidaemia is largely symptomless until they develop a CVD. Therefore, individuals with dyslipidaemia can present to any medical service, i.e.: primary, secondary, tertiary healthcare services in the state or private sector. Identifying them then and there and treating them would be helpful. Therefore, up-to-date knowledge in the diagnosis and management of dyslipidaemia among medical officers is important in both primary and secondary prevention of CVDs. The degree of knowledge and adherence to dyslipidaemia management guidelines among Sri Lankan medical officers is not reported. Moreover, it is reported that there is a high rate of non-adherence to clinical guidelines in developing countries.(11)

Therefore, we aimed to study the knowledge on dyslipidemia guidelines and adherence among medical officers in Gampaha, Sri Lanka.

Methods

We conducted a cross-sectional hospital-based study of doctors working in five state sector hospitals (secondary and tertiary care hospitals) of Gampaha District, Sri Lanka from 1st to 31st of January 2022. The study sites were Colombo North Teaching Hospital, Ragama, District General Hospital Gampaha, District General Hospital Negombo, Base Hospital Wathupitiwala, and Base Hospital Kiribathgoda. We studied the knowledge and adherence of medical officers to the 2020 dyslipidaemia management guideline of the National Institute for Health and Care Excellence, United Kingdom, which was the latest and most familiar guideline at the time the study was conducted.(8) All the medical officers working at medical wards, outpatient clinics, emergency rooms, and outpatient departments of the five hospitals during the study period were included in the study. Data was collected using a self-administered questionnaire distributed as a hard copy or soft copy depending on the preference of the medical officers. Ethical approval for the study was obtained from the Ethics Review Committee of the Faculty of Medicine, University of Kelaniya. Responding to the questionnaire was completely voluntary and was anonymised.

The questionnaire consisted of 3 sections with 25 close-ended questions checking the knowledge and adherence to basic principles in dyslipidaemia treatment, follow-up, and management of adverse drug reactions. Each question was scored “1” and the cumulative score was converted to a percentage. A score of more than 80% was considered as having “good knowledge and adherence” and the association of it was studied using binary logistic regression. We defined MOs with age < 45 years as being young as normally Sri Lankan doctors start internship training around the age of 27 years and retire around the age of 63 years. Data were analysed using SPSS version 22. The significance level was set at $p < \cdot 05$.

Results

A total of 413 medical officers, mean age 45 ± 7.6 years, female 262 (63.4%) participated in the study. The baseline characteristics of the study population are shown in Table 1.

We studied the knowledge and adherence to basic principles in dyslipidaemia management using the 2020 NICE guideline as a reference (Table 2).

Table 1 - Baseline characteristics of medical officers

	n (%)(n = 413)
Study site	
Colombo North Teaching Hospital, Ragama	157 (38.0)
District General Hospital Gampaha	76 (18.4)
District General Hospital Negombo	77 (18.6)
Base Hospital Kiribathgoda	51 (12.3)
Base Hospital Wathupitiwala	52 (12.6)
Mean age (SD), years	45 (7.6)
Gender	
Female	262 (63.4)
Mean duration in clinical practice as a medical officer (SD) year	18 (7.3)
Previous work experience in a medical ward present	302 (73.1)
Engagement in postgraduate training	232 (56.2)
Engagement in part time private practice	282 (68.3)
Participation in Continuous Medical Education during last 6 months	165 (40)

Table 2 - Knowledge and practices related to dyslipidaemia management according to 2020 NICE guideline

	Knowledge and adherence practices studied	Correct/yes (n = 413) n (%)
Knowledge on basic principles of the management of dyslipidaemia		
1	The LDL-C goal in primary prevention of CVD is <100 mg/dL.	318 (77.0)
2	The LDL-C goal in secondary prevention of CVD is <70 mg/dL.	339 (82.1)
3	Statin is the first-line medication for treatment of hypercholesterolemia.	412 (99.8)
4	Statin is the first-line medication for treatment of moderate hypertriglyceridemia.	387 (93.7)
5	The starting dose of atorvastatin for primary prevention of CVD is 20mg.	361 (87.4)
6	The starting dose of atorvastatin for secondary prevention of CVD is 40mg.	356 (86.2)
7	The starting dose of atorvastatin for secondary prevention of CVD in CKD patients is 20mg	399 (96.6)
8	The main reason to starting rosuvastatin instead of atorvastatin is intolerance for atorvastatin	339 (82.1)

Table 2 - Knowledge and practices related to dyslipidaemia management according to 2020 NICE guideline continued

9	Statins should be continued in the same dose following reaching treatment goals	322 (78.8)
10	Statin is not indicated if LDL-C <190 mg/dL inpatients with low CVD risk and without CVD/CVD equivalents	309 (74.8)
11	Statin is recommended in patients with high CVD risk even without LDL-C <190 mg/dL for primary prevention of CVD	398 (96.4)
12	The LDL-C goal in a patient with type II DM and CVD is <70 mg/dL	360 (87.2)
13	Statin prescription for primary prevention of CVD in patients with type 2 diabetes also depends on their calculated CVD risk	392 (94.9)
Clinical practices of medical officers in dyslipidaemia management		
14	Calculate 10-year CVD risk before prescribing statins	350 (84.7)
15	Advise on diet control and statin prescription together for control of dyslipidaemia	413 (100)
16	Advise on physical exercise and statin prescription together for control of dyslipidaemia	408 (98.8)
17	Repeat the lipid profile within 6 to 12 weeks after initiating statin therapy	411 (99.5)
18	Assess transaminase levels before initiating statins	408 (98.8)
19	Does not routinely assess CPK levels before initiating statins	313 (75.8)
20	Assess CPK only if patients are symptomatic	405 (98.1)
21	Routinely do a TSH in all with hyperlipidaemia	229 (55.4)
22	Use fibrates when statin monotherapy is unable to control triglycerides	371 (89.8)
23	Statins will be stopped if a patient present with vomiting, loss of appetite, and yellowish discoloration of the eyes	315 (76.3)
24	Statins will not be stopped in an asymptomatic patient with mildly raised CPK 4 times above upper limit of normal	321 (77.7)
25	Management of statin intolerance	
	Refer to a physician	251 (60.8)
	Give a lower dose of atorvastatin	108 (26.2)
	Give rosuvastatin	24 (5.8)
	Start fish oil	24 (5.8)
	Give fibrates	6 (1.5)

CKD; chronic kidney disease, CPK; creatinine phosphokinase, CVD; cardiovascular disease, DM; diabetes mellitus, IHD; ischemic heart disease, LDL-C low-density lipoprotein cholesterol, TSH; thyroid stimulating hormone

Table 3 - Factors associated with good knowledge and adherence to the 2020 NICE dyslipidaemia guidelines among medical officers in Gampaha, Sri Lanka

Variable study sample =413	Knowledge and adherence		p-value
	Poor(n = 289)	Good(n = 124)	
Age < 45 years	125	73	.004
Working in a tertiary care hospital	206	104	.007
Previous experience in a medical ward	178	124	<.001
Having or currently in a training for postgraduate qualifications	144	88	<.001
Involved in private practice	184	98	.002
Service years	-	-	.120
Gender (Female)	182	80	.766
Participation in continuous medical education programmes	120	45	.320

The median score for knowledge and adherence to the dyslipidaemia guideline was 80.00 (range 44 to 92 marks) and the mean score was 77 ± 9.3% (95% CI 76.10 - 77.89). Good knowledge and adherence to guidelines (i.e., > 80%) was seen in 124 (30%) medical officers.

Factors associated with good knowledge and adherence are shown in table 3. Good knowledge and adherence to the guideline was significantly associated with being less than 45 years in age, having work experience in a medical ward, having post-graduate training, working in a tertiary care hospital, and being involved in a private practice. There was no significant association between good knowledge and adherence to guidelines and attendance at continuing medical education programmes or the duration of service in years.

Discussion

We observed that the knowledge and adherence to NICE-2020 dyslipidaemia guidelines was inadequate and needs to be improved among medical officers of the Gampaha district. Additionally, we observed that the knowledge and adherence to the guideline was better among MOs of younger age, in postgraduate training, with experience in working in medical wards, at tertiary care hospitals or engaged in private practice. This is the first study reporting dyslipidaemia guideline knowledge and adherence of Sri Lankan medical officers. Good knowledge and adherence to current/latest management guidelines is important in achieving lipid control among Sri Lankans. This helps not only to improve dyslipidaemia control but also to avoid unnecessary treatment causing unnecessary cost, side-effects or pill burden reducing medication compliance.

One important possibility for inadequate knowledge and adherence could be not having regular updates in national guidelines in Sri Lanka. There had not been an update from 2005 to 2023. Clinical practice guidelines are designed to synthesise and disseminate the best available evidence to guide clinical practice. The goal is to increase high-quality care while decreasing inappropriate interventions. (12) Regular updates, circulars, posters with simplified palatable flow charts distributed by the Ministry of health would help to improve guideline knowledge and adherence among doctors. Other reasons for reduced adherence would be lack of knowledge, following different guidelines due to a lack of consensus of guidelines in the county, lack of passion and self-motivation to go for treatment goals or mere inertia of medical officers.

Good adherence among those having experience in working in medical wards, teaching hospitals and in postgraduate training is self-explanatory as they do

get exposed to new and changing knowledge as demonstrated by previous studies.(13,14) Giving all doctors the opportunity to work in a medical ward and encouraging them to enrol in postgraduate studies may increase knowledge and adherence to guidelines.

However, the fact that attendance at CME was not associated with good adherence was not expected. This brings up an important point that just doing CME programmes may not help improve adherence to dyslipidaemia or any guideline and we may need to think of changing the way the knowledge is delivered, probably may need to have workshops with some interaction than just hosting lectures. The other important point identified in the study is that the doctors who do private practice have good knowledge and adherence to guidelines. Maybe they were enthusiastic to learn and practise up-to-date medicine as it gives personal benefit to the medical officer as well. This suggests we need to promote the enthusiasm of doctors to update their knowledge. Introducing an appraisal system for all doctors may encourage them to attend and update their knowledge.

Despite doctors reporting to use dyslipidaemia guidelines and having updated knowledge, their adherence to guideline in clinical practice has shown to be low in literature (15,16) and this could be due to several reasons including rising healthcare costs, increased demand for care, variations in service delivery among providers, hospitals, and geographical regions and the intrinsic desire of healthcare professionals to offer, and of patients to receive, the best care possible.(17) These are some important aspects in the translation of knowledge into clinical practice.

Limitations

There are few limitations of this study. Our sample was from Gampaha district and did not cover hospitals lower than secondary care hospitals. Therefore, this study may not exactly depict the situation of all first contact doctors in the state sector of Sri Lanka. However, this gives an estimate, and we could expect a lesser degree of adherence when in primary care hospitals. Furthermore, there is a possible bias of not capturing data of doctors who were not interested in filling out the questionnaire since we used a voluntary self-administered questionnaire. We used the NICE 2020 guideline as our reference as there was no updated national guideline at the time the study was done after 2005. NICE 2020 guideline was specifically selected than the AHA 2018 or ESC 2019 guidelines as Sri Lankan healthcare system is mostly adhering to National Institute for Clinical Excellence (NICE) guidelines which consider cost-effectivity as well in recommendations which suits Sri Lanka being a low-middle-income country. However, doctors may not have been aware of this guideline unless they are very keen on the continuously changing guidelines, but we assessed the actual awareness of the doctors according to evidence-based practice at the time the study was done.

Conclusion

Knowledge and adherence to NICE-2020 dyslipidaemia guidelines was inadequate among MOs of the Gampaha district. However, the knowledge and adherence to guidelines was better in MOs who are young, in postgraduate training, with previous experience in medical wards, working in tertiary care hospitals or engaged in private practice.

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Authors' contribution
AnA, AkA, AE, SA, ShA and CM All authors contributed to the conceptualization and design of the study. AnA, AkA, AE, SA, and ShA contributed to the acquisition of data. KF conducted the data analysis. KF and CM contributed to data interpretation and writing the manuscript. All authors read and approved the final manuscript.

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Declarations

Ethics approval and consent to participate
Ethical approval for the current study was granted by the Ethics review committee of Faculty of Medicine, University of Kelaniya

Conflict of interest
None

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Ageing, gerontology; geriatrics and Sri Lanka

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"Ageing is not about decline, it's about growth, expansion, and development of the full human potential." - Ken Dychtwald

Ageing is a universal phenomenon. No living being is exempted from ageing. Studying ageing communities has been in existence since the beginning of the 19th century. It is a mystery why we have to age. There are various theories that explain ageing in different perspectives but the major views expressed are twofold. The first theory suggests wear and tear phenomenon, in which the building up of waste products that takes place over the years and failure to clear up and repair that eventually leads to gradual breakdown of the system that results in cellular ageing (Stochastic theories). The second view is, based on our genetic memory. It argues that our internal molecular clock is set to a particular timetable for each species. Support for this theory comes from animal studies where scientists have been able to cause an increased life span in some animals by altering just one gene.

Although there are many theories about how and why ageing occurs, as of now, there's no "cure" against ageing, and probably there will never be. Instead of struggling with getting older, we should endeavour to make the later years more enjoyable and productive. As stated by Daniel Francois Esprit Auber, a French composer, "growing old is the only way to lead a long life". As a country trying hard to qualify to be included in the "developed" category Sri Lanka needs to plan for policies that will sustain our demographic trend in a favourable economic and social environment. We have already achieved longevity and the path to happy healthy longevity remains an achievable goal with more focus and commitment from policy makers and health care professionals.

Sri Lanka is Ageing

According to statistics, Sri Lanka has a very fast ageing population and it is interesting to note that elderly population (Over the age of 60 years) in Sri Lanka in 2003 had a figure of 5.4% and in 2023 it has increased to 17%. It is estimated to be 27% in 2050. This rapid rise of the older population has direct implications on our existing health system and the socio-economic constitution of the country. A population with a longer lifespan is a success story of any health system in the world, yet it invariably translates into high dependency ratios, high disability figures and social poverty in a developing economy. Unless a country has planned well ahead of time to face this and celebrate this high longevity, the figures and statistics of older people in a community may not be a feature that can be celebrated for long.

Gerontology vs Geriatrics

For most Sri Lankans, Gerontology is not a familiar word. Even geriatrics became familiar to Sri Lankans very recently, after the formation of Sri Lankan

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Association of Geriatric Medicine in 2011 and the incorporation of Geriatric Medicine to the postgraduate curriculum in 2013 by the postgraduate Institution of Medicine Colombo. More Often than not, Geriatrics and Gerontology were used in the same context and many used to think of these two terms have the same meaning. In fact, it is not so. Geriatrics focuses on the health of the ageing body, and Gerontology is the science, or the study of physical, mental and social aspects of ageing. Geriatrics is actually a subset of Gerontology since Gerontology takes a broader perspective.

Gerontology was first attributed to Nobel Laureate, Elie Metchnikoff who first used it in 1903. Geriatrics was introduced in 1909, by Ignatz Leo Nascher, a New York City physician, to describe the medical care of elderly patients. At that time, the population of older adults was growing, and physicians began to recognize that older patients often had unique healthcare needs that required specialised knowledge and training. Over time, the field of Geriatrics developed as a distinct area of study, encompassing a wide range of topics related to ageing and the health of older adults.

Gerontology: How can it improve the Quality of life of our population?

Gerontology is essentially a multidisciplinary science that integrates several study areas. This specialty combines a staff working together that includes doctors, nurses, behavioural and social scientists, social workers, biologists, economists, psychologists, those who study the humanities and the arts, policy experts, and many other scholars and researchers. Gerontology includes investigation into changes in society that come from the ageing process, studying the mental, physical, and social changes of individuals as they age and the application of this knowledge to programmes and policies dealing with older communities.

As stated earlier the demographic profile of Sri Lanka is fast changing. Scrutiny into our economic stability, inflation rates, and per capita income projections shows that our poverty rates will not be declining for the next few decades. This will severely impact the socially deprived communities like older people especially most vulnerable groups like elders without social protection schemes or fixed pension-based income. As such, though our population dynamics show staggeringly high figures of older people the question is will they be disability free with the added years to life? Will they have good quality silver years or are we just adding years to their lives with more disability and poverty? Medical field in the country has recognized geriatrics as a medical specialty and few universities have included it in final year medical school curricula. However, apart from recognizing the diseases and disabilities of older age the country's responsiveness to sufficiently handle the demographic change is questionable.

Ageing does not start when one is at 60 years of age or 70 years of age .The current view is that it starts during the time of conception. As such the planning for old age on a personal basis as well as planning for its ageing population from a country perspective, has to be done fairly early. The modern-day life needs proper goal setting and planning to prevent wastage of money from a population point of view as well as to improve the quality of life from a personal standpoint.

Planning for an ageing population is important for any country to ensure that the needs of older adults are met, and they can age with dignity.

We need to develop policies that support healthy ageing. These can help older adults stay active, engaged, and independent. This can include initiatives to promote healthy lifestyles, provide access to healthcare, and ensure that older adults have access to community resources and services. It is true that we have a directorate in the Ministry of Health to cover the needs of older people. But the concept of Healthy Ageing needs much more robust country wide dissemination and in this regard media plays a major role.

From a country perspective, If we look at the lifestyle of an average middle aged Sri Lankan man or woman how many are overweight? How many suffer from diabetes, hypertension and other non-communicable diseases? The disease burden, hospital costs, medication costs and loss of work force power of caregivers all add to the already frail economy of the country in a dramatic manner. The focus on healthy ageing from a gerontological perspective is vital for the next few decades as we move forward with the exponentially expanding ageing population.

From an individual perspective, how many people think exercise is important for life and really engage in physical activity? How many people are prepared to plan for their old age at 30 years or 40 years of age? How many have a rough plan of how they are going to spend their life when they are 70 years and above? How many have income security at old age?

Old age does not happen overnight and hence early preparation and planning for stress free, poverty free, disability free old age is vital to a low-income country like Sri Lanka.

The answers to above questions need input from both health care providers and sociologists. In short, these issues need full focus if they are to make old age self-sufficient from health and economic perspectives.

Furthermore, due to the current economic crisis we do witness a large number of young people migrating looking for greener pastures. Though they do bring along foreign revenue to the country , the elderly parents are often neglected and are helpless and vulnerable due to economic insecurity , poverty and lack of caregivers. We are moving away from large families to nuclear families and family based social support is becoming a rarity.

As we boast of longevity in Sri Lanka we also need to invest in infrastructure: Infrastructure that supports older adults can include accessible transportation, age-friendly housing, and community facilities that support social and recreational activities. We also need more regularised caregiver training programmes apart from the few ad hoc ones we currently have. Thereby, we can get employment opportunities to the young while benefiting the older community. These investments can help older adults remain independent and connected to their communities.

Despite our economic constraints and poverty, we need to at least plan for provisions of financial security in old age. Many older adults rely on fixed incomes, such as social security or pensions, to meet their basic needs. Providing financial security through policies such as social security and retirement savings programmes can help ensure that older adults have the resources they need to live with dignity.

The other important issue is addressing ageism: Ageism, as described in the WHO refers to stereotypes (how we think), prejudice (how we feel) and discrimination (how we act) towards others or oneself based on age, can be a barrier to healthy ageing. Addressing ageism through education, awareness campaigns, and policies that promote age-friendly environments can help ensure that older adults are treated with respect and dignity. Certain measures are already taken to give priority to old people at government hospitals and some institutions. However, the concept is not fully functional and it is saddening to note that if we visit a government hospital, we can still witness many old and in fact very old people who come to obtain health services without a caregiver staying in long queues for long hours not being considered for any priority care.

Sri Lankan perspective- Collaboration between Geriatrics and Gerontology

Sri Lanka has now taken steps to include geriatrics in medical school curriculum and introduced the postgraduate training in geriatrics as a specialised field which is a very timely and wise approach. In a couple of years we would be having our first qualified Geriatricians in the country.

There are few Gerontology courses that are being conducted in Sri Lanka. The National Institute of Social Development offers a Diploma in Gerontology, a one-year programme that provides training in geriatric care for healthcare professionals and caregivers. Institute of Gerontology, University of Colombo, offers a range of short courses and workshops in geriatric care for healthcare professionals, including doctors, nurses, and caregivers. However, while there are around 8 medical faculties only the University of Sri Jayewardenepura conducts a post graduate master's programme in Gerontology. It would be appropriate for other Universities to start graduate and postgraduate programmes in Gerontology and link it with Geriatric postgraduate education so that these professionals can work efficiently and bring about a visible and tangible productive change to our ageing population.

1. Research collaborations: Geriatrics and Gerontology researchers can collaborate on studies that investigate the health and well-being of ageing communities. This can lead to a better understanding of the needs of ageing communities and inform the development of interventions and policies.
2. Community partnerships: Geriatrics and Gerontology professionals can partner with community organisations and groups to provide outreach, education, and support to ageing communities. This can include programmes and services that address social isolation, housing, transportation, and other issues that impact the well-being of ageing communities.
3. Advocacy and policy development: Geriatrics and Gerontology professionals can work in close liaison, to advocate for policies and programmes

that support the needs of ageing communities. This can include initiatives to improve healthcare access, affordability, and quality of care, as well as policies that address social determinants of health.

Collaborations between Geriatrics and Gerontology can lead to better outcomes for ageing communities by providing comprehensive and personalised care, advancing research and knowledge, and promoting advocacy and policy development for improved quality of life for the Silver age population in Sri Lanka.

Summary

Sri Lanka is experiencing a demographic shift towards an ageing population. As the population ages, the demand for specialised healthcare services for older adults is increasing.

In this country, there is a strong cultural tradition of caring for older adults within the family. However, as the demands of modern life increase, it can be challenging for families to provide the care that older adults need. While Geriatricians provide specialised care for older adults, Gerontologists can work with communities to develop care plans that support their cultural values and traditions. Sri Lanka has limited healthcare resources, and intersectoral collaboration of geriatrics and gerontology can help to optimise the use of these resources by providing specialised care for older adults that is tailored to their unique healthcare needs.

Geriatrics as well as Gerontology and their interdisciplinary collaboration is important for Sri Lanka because it can help to address the multifaceted healthcare needs and social needs of an ageing population. It will facilitate the provision of specialised care for older adults, optimise the use of limited healthcare resources, and provide disability free ,high quality of life while ensuring income security in the twilight days of life.

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Indian traditional diet may prevent COVID-19-related mortality: A narrative review

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Abstract

During the COVID-19 pandemic, the mortality rate in densely populated India was reportedly 5 to 8 times lower than in less populous western countries. An international team of scientists from India, Brazil, Jordan, Switzerland, and Saudi Arabia conducted the research suggesting that Indian dietary components suppress cytokine storm and other severity-related pathways of COVID-19 and may play a role in reducing the severity and mortality rates of COVID-19 in India compared to western populations. The findings indicated that the constituents of Indian diets, which ensure high iron and zinc concentrations in blood and ample fibre in foods, played a role in mitigating the severity of COVID-19 caused by carbon dioxide retention and lipopolysaccharide. This narrative review highlights various facets of Indian Traditional Diet which has helped in preventing COVID 19-related mortality.

Key words: COVID-19; diet, traditional; Indian; mortality

Introduction

In India and the South Asian subcontinent, COVID-19 mortality was lower than in the western world. Several explanations for this differential mortality related to COVID-19 were younger population, lower D allele frequencies compared to Europeans, difference in HLA gene variant, mutant strains of SARS CoV 2 virus, temperature variation and humidity, lockdown effect, BCG vaccination, delayed presentation of pandemic, HCQ use etc.(1) During the COVID-19 pandemic, the fatality rate in highly populated India was claimed to be 5-8 times lower than in less densely populated western nations.(2)

Dietary habits of Indians and low death rate from COVID-19

By causing cytokine storm-related pathways, intussusceptive angiogenesis, hypercapnia, and elevated blood glucose levels, high levels of sphingolipids, palmitic acid, and byproducts like carbon dioxide (CO_2) and lipopolysaccharide (LPS) that are linked to increased dietary intake of red meat, dairy products, and processed food items by Western populations could increase the severity and death rate. Palmitic acid is also known to raise the incidence of infection by inducing angiotensin converting enzyme-2 (ACE-2) expression. Coffee and alcohol, which are widely consumed in Western nations, may also worsen the severity and mortality rate of COVID-19 by deregulating blood iron, zinc, and lipid levels. On the contrary, the components of Indian diets keep blood iron and zinc levels high, and the substantial fibre content of their meals may help to reduce CO_2 and LPS-mediated COVID-19 severity. Indians who drink tea on a regular basis maintain high high-density lipoproteins (HDL) and low triglyceride levels in their blood because catechins in tea function as natural HMG-CoA reductase

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inhibitors. Importantly, Indians' constant use of turmeric in daily diet further maintains robust immunity, and curcumin in turmeric may inhibit pathways and processes related with SARS-CoV-2 infection and COVID-19 severity, as well as lessen the mortality rate.(2) Plant-based meals, pescatarian and Mediterranean diets, and limiting red and processed meat intake have all been demonstrated to decrease cholesterol (3) and the proclivity for moderate-to-severe COVID-19 disease.(4) It has been shown that meals (5) enriched with vitamins and zinc may lower the severity of COVID-19. Higher intake of a Western diet, on the other hand, was linked to increased COVID-19 risk and severity.(6) When comparing the nutritional value of half-cooked (or lightly cooked) food commonly consumed in the Western world with thoroughly cooked food typically found in traditional Indian cuisine, several factors come into play. The method and duration of cooking have a significant impact on the nutritional composition of food. For instance, heat-sensitive vitamins such as vitamin C and certain B vitamins may be lost during prolonged cooking. As a result, lightly cooked or raw vegetables often retain higher levels of these nutrients compared to thoroughly cooked ones. In the context of India, there is a growing trend of incorporating fresh fruits into the diet to enhance intake of essential vitamins and minerals, potentially mitigating the aforementioned concerns. Fresh fruits serve as a valuable source of vital nutrients, providing a natural means to address potential nutrient losses resulting from cooking methods. By consuming a diverse range of fresh fruits, individuals can obtain a spectrum of vitamins and minerals crucial for overall health and well-being. Incorporating these nutrient-rich fruits into the diet can contribute to a more balanced nutritional profile, potentially compensating for any potential nutrient loss due to cooking practices. However, it is important to note that cooking can also enhance the availability of certain nutrients. For example, cooking tomatoes increases the bioavailability of the antioxidant lycopene. Additionally, cooking can improve the digestibility of proteins in meat, rendering them more readily absorbable by the body. Thus, the nutritional impact of cooking is complex and dependent on various factors, including the specific food item and cooking technique employed.

In COVID-19, low serum iron and zinc levels are related to greater severity and fatality rates.(7,8) Zinc is employed in the treatment of COVID-19.(8) Dairy products contain less iron, while alcohol intake lowers plasma zinc levels. Notably, Idli (zinc 23.4 mg/g, iron 46.4 mg/g, 3-4% fibre) has more zinc and iron than meat (9), and its zinc concentration is double that of vitamin pills containing zinc, which were regularly ingested (10 mg) during the COVID-19 pandemic. Rice, lentils, wheat, chickpeas, and Rajma, which are staples in the north Indian diet (10), are also high in vitamins, minerals, zinc, and iron. As a result, unlike the Western diet, Indian cuisine can maintain high blood zinc and iron levels, which can reduce COVID-19 severity and fatality rates in India. (7,8)

As shown, reduced plasma HDL-C along with elevated triglyceride levels make COVID-19 outcome more severe.(11) Western countries' high alcohol consumption raises plasma triglyceride levels. Atorvastatin decreases COVID-19 severity, shortens hospitalisation, and lowers COVID-19 mortality.(12) Catechins found in tea are natural HMG CoA Reductase inhibitors. Catechin and Epigallocatechin-3-gallate (EGCG) present in tea inhibit interactions between SARS-CoV-2 Spike RBD and ACE-2, preventing SARSCoV infection. India is the world's greatest tea user, with more than 64% of Indians drinking tea.(13) Furthermore, curcumin, which is often taken in India, increases the permeability and lipid-lowering action of EGCG. Caffeine, on the other hand, diminishes statin action, lowers zinc levels, and inhibits iron absorption.(14) Coffee is the most common source of caffeine and is taken in high quantities per capita in Western nations, but consumption in India is low. Therefore, while coffee drinking contributes to COVID-19 severity in Western nations, increased tea consumption in India may be related with a less severe type of COVID-19 and lower fatality rates. Western cuisine with low zinc and high palmitic acid (PA) content stimulates pro-inflammatory PPAR signalling and accelerates SARS-CoV-2 pathogenesis by activating pro-inflammatory cytokines, chemokines, NF-B, and ACE-2.(15) Sphingolipids, which trigger the SphK1/S1P/S1PR (S1P) hyperinflammatory response pathway and enhance COVID-19 severity (16), are also abundant in Western meals. Research scientists discovered that PA and sphingolipids, two important metabolites in Western diets, were linked to COVID-19 severity pathways activation and higher death rates in Western nations.(7,17)

Hypercapnia and respiratory acidosis are caused by meat, fish, eggs, cheese, and alcohol.(18) Furthermore, diets heavy in animal fat and protein but low in fibre, are known to produce gut microbial dysbiosis, which results in increased CO_2 and hypercapnia, as well as LPS-induced elevated blood glucose levels.(19) COVID-19 severity is linked with

both hypercapnia and elevated blood glucose levels. (2,7,17) CO_2 RGs are substantially enriched in COVID-19 patients in Western nations but not in India. As a result, the western diet may be related with hypercapnia and elevated blood glucose levels, which may contribute to greater severity and fatality during COVID-19 in western cultures. Curcumin, the main ingredient in turmeric, is a preventive agent, and curcumin therapy (20) lowers the severity and mortality from COVID-19.(20) Curcumin increases serum zinc levels (21), inhibits the interaction between Spike RBD and ACE2, lowers cholesterol and triglyceride levels, and hinders hypercapnia, IFN, TNF, chemokine, cytokine, VEGFA-VEGFR2-mediated intussusceptive angiogenesis, and NOD-like receptor signalling pathways, which have all been associated with COVID-19 cytokine storm.(22) All of these pathways were shown to be selectively elevated in western samples but not in Indian samples. Curcumin was also shown to be inversely related to COVID-19 related complications. Curcumin is the active ingredient in turmeric, and turmeric is a popular spice/condiment in India (>2 g/day/capita), but not in Western nations.(2) As a result, everyday turmeric consumption in India maintains a high concentration of body curcumin, which inhibits practically all molecular processes. Mechanisms linked to SARS-CoV-2 infection and COVID-19 severity, result in a less severe illness outcome and lower mortality rates in India as compared to other Western countries.(2)

Finally, findings of Barh, Debmalya et al. revealed that Indian eating practices and food components may be related with lower severity and fatality associated with COVID-19 infections in India. While the western diet and food components appeared to contribute to the severity of COVID-19 disease, Indian dietary patterns and food ingredients may have a role in reducing COVID-19 disease severity. Regular intake of plant-based foods, Idli, whole cereals, legumes, vegetables, tea, and turmeric (curcumin) likely contributed to reduced severity and lower mortality rates from COVID-19 in India, despite the country's significantly higher population density.(2) However, further large-scale and intervention trials are needed to make solid conclusions in this area. A notable limitation of this narrative review is our inability to delve into the study results and clinical research evidence. Consequently, we were unable to present concrete findings to support our hypothesis. However, we hope to inspire future researchers to pursue clinical studies in order to investigate our proposed hypothesis.

Conclusion

Already around 3000 BC, the Sanskrit phrase from the Rig Veda, "Aham Annam" meant "we are what we eat." Professor Franz Halberg transformed the subject of nutrition by demonstrating that what we eat can make the difference between life and death in the laboratory and weight growth or loss in ordinary life.(23) COVID 19 pandemic had taught us the importance of traditional Indian diet and emphasizes the way of right eating in prevention of atrocities.

A few important take home messages:

1. During the COVID-19 pandemic, the mortality rate in densely populated India was reportedly 5 to 8 times lower than in less populous western countries.
2. An international team of scientists from India, Brazil, Jordan, Switzerland, and Saudi Arabia conducted the research suggesting that Indian dietary components suppress cytokine storm and other severity-related pathways of COVID-19 and may play a role in reducing the severity and mortality rates of COVID-19 in India compared to western populations.
3. The findings indicated that the components of Indian diets, which maintain high iron and zinc concentrations in blood and abundant fibre in foods, played a role in preventing COVID-19 severity mediated by CO_2 and LPS.
4. Regular tea consumption by Indians contributed to the maintenance of high HDL, also known as "good" cholesterol. Tea's catechins also acted as natural HMG CoA reductase Inhibitors in lowering triglyceride levels in the blood.
5. Regular consumption of turmeric in Indians' daily diet led to a robust immune system. According to the researchers, the curcumin in turmeric may have prevented pathways and mechanisms associated with SARS-CoV-2 infection and COVID-19 severity and reduced the mortality rate.
6. Conversely, increased consumption of red meat, dairy products, and processed foods led to an increase in COVID severity and mortality in western populations. Due to the high levels of sphingolipids, palmitic acid, and by-products such as CO_2 and LPS, these foods "activate cytokine storm-related pathways, intussusceptive angiogenesis, hypercapnia, and increase blood glucose levels," as stated in the study.
7. Palmitic acid is a saturated lipid that occurs naturally in some animal products, such as meat and dairy, and in palm oil. Furthermore, it raises infection rate and activates ACE2 expression.

8. By deregulating blood iron, zinc, and triglyceride levels, the high consumption of coffee and alcohol in western nations also contributed to an increase in COVID-19's severity and mortality rate.

Already around 3000 BC, the Sanskrit phrase from the Rig Veda, "Aham Annam" meant "we are what we eat." Professor Franz Halberg transformed the subject of nutrition by demonstrating that what we eat can make the difference between life and death in the laboratory and weight growth or loss in ordinary life.(23) COVID 19 pandemic had taught us the importance of traditional Indian diet and emphasizes the way of right eating in prevention of atrocities.

Authors' contribution

All authors contributed to the conceptualization and design of the study. SRJ, SSS, SM and SS contributed to the acquisition of data. SSS, SRJ, SM and SS contributed to literature search and writing the manuscript. All authors read and approved the final manuscript.

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Declarations

Conflicts of interest

None

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Novel therapies in clinical use for the management of hyperlipidaemia

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Abstract

Optimal control of low-density lipoprotein cholesterol (LDLc) is identified as a major target in reducing cardiovascular disease burden globally. However, existing lipid-lowering therapies have not been able to achieve LDLc targets even in developed countries. Therefore, novel therapies for the management of hyperlipidaemia are being trialled. Currently, there are three main groups of newer medicines; bempedoic acid, PCSK9 inhibitors and inclisiran, in addition to statins and ezetimibe in use for the management of hyperlipidaemia. This article aims to introduce these newer medicines and their clinical use in the treatment of hyperlipidaemia.

Key words: Novel therapies, hyperlipidaemia, LDL, bempedoic acid, PCSK9 inhibitors, inclisiran, siMRNA

Introduction

Controlling hypercholesterolaemia is a major target in the reduction of cardiovascular disease (CVD) burden in the world.(1-3) Statin was a landmark invention in this regard and has been the first line in the management of hyperlipidaemia since 1976.(4) Even though statins are able to reduce low-density lipoprotein cholesterol (LDLc) by more than 50%, there is still a huge unmet need for cholesterol control in the world attributed to statin intolerance, poor compliance, and tolerance to statin.(5-7) This led to the development of newer medications to assist statins in the control of LDLc.

Several newer medications are being trialled currently. There are three main groups of newer medicines in the current practice, especially in developed countries in addition to statins and ezetimibe which are already in use in most countries. This article is aimed to introduce the newer medicines and their clinical use in the treatment of hyperlipidaemia.

(1) Bempedoic acid

Bempedoic acid is an adenosine triphosphate citrate lyase inhibitor. It inhibits the cholesterol biosynthesis pathway in the liver as the statins but inhibits at a different step upstream of HMG-CoA reductase (Figure 1).(8) Unlike statins, bempedoic acid is a pro-drug which gets activated only in the liver and not muscles and hence is unlikely to give rise to muscle-related side effects of statins. Therefore, bempedoic acid is FDA approved in the USA as an adjunct to maximally tolerated statin therapy for the treatment of hyperlipidaemia and cardiovascular outcome and is especially indicated in patients with statin intolerance as a monotherapy or in combination with ezetimibe. Bempedoic acid was first licensed in 2016. It is recommended for both primary and secondary prevention of CVDs. It is reported to reduce LDLc up to 27% when used as monotherapy and by further 28% when combined with ezetimibe (9) and up to 18-24%.(10,11) Among statin intolerant patients, treatment with bempedoic acid was associated with a lower risk of major adverse cardiovascular events.(9)

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The main adverse effects of bempedoic acid is that it can predispose to gout attacks.(9) However, there are no serious drug interactions reported.

(2) PCSK9 inhibitors

These are serine proteases, mainly expressed in the liver, that target LDL-R. It leads the receptors to lysosome-mediated degradation, thus diminishing their recycling and decreasing the removal rate of circulating LDL particles in the liver.

Proprotein convertase subtilisin kexin type 9 (PCSK9) inhibitors are the first injectable medicines licensed for the treatment of hyperlipidaemia which came into the market in 2015. These are monoclonal antibodies against the PCSK9 protein. PCSK9 protein impairs LDLc scavenging by the liver by leading to lysosome-mediated degradation of LDL receptors and reducing LDL receptor recycling.(13) PCSK9 inhibitors bind PCSK9 protein and inhibit its binding with LDL receptors thus preventing LDL receptor degradation. This allows the liver to clear LDLc in the blood.

Evolocumab or alirocumab are two PCSK9 inhibitors used in practice. PCSK9 inhibitors have efficacy in reducing LDLc by 60% and are a valuable add-on therapy to statins.(14) It is recommended for subcutaneous, self-injection, twice a month and therefore is good to improve drug compliance. It has been shown to reduce the rate of major cardiovascular events and deaths by 15% over an average follow-up period of 2.2 years in clinical trials. (15-17) It is also shown that the higher the patients' risk –the higher the benefit they gain. Its adverse effects include flu-like symptoms with injections and nasopharyngitis. There was no increase in liver or muscle-related complaints nor clinically significant drug interactions. The main limitation of PCSK9 inhibitors is their high cost. Therefore, it is recommended mainly for secondary prevention of CVD in high-risk patients who have an LDLc of more than 130 mg/dL in 2023 National Institute for Health and Care Excellence (NICE) guidelines. (18) It has a limited recommendation to be used for primary prevention of CVD in patients with primary heterozygous-familial hypercholesterolaemia.

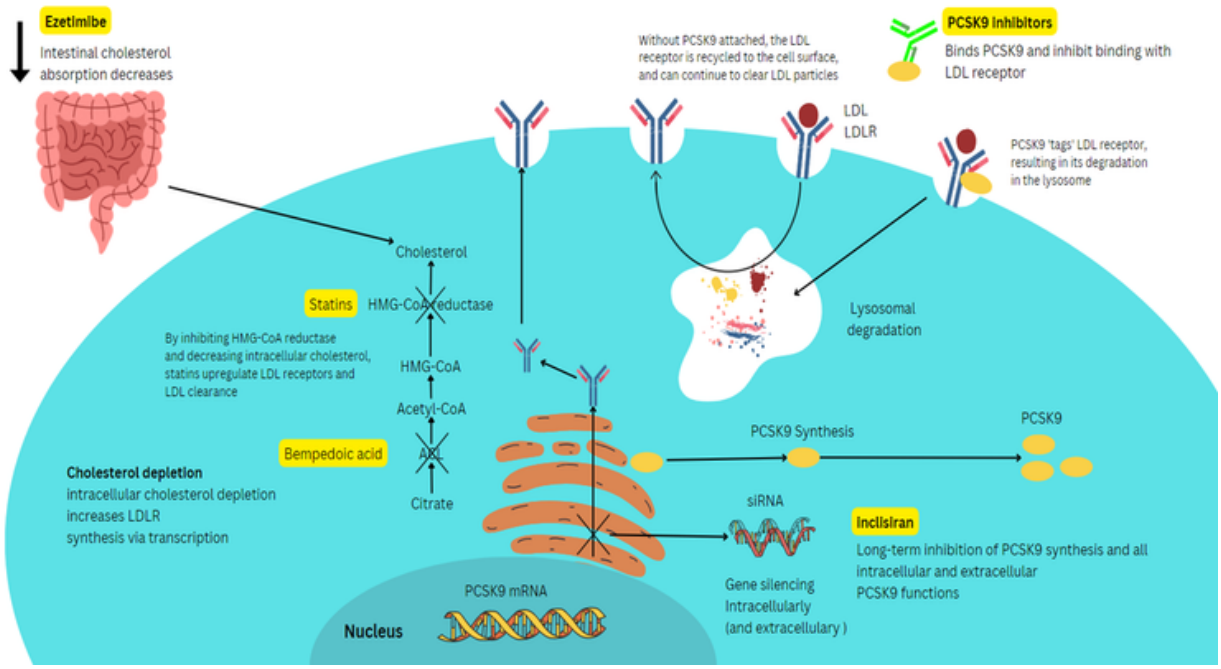

Figure 1 - Therapeutic approaches to reducing LDLc

Adapted from Nordestgaard BG et al. Nat Rev Cardiol. 2018 (12)

ACL – ATP-citrase lyase; CoA – coenzyme A; HMG – 3-hydroxy-3-methylglutaryl; LDL – low-density lipoprotein; LDLc – low-density lipoprotein cholesterol; LDLR – low-density lipoprotein receptor; mRNA – messenger ribonucleic acid; PCSK9 – proprotein convertase subtilisin/kexin type 9; siRNA – small interfering ribonucleic acid

(3) Inclisiran

Inclisiran works by stopping PCSK9 production by acting on the nucleus of liver cells by silencing the mRNA responsible for the PCSK9 protein production. It acts through small interfering RNA (siRNA) technology. This was first licensed in 2021 and is used as an add-on therapy for statins. Inclisiran reduces LDL cholesterol levels by 50% and has sustained efficacy for a long time therefore it needs to be given twice a year starting from 3 months after the 1st injection.(19) This is even better than PCSK9 inhibitors in terms of compliance. Since it is not involved in the Cytochrome P450 enzyme, it does not cause drug interactions. The main adverse drug reaction reported is a minor reaction at the injection site. It does not need dose reductions in the elderly, mild to moderate liver impairment or renal impairment.(20) Continuous production of PCSK9 protein at the same time statins reduce LDLc is thought to be the reason for statin tolerance. Since inclisiran blocks the final common pathway of PCSK protein production, it is effective in overcoming statin tolerance which is an added advantage of this drug. High cost is a limiting factor but is subsidised in the National Health Service, England considering its benefits to the patient. Therefore, it is recommended as an add-on therapy in both primary and secondary prevention of CVDs in patients with an LDLc >100 mg/dL despite being on statin.(18) However, there is no confirmed trial evidence on CVD outcomes of inclisiran which is being tested in the ORION4 trial conducted by the University of Oxford and the early results are expected at the end of 2024.

Conclusion

Statin remains the cornerstone in the management of hyperlipidaemia at present and the novel bempedoic acid, PCSK9 inhibitors and inclisiran are useful add-on therapies or alternatives in statin intolerance. There are some other newer medications currently being trialled in addition to the above, that are yet to come to clinical practice.

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Non-diabetic hypoglycaemia

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Abstract

Hypoglycaemia is diagnosed by the presence of symptoms of hypoglycaemia, documented low plasma glucose (often less than 50 mg/dL) at the time of symptoms, and recovery of symptoms by correction of glucose. If plasma glucose is normal at the time of symptoms, causes other than hypoglycaemia should be considered. If hypoglycaemia has been documented, the cause of hypoglycaemia should be investigated. Only after documentation of spontaneous endogenous insulin secretion causing hypoglycaemia should we proceed with localization of the tumor. Surgery will cure hypoglycaemia in about 90% of patients with insulinoma. Dumping syndrome can cause postprandial symptoms in people who have had upper gastrointestinal (GI) surgery (and rarely without surgery). The symptom complex in dumping syndrome includes the ones caused by GI stretching and GI hormones, or hypoglycaemia, or both. Dumping syndrome often needs to be managed by dietary interventions with or without pharmacotherapy.

Key words: hypoglycaemia, dumping syndrome, insulinoma

Introduction

Symptoms of hypoglycaemia can be classically divided into adrenergic and neurological (Table 1). In a person on anti-diabetic medications, clinical features or if in doubt, a glucometer or glucose sensor reading is sufficient for diagnosis and treatment of hypoglycaemia. However, in non-diabetic hypoglycaemia, capillary meter glucose or sensor interstitial glucose values are not sufficient to reach a diagnosis. In a person without diabetes (not known to be on diabetes medications) diagnosis of hypoglycaemia requires documentation of the Whipple's triad.(1)

History and physical examination

Precipitants

People who experience episodes of symptoms, often know what precipitates their symptoms. These may include:

Precipitants suggestive of hypoglycaemia as a cause of symptoms

- Fasting for longer periods of time (eg., delaying breakfast) is more likely to precipitate a symptomatic episode
- Physical activity
- Avoiding carbohydrates

Precipitants suggestive of hypoglycaemia and/or other causes of symptoms

- Postprandial symptoms (E.g., after Gastric Bypass, suggestive of dumping syndrome with or without hypoglycaemia). These are often associated with:
    - large meals
    - eating rapidly
    - eating refined carbohydrates
    - drinking with food (even water)
    - drinking fizzy drinks (carbonated drinks like Coca Cola, plain soda)
    - alcohol

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Precipitants not indicating hypoglycaemia as a cause of symptoms

- Postural symptoms caused by getting up too fast from lying or sitting posture (suggestive of postural hypotension as a cause of symptoms), including vasovagal episodes
- Changes in mood, stress level
- Changes in weather/temperature

Prevention and self-treatment of the episodes

Patients often already know how to prevent the symptomatic episodes. They may be avoiding the precipitants. They may be consuming sweets, sugar-containing drinks and bread to prevent the episodes from getting worse. Patients may get up past midnight to eat an extra meal to prevent early morning hypoglycaemia.

Dietary protein does not prevent or treat hypoglycaemia. Dietary fat delays the recovery from hypoglycaemia by delaying the motility and digestion of food and absorption of glucose.

Symptoms not relieved by fast acting carbohydrates (sugar or refined starch) but relieved by food containing predominantly protein and fat (e.g., meat, cheese, paneer, etc.) are likely not from hypoglycaemia. Symptoms relieved by consuming fast acting carbohydrates may be from hypoglycaemia. Usually, resolution of symptoms by consuming fast acting carbohydrates take about 10-15 minutes, though some symptoms may persist for the next hour or two. If symptoms take one hour or more to start improving, they are unlikely to be from hypoglycaemia.

Differential diagnoses of spells suspected to be hypoglycaemia

Cardiovascular, neurologic, gastrointestinal and endocrine causes of symptoms can be confused with the symptoms of hypoglycaemia. Plasma glucose documented at the time of a typical spell guides the diagnosis.

If hypoglycaemia is suspected in a nondiabetic person, venous blood should be drawn before treatment if it can be safely accomplished.(2) Blood should not be drawn if the symptoms are only minimal; or after attempted correction. Venous blood glucose levels are not comparable to finger-prick capillary (or sensor interstitial) glucose levels. During a spell with pallor, finger-prick capillary blood glucose (and interstitial glucose by continuous glucose monitor (CGM)) may be low while plasma glucose is normal.

If the blood is drawn during a typical and severe episode and the plasma glucose is > 60 mg/dL, irrespective of whether the patient feels better after consuming food or drink, it can be concluded that hypoglycaemia is not the cause of the symptoms. Therefore other possible causes are entertained.

The diagnosis of hypoglycaemia is made with the confirmation of the Whipple's Triad; with typical symptoms, documented low plasma glucose (≤60 mg/dL, esp. if ≤50 mg/dL) and the improvement of symptoms and plasma glucose on taking carbohydrates.

Table 1 - Symptoms and signs of hypoglycaemia

Adrenergic	Neurological
Shakiness Trembling Anxiety Nervousness Palpitations, tachycardia Clamminess/ Sweating Dry mouth Hunger Pallor Pupil dilation	Irritability Paresthesia Headaches Difficulty in thinking/ speaking Confusion, abnormal mentation Slurred speech Diplopia Ataxia Seizures Stupor/ Coma

Differential Diagnoses of hypoglycaemia

After a documented Whipple's Triad the cause of hypoglycaemia is investigated.(2)

hypoglycaemia in a sick person

hypoglycaemia in a hospitalized sick person is often caused by medications and comorbidities. Many medications have been associated with hypoglycaemia, especially with comorbidities (Table 2). Specific diseases have been associated with hypoglycaemia, especially with certain specific medications (Table 3).

hypoglycaemia *in an otherwise healthy person*

If Whipple's triad is documented in an otherwise healthy person, further investigations are required; serum beta-hydroxybutyrate, plasma insulin, plasma C-peptide, plasma Proinsulin, and hypoglycaemia agent screen. These are performed on the same blood sample drawn during the symptomatic hypoglycemic episode. If possible, plasma glucose response to injection of glucagon (plasma glucose level at the baseline, 10, 20 and 30 minutes after glucagon) is documented (Figure 1).

Table 2- Medications (other than diabetes medications) associated with

Medications known to cause hypoglycaemia
• Pentamidine, especially if used systemically
• Trimethoprim–sulfamethoxazole- in the presence of renal failure
• Propoxyphene (dextropropoxyphene) - in the presence of renal failure
• Quinine
• Quinidine
• Salicylates- in the presence of renal failure

In the presence of hypoglycaemia (symptoms with a plasma glucose <60 mg/dL) if beta-hydroxybutyrate is elevated, and plasma glucose response to glucagon is poor (<25 mg/dL) hypoglycaemia is not being caused by insulin-like action. The causes include normal prolonged fasting, glycogen storage disorders (usually these people present during their childhood) and hypothalamic, pituitary and/ or adrenal insufficiency (Table 3).

If beta-hydroxybutyrate is suppressed and plasma glucose response to glucagon is robust (≥25 mg/dL) it implies insulin-like action causing hypoglycaemia. In such a situation, if plasma insulin is suppressed, the insulin-like action is not due to insulin. Possible causes include injection of insulin analogues and tumor derived Insulin like Growth Factor-2 (IGF-2).

If there is insulin-action and non-suppressed insulin, in the presence of suppressed C-peptide and proinsulin, it is implied that hypoglycaemia is not due
to endogenously secreted insulin; but due to insulin being injected.

Table 3 - Medical conditions associated with

• Severe prolonged malnutrition
• End-stage liver disease (ESLD, esp. with ESRD, or with certain medications)
• End-stage kidney disease (ESRD, esp. with ESLD, or with certain medications)
• Panhypopituitarism (esp. if severe and involving Growth hormone and ACTH deficiency)
• Addison disease (esp. severe, or in Addisonian crisis)
• Septicaemia
• After stopping parenteral nutrition (esp. after overnight total parenteral nutrition)
• After stopping continuous enteral nutrition (esp. after overnight enteral feeding)

If there is insulin-action, non-suppressed insulin, elevated levels of C-peptide and proinsulin, it indicates that endogenously secreted insulin is causing hypoglycaemia. hypoglycaemia agents (sulfonylureas or meglitinides) are therefore measured from that sample.

If hypoglycaemia is being caused by endogenously secreted insulin and hypoglycaemia agents screen is negative, spontaneous endogenous hyperinsulinemic hypoglycaemia is diagnosed and the source of insulin from the pancreas should be localized. The least invasive method; ultrasound or CT of the pancreas is used first. Then more invasive methods such as endoscopic ultrasound and gallium Ga 68-DOTATATE PET scan are used. Finally the most invasive method; selective pancreatic arterial calcium stimulation test may be used.(3)

Postprandial Symptoms

Postprandial hypoglycaemia can be seen in about 25% of people with insulinoma. Postprandial symptoms are exclusively seen only in about 5%. Most people who experience postprandial episodic symptoms 0.5 to 3 hours after eating do not have insulinomas. These symptoms may also include some that are not characteristic of hypoglycaemia, called dumping syndrome.

Abnormal distension of small intestine and release of vasoactive agents: neurotensin, vasoactive intestinal

peptide (VIP), cholecystokinin, glucagon, incretins; glucose-dependent insulinotropic polypeptide, gastric inhibitory polypeptide (GIP), glucagon like peptide-1 (GLP-1) are thought to be responsible for the postprandial symptoms of dumping syndrome, often called gastrointestinal dumping. Rapid transit of food to the small intestine (pyloric sphincter incompetence, post gastric bypass surgery) can be associated with postprandial hyperglycemia followed by excessive insulin secretion causing hypoglycaemia. Normal postprandial insulin secretion is followed by ongoing delivery of food to the intestine by gastric emptying over the next 1-3 hours. However, in the presence of incompetent or absent pylorus there is no gradual delivery of food to the intestine. Therefore, excessive insulin secretion along with inadequate ongoing supply of carbohydrates from the meal lead to postprandial hypoglycaemia. This endocrine dumping is often precipitated by food containing easily digestible carbohydrates (esp. without protein), often with symptoms of gastrointestinal dumping.(4)

Therefore, the symptoms associated with the episodes of postprandial symptoms especially after Gastric Bypass surgery are multifactorial in origin and are derived from abnormal vasoactive hormones, gastrointestinal motility and glycemic excursion.

Postprandial symptoms (including postprandial hypoglycaemia) are typical and "normal" in a person who has dumping syndrome (eg., after gastric bypass) if a person consumes fast-acting carbohydrates (eg., sugar, glucose, etc.). Oral glucose tolerance test has no role in diagnosis or differential diagnoses of hypoglycaemia.

Treatment of hypoglycaemia

Prevention and Treatment of Hypoglycemic Episodes

Patients usually know how to prevent the onset, blunt the progression or reverse the symptoms of the hypoglycemic episodes. Patients should be directed to use rapid-acting carbohydrates (usually 15-20 g of the usual sugar, glucose, sugar containing drinks, juice, candy, sweets, etc.). Sometimes, treatment of the hypoglycemic episode with rapid acting carbohydrates needs to be followed by complex carbohydrates (bread, lentils, beans, rice, sandwich etc.) to prevent recurrence of hypoglycemic episodes over the next few hours.(5)

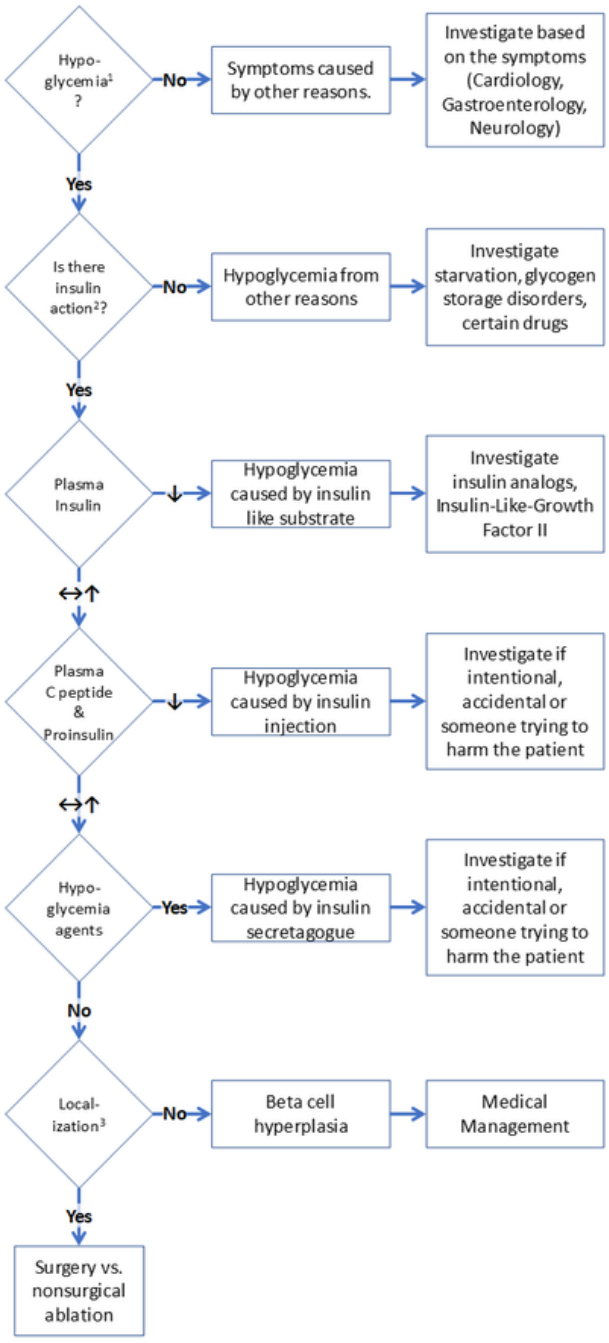

Figure 1 - Investigative strategy in a person suspected to have hypoglycaemia.

[1]Whipple's Triad
[2]Suppressed beta hydroxybutyrate and a robust (delta >25 mg/dL) response to injection glucagon
[3]CT abdomen, Endoscopic Ultrasound, Dotatate PET scan, Selective Pancreatic Arterial Calcium Stimulation Test

↔↑: nonsuppressed or high; ↓: suppressed

Dietary protein and fat are not useful to prevent nor to treat hypoglycemic episodes.(6)

Treatment of the cause of hypoglycaemia

Insulinoma

Insulinoma is usually surgically treated. The type and extent of surgery depends on the malignant potential, size and location of the tumor in the pancreas, relationship to the pancreatic ducts and blood vessels, and patient's surgical risk. Other options for treatment include alcohol injection to the tumor (if safe), diazoxide (with some serious adverse effects), and somatostatin.(7)

Surgical treatment of benign insulinoma has a success rate of about 90%. About 10% have recurrence of the index tumor or another tumor.(8)

Management of malignant insulinoma requires surgical removal or debulking of the primary and metastatic disease followed by chemotherapy (including biological agents and inhibitors of mammalian target of rapamycin (mTOR) like everolimus), and resection of the metastatic disease. (9)

Postprandial symptoms

Avoidance of precipitants will reduce the frequency and severity of the episodes. Other measures include: agents that increase meal viscosity (guar gum, pectin), prevention of digestion of carbohydrates using acarbose or miglitol with meals (usually not well-tolerated), prevention of the release of hormones: vasoactive gastrointestinal hormones and insulin, using fast-acting somatostatin or insulin release alone using diazoxide (with significant adverse effects).

Conclusions

Diagnosis of hypoglycaemia should precede determination of the cause. Localization of insulinoma should be sought after a diagnosis of spontaneous endogenous hyperinsulinemic hypoglycaemia. In the absence of insulinoma there is no surgical cure for episodic symptoms from hypoglycaemia or from other causes.

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(1) Picture A and B are from a 35-year-old man. Picture A depicts his initial presentation while B is taken following a bedside test to arrive at a diagnosis.

What is the bedside test that has been performed?

(A) Edrophonium test
(B) Electromyography (EMG)
(C) Fatigability test
(D) Ice pack test

(2) This 42-year-old woman presented with three episodes of generalised tonic clonic seizures within a week. MRI of the brain showed a giant cell Astrocytoma. (See Picture C)

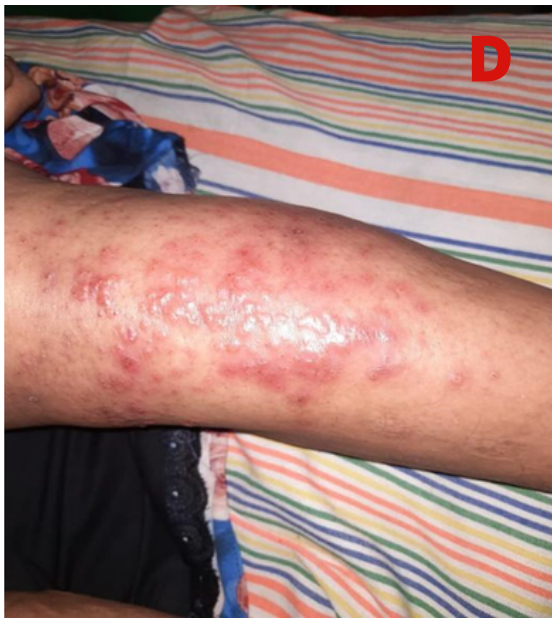
What is the possible diagnosis?

(A) Rosacea
(B) Sturge-Weber syndrome
(C) Systemic lupus erythematosus
(D) Tuberous sclerosis

(3) A 52-year-old woman presented with dysphagia for 6 months and a long standing history of itchy lesions (Picture D). In addition she had monoclonal gammopathy.

What is the diagnosis?

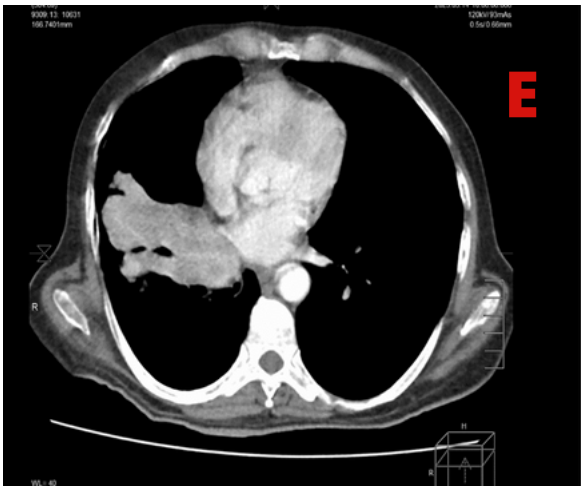
(A) Carcinoma of the oesophagus
(B) Scleromyxedema
(C) Plummer-Vinson syndrome
(D) Polymyositis

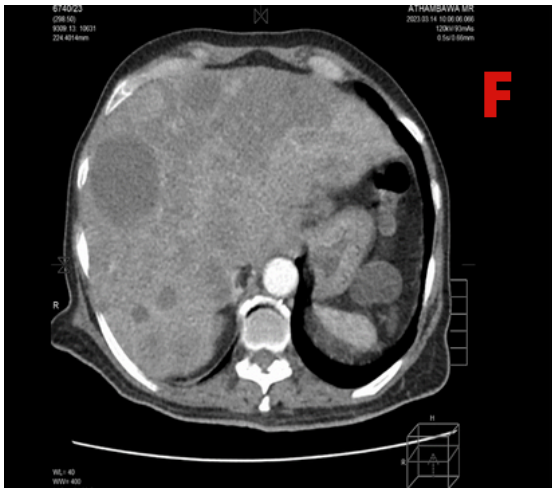


(4) Picture E and F are from the same patient with loss of appetite and weight loss.

What is the underlying diagnosis?

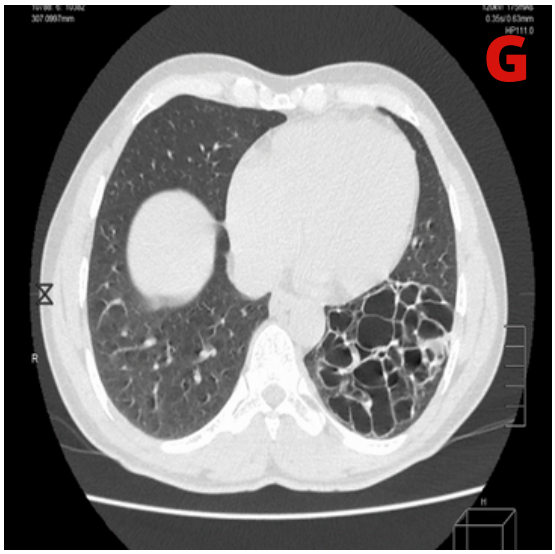
(A) Lung and multiple liver abscesses
(B) Melioidosis
(C) Bronchial carcinoma with multiple hepatic metastasis
(D) Right sided infective endocarditis





(5) This 68-year-old man presents with fever and cough with greenish sputum for 2 weeks. His HRCT is shown below (Picture G)

What is the diagnosis?



(A) Bronchiectasis with superadded infection
(B) Cystic lung carcinoma
(C) Lymphangioleiomyomatosis
(D) Pulmonary alveolar proteinosis

N.B.: The above photographs were published with consent from the respective patients.
*Refer the PICTURE QUIZ-KEY on page 89 for answers and explanations.

Multisystemic chronic sarcoidosis: unmasking of a true masquerader

Tasnim R[1], Nahar A[2], Islam QT[3]*

Abstract

Sarcoidosis is a diverse disorder that can potentially affect almost every organ system, and mimics a wide-range of diseases. Here, we present a case of multisystemic chronic sarcoidosis affecting lung parenchyma, intrathoracic and extrathoracic lymph nodes and skin. The organ specific clinical manifestations developed over a course of time that did imitate different diseases at different times. Only after the full-blown disease, symptoms and investigations could be placed altogether as sarcoidosis.

Key words: Sarcoidosis, multisystem, cutaneous sarcoid, lupus pernio, hypovitaminosis D, tuberculosis

Introduction

In 1877, sarcoidosis was first reported by Jonathan Hutchinson in London but Caesar Boeck is credited as being the first to use the term sarkoid (sarcoid).(1) Sarcoidosis could affect all ages, with a peak incidence among those between the ages of 20 to 39 years, and nearly two-third of cases are in women. Also, it is more common in non-smokers and rural inhabitants.(1,2) According to studies, a complex interaction of host immunologic, genetics and environmental variables is responsible for the pathogenesis of sarcoidosis.(3)

More than 90% of patients manifest pulmonary and intra-thoracic lymph node involvement. In extra-pulmonary cases, the most involved organ is skin (49.3%) followed by eyes (23.6%), liver (20.7%), extra-thoracic lymph-nodes (13.7%), parotid/salivary glands (5.7%) and bone/joints (1.4%) .(4) Three main criteria need to be fulfilled for the diagnosis of sarcoidosis : a consistent clinical picture; the presence of non-caseating granuloma in more than one organ, and the elimination of other possible causes of granulomatous illness.(5) If symptoms involve at least two organ systems it is termed as systemic sarcoidosis.(4) The diagnosis of sarcoidosis essentially depends on the clinician's assessment. The differentials are crucial to rule-out, as misdiagnosis and inappropriate treatment may cause deleterious health effects.

Case presentation

A 35-year-old woman initially presented with the complaints of chest discomfort, shortness of breath, occasional productive cough and generalized weakness, not associated with any fever or weight loss. On examination her vitals were stable with saturation of peripheral oxygen (SpO2) 99% in room air. Bilateral axillary and epitrochlear lymphadenopathy were noted. Investigations showed full blood count within normal limits, erythrocyte sedimentation rate (ESR) 27mm per first hour. Chest radiography revealed bilateral hilar and right paratracheal lymphadenopathy [Figure-1A]. High resolution computed tomography (HRCT) of the chest revealed extensive mediastinal and axillary lymphadenopathy and reticulonodular shadows affecting the whole of both lung fields [Figure-1B].

Electrocardiography, echocardiography,

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ultrasonography of the whole abdomen, serum lactate dehydrogenase, liver and renal function tests and other routine blood tests were within normal limits. Mantoux test was 3 mm in 72 hours. Three samples of sputum for acid-fast bacilli were negative. Sputum for Gene-Xpert didn't detect any Mycobacterium tuberculosis. Fine needle aspiration from the right epitrochlear lymph node was done initially, and cytology was suggestive of granulomatous inflammation (small clusters of epithelioid cells on the background of lymphocytes, fatty tissue fragments, necrotic material and blood). She had been started on a therapeutic trial of anti-tubercular therapy (ATT) due to the endemicity of tuberculosis in Bangladesh.

She didn't have any symptomatic benefit or radiological improvement on her regular follow up visits. Moreover in the 5th month of her illness while on ATT, she developed multiple itchy erythematous papules and plaques involving her back and upper limbs, sparing the palm and sole. Over her left ala of nose there was another single erythematous infiltrative shiny papule with telangiectasia, suggestive of lupus pernio [Figure-2]. She also complained of generalized myalgia, but no specific joint pain.

Repeat HRCT chest was consistent with the previous report but with more progressive features [Figure-3].

She manifested restrictive lung function on spirometry. [Figure-4].

Biopsy from the skin lesion unveiled multiple small discrete non-caseating granulomas made of epithelioid cells over the dermis, consistent with the histopathologic picture of sarcoidosis.
She was eventually diagnosed to have "**Multisystemic Chronic Sarcoidosis (Pulmonary Stage II, Lymph nodes and Skin) with Severe Hypovitaminosis D**". We had stopped her ATT, and started her on oral prednisolone at a dose of 1mg/kg/day with oral Vitamin D supplement. She showed impressive recovery over next 4 months in terms of symptomatic wellbeing, reduced serum ACE (Angiotensin converting enzyme) level (48 U/L) indicating reduced granuloma burden, healed cutaneous lesions [Figure-5] and resolving radiological shadows [Figure-6].

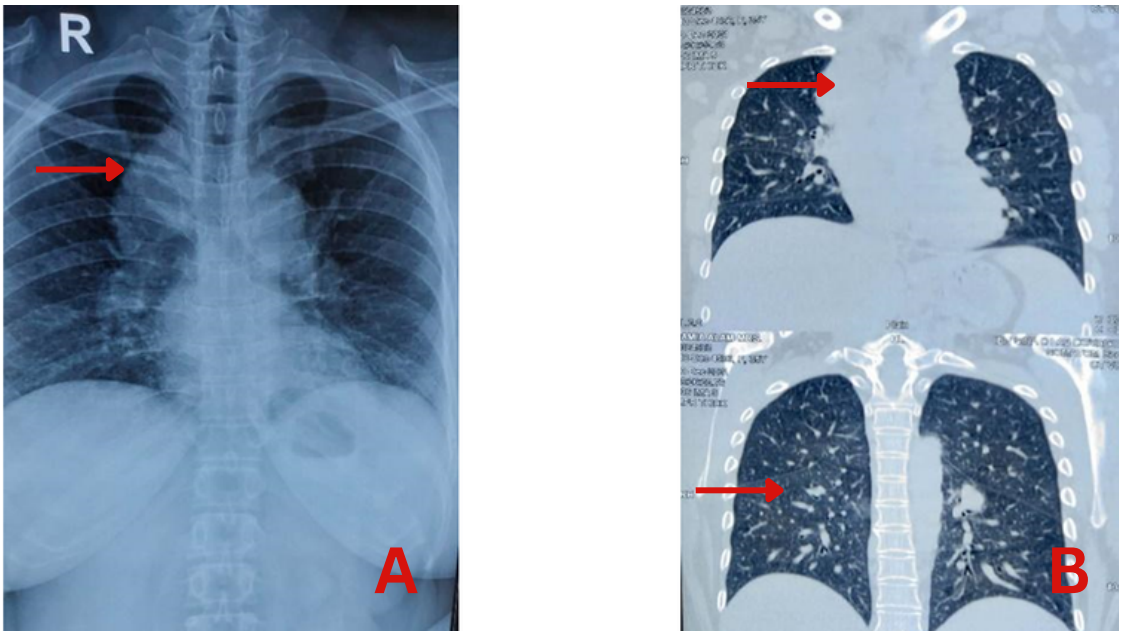

Figure 1 - Initial imaging:

A: Chest radiograph (P/A view): Bilateral hilar and right paratracheal lymphadenopathy.
B: HRCT chest: Extensive mediastinal (pre, para tracheal, aorto-pulmonary window, azygo-esophageal recess, pre and subcarinal regions) lymphadenopathy. Reticulonodular shadows affecting the whole of both lung fields.

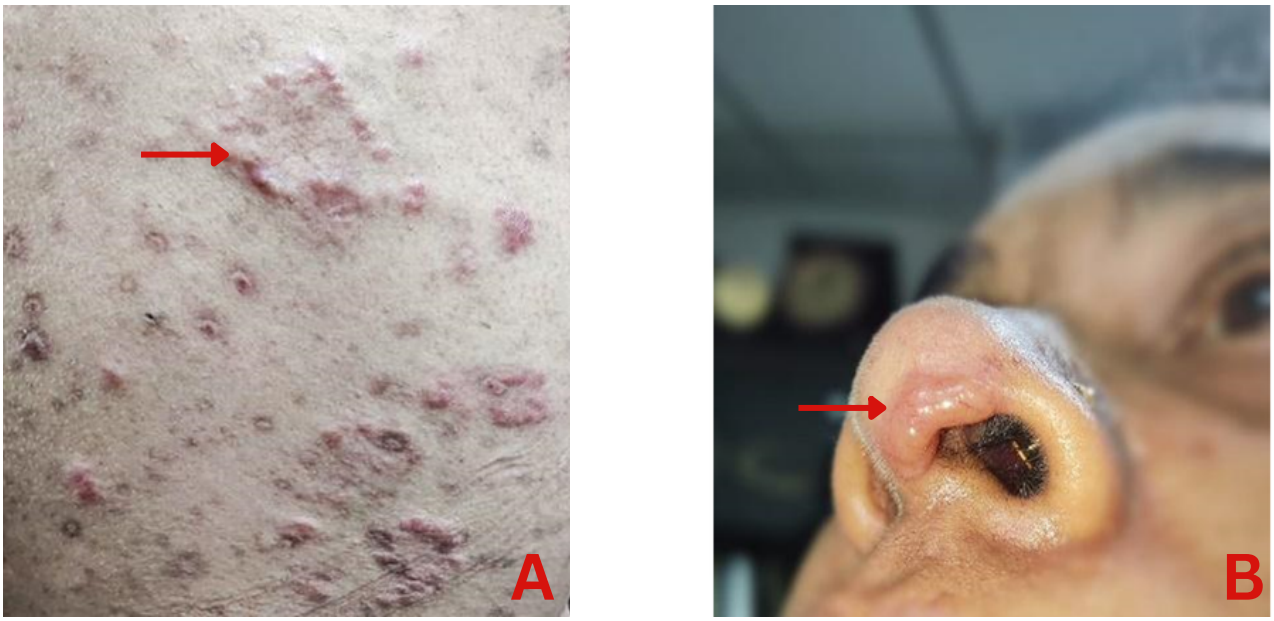

Figure 2

A: Erythematous and infiltrative papules along with annulare plaques having infiltrative elevated border and central clearing involving the back.
B: Lupus pernio.

Table 1 - Repeat investigations

Investigation	Result	Reference range
Hemoglobin	10.3 g/dL	12-16
Total white blood cell count	2,920×10^9/L	4,500-11,000
Neutrophil	51%	
Lymphocyte	35%	
Platelet count	123,000×10^9/L	150,000 - 450,000
ESR	53 mm in 1st hour	0-20
Serum calcium level	9.28 mg/dL	8.5-10.3
Serum angiotensin converting enzyme (ACE) level	199 U/L	20-70
Serum Vitamin D (25-OH) level	10.40 ng/mL	30-100
serum lactate dehydrogenase	166 U/L	100-190

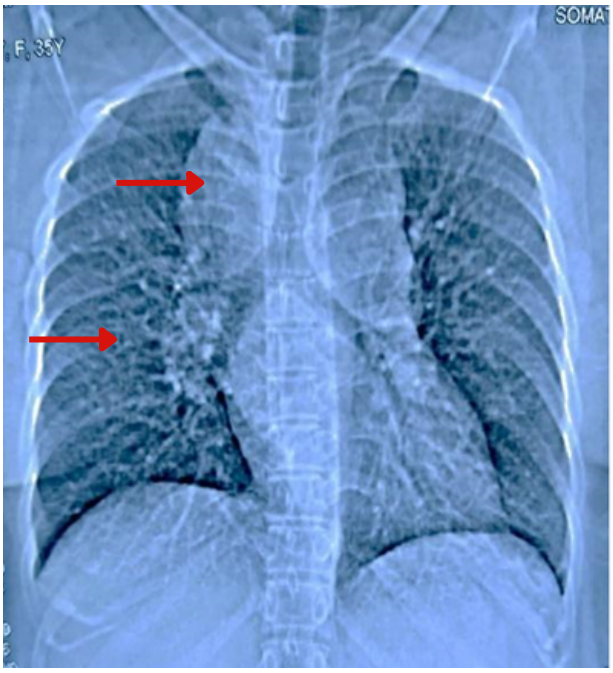

Figure 3 -Repeat HRCT chest:
Extensive mediastinal lymphadenopathy with bilateral pulmonary reticulonodular shadowing. [Bilateral axillary and upper abdominal lymphadenopathy were also reported, not shown on this image].

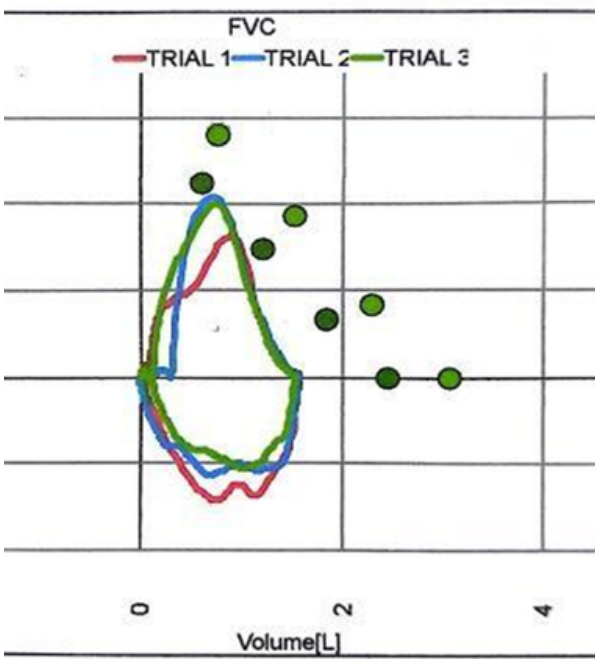

Figure 4 -Spirometry:
Moderate-severe restrictive picture

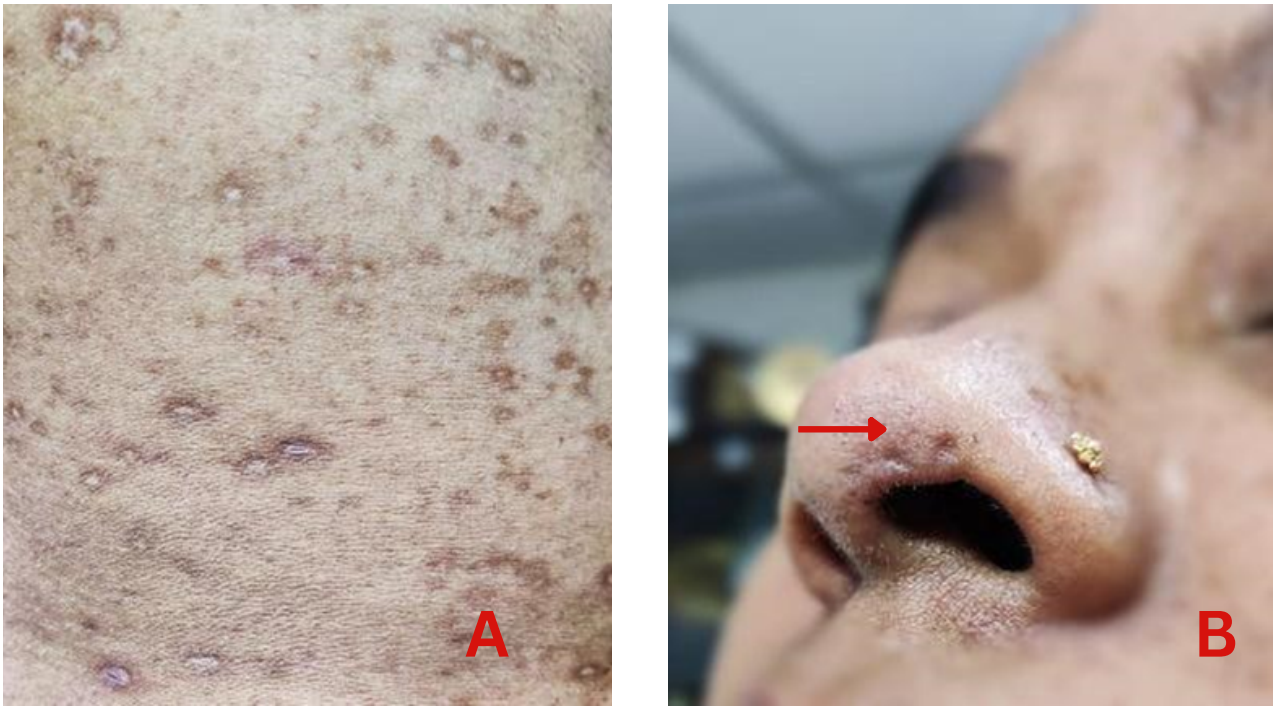

Figure 5 Follow-up visit on treatment:

A: Healed atrophic scars over back.
B: Healed scar of lupus pernio

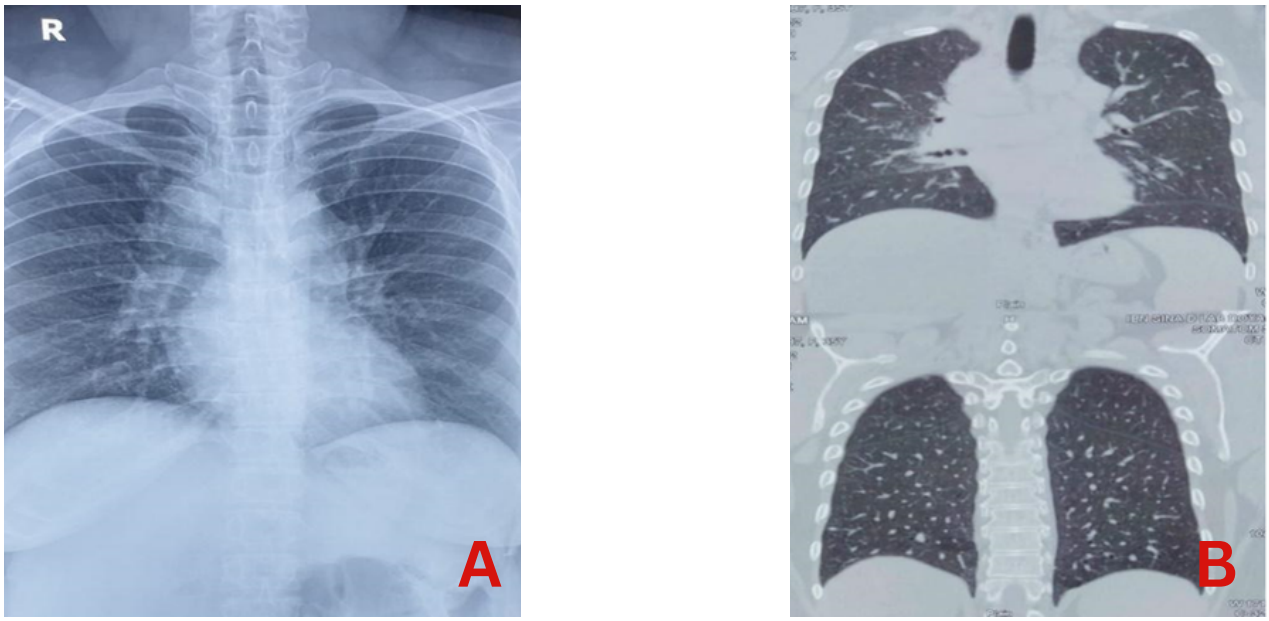

Figure 6 - Follow-up imaging:

A: Chest radiology (P/A view): Resolving shadows of mediastinal lymphadenopathy
B: HRCT chest: Reduced shadows of mediastinal lymphadenopathy with almost clear lung fields

Discussion

Sarcoidosis can involve any organ, clinical and radiological appearances are diverse in nature and the characteristic non-caseating granulomas can mimic tuberculosis, lymphoma, carcinoma, fungal disease, and berylliosis.(6) The case presented here was a tuberculosis (TB) mimic. All the symptoms of sarcoidosis were not present since the beginning of the illness. Her late presentation of cutaneous features made the diagnosis difficult. However, unresponsiveness to empirical ATT went in favor of sarcoidosis. Studies suggest, the lung parenchyma is almost always affected and enlarged bilateral hilar and right paratracheal lymph nodes are the most common radiological deviation; which was consistent with our finding. The granulomas resolve gradually or heal by fibrosis.(6) In almost two-third of cases it is self-limiting. Chronicity occurs in approximately 30% of cases and fatalities occur in 1 to 4%.(7) Respiratory failure is the most frequent cause of death associated with sarcoidosis.(8)

Micro-papules, papules, plaques, erythema nodosum, subcutaneous nodules, lupus pernio, ulcer, scar sarcoidosis, and alopecia are common cutaneous manifestations. Sarcoid papules can be a lichen planus mimic. Ernest Besnier in 1889, marked lupus pernio as an indicator of chronic sarcoidosis.(2) In our case we have got lupus pernio which established the chronicity of the disease. Mild anemia (hemolytic or non-hemolytic), leucopenia, neutropenia, monocytosis, eosinophilia and thrombocytopenia have been documented (9), as we have demonstrated in our case except monocytosis and eosinophilia. Serum ACE level represents the overall granuloma burden in sarcoidosis as it is produced by the epithelioid cells; but it does not have any prognostic value.(10)

Hypovitaminosis D has been proven to lead the pulmonary sarcoidosis from stage-2 towards stage-4, and has a strong positive association with disease hronicity.(11) Even so, it has no correlation with the lymph node involvement or the skin manifestations of sarcoidosis.(11) The role of vitamin-D therapy as treatment or prophylaxis of sarcoidosis can act as a double-edged sword. It might reduce the development and spread of granulomas, but in around 10% of cases it may cause asymptomatic hypercalcemia and hypercalciuria.(12) Under close monitoring, we treated her with vitamin-D supplements, and no adverse outcome was noted.

For sarcoidosis, we have treated our patient with corticosteroids which is the first line therapy and she responded well. Steroid-sparing therapy may be needed in uncontrolled diabetes and/or

hypertension, decompensated heart failure, glaucoma, severe obesity or as add-on therapy in neuro-sarcoidosis, severe infiltrative heart disease or ophthalmic injury. In the chronic disease course, the duration of therapy is generally considered to be approximately a year, as shorter courses have been reported with an increased risk of relapse.(12)

Conclusion

It is important to lower the threshold to consider sarcoidosis taking into account its deceptive nature which can easily lead to misdiagnosis and late diagnosis, especially in the TB endemic areas.

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Tuberculosis-immune reconstitution inflammatory syndrome in an immunocompetent patient

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Abstract

Tuberculosis-immune reconstitution inflammatory syndrome is commonly seen among patients with acquired immunodeficiency syndrome either as a paradoxical worsening of an already diagnosed disease or as an uncovering of a dormant infection. There is evidence of paradoxical worsening of central nervous system tuberculosis (CNS-TB) once the treatment is instituted even among immunocompetent patients leading to significant morbidity. We report a case of a previously well young woman with paradoxical worsening of CNS-TB after commencement of treatment. This case highlights an important possible clinical sequelae of CNS-TB, a practicing physician should be aware of.

Key words: Tuberculosis-immune reconstitution inflammatory syndrome, central nervous system tuberculosis

Introduction

Tuberculosis (TB) is an intracellular bacterium manifesting commonly as a chronic pulmonary infection in the tropics with poor socio-economic backgrounds. TB has contributed immensely to the healthcare burden of Sri Lanka with around 8000 cases reported every year.(1) Tuberculosis-immune reconstitution syndrome (TB-IRIS) is a paradoxical worsening of an already diagnosed TB or unravelling of a dormant TB infection upon restoration of a previously obtund immune system. This usually occurs in the setting of treating an acquired immuno-deficiency syndrome (AIDS) or stopping an immunomodulating drug like Infliximab.(2-5) Even among immunocompetent patients paradoxical worsening of central nervous system tuberculosis (CNS TB) once the treatment is instituted has been reported.(6-10)

Case presentation

We discuss a 22-year-old woman, who presented with an insidious onset dry cough, shortness of breath and constitutional symptoms for three months. The patient lived in a congested home with her extended family. However, there was no contact history of tuberculosis (TB). The patient was diagnosed with miliary TB with a positive sputum GeneXpert study and a chest x-ray demonstrating miliary mottling. The bacterial cultures were negative. She was started on anti- TB therapy.

A week into the treatment she complained of a severe headache with neck stiffness. The cerebrospinal fluid (CSF) analysis revealed 121.8 mg/dL of proteins, 60 lymphocytes / mm^3, with a significant CSF sugar drop and a positive CSF TB PCR. MRI scan of her brain revealed multiple rim

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enhancing tuberculomas in both cerebral hemispheres and cerebellum.

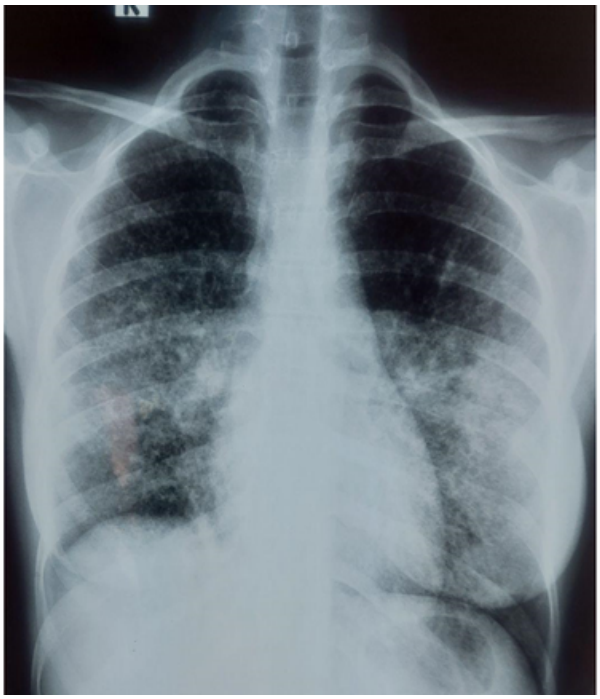

Figure 1 -Chest X Ray showing miliary mottling

For management of CNS-TB intravenous dexamethasone regimen was commenced and continued for four weeks. It was subsequently converted to oral prednisolone. The patient was stable and was discharged.

Two weeks later she presented to us again with a worsening headache and early morning vomiting without focal neurological signs. Further imaging revealed multiple new tuberculomas and enlargement of the existing lesions.

Repeat CSF analysis showed 206 mg/dL of proteins, 32 polymorphs and 09 lymphocytes per mm3 and an ADA of 5.1 U/L. The CSF TB PCR, TB culture and pyogenic culture were negative. The sputum TB culture which was done during the last admission was traced and it did not show antibiotic resistance. The erythrocyte sedimentation rate was 55 mm and the c- reactive protein was only 9 mg /dL. However, the patient had ongoing fever spikes. Blood and sputum cultures were repeatedly sterile.

Paradoxical worsening of her clinical condition made us consider TB-IRIS. Thus, the patient underwent further evaluation to look for an immunocompromised status. The HIV status was negative. The full blood count, immunoglobulin and complement levels, neutrophil function tests and flow cytometric assessment of lymphocytic sub-types revealed an adequately functioning immune system. TB-immune reconstitution inflammatory syndrome occurring in an immunocompetent patient was considered as the working diagnosis after a multi-disciplinary discussion. . The patient was started on an IV dexamethasone regimen with 0.4 mg /kg for 2 weeks, 0.2mg/kg during the third week and 0.1mg/kg in the fourth week. After a course of IV steroids, she showed a considerable response and was started on oral prednisolone 1mg/kg upon discharge. Patient had an uneventful recovery.

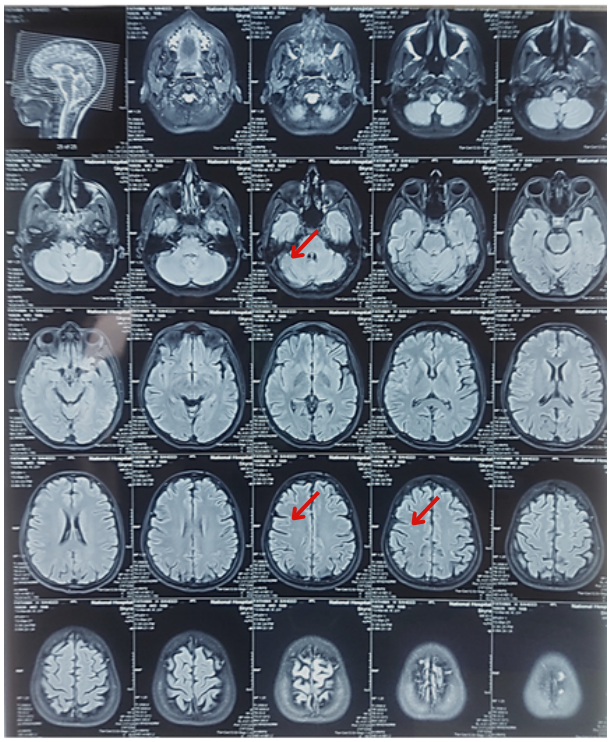

Figure 2 -showing multiple tuberculomas with few ring enhancing lesions (denoted by red arrows)

Discussion

Disseminated TB in an immunocompetent young girl is uncommon. Furthermore, the development of TB-IRIS is even rarer among immunocompetent individuals. In this case, an alternative explanation for the deterioration of central nervous system tuberculosis (CNS-TB) such as non-compliance to drugs, sub-optimal quality of the drugs, drug resistance in the given epidemiological background or poor delivery of the anti-TB therapy into the deep brain matter should be thought of.

There is evidence of resolution of infection in the lungs of this patient with treatment. Therefore, a

drug resistant variant or non-compliance is less likely albeit a selective non-penetrance of the brain parenchyma could be an issue. Isoniazid is said to have good CNS penetrance as opposed to rifampicin whose CNS bioavailability is roughly around 20% that of plasma. It is also postulated that even though rifampicin has poor CNS penetrance the amount of active drug in CSF is comparable to that of plasma. (11,12) The negative culture and PCR in subsequent cerebrospinal fluid could be considered as evidence of resolving parenchymal infection in this patient.

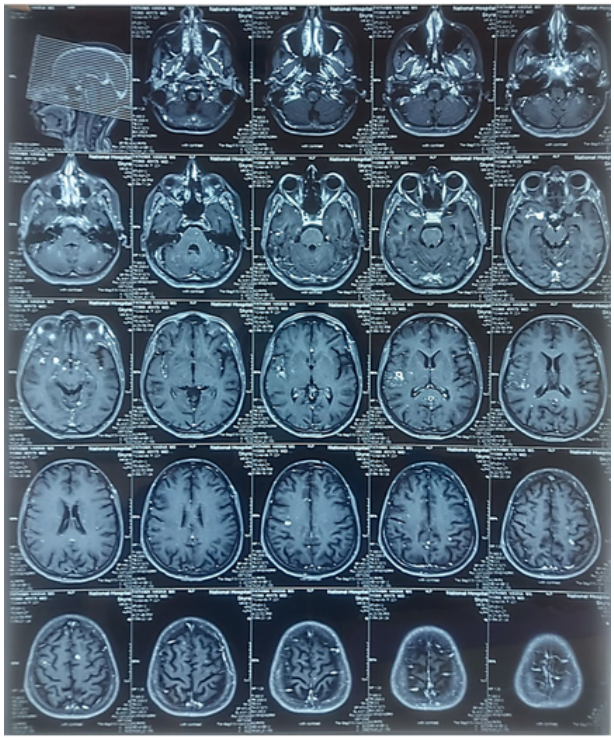

Figure 3 -showing worsening of enhancing lesions

However, there is increasing evidence of TB-IRIS among patients on biological therapy upon their withdrawal.(4) Interestingly, there are many instances of paradoxical worsening of TB among immunocompetent patients with good initial response recorded in literature.(7,10). Paradoxical worsening of CNS TB is known to cause significant short-term morbidity as well as disease burden.(13) Manifestations such as optochiasmatic and spinal arachnoiditis and hydrocephalus could occur leading to neurological disability. Most have been responsive to treatment with steroids.(6,8,14) There are case reports and small studies exploring the use of tumor necrosis factor alpha inhibitors, thalidomide and cyclophosphamide in the treatment of steroid resistant cases of paradoxical worsening of CNS TB. (15-17) We could not find similar case reports from Sri Lanka where tuberculosis is endemic. Unfortunately, there is a lack of data on treatment options of this condition with high morbidity.

Conclusion

The paradoxically worsening CNS-TB in an immunocompetent individual is increasingly identified. This case highlights an important entity that internists in our region should be aware of as South East Asia carries a high disease burden of TB. We would like to emphasize the importance of adherence to glucocorticoid regimen when treating CNS-TB.

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Rifampicin induced acute interstitial nephritis in a patient with tuberculosis: A case report

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Abstract

Interstitial nephritis is a rare complication of anti-tuberculosis treatment, most commonly rifampicin. This case report describes a 65-year-old woman with diabetes who presented with loss of consciousness due to a major hypoglycemic episode precipitated by severe acute kidney injury, one month after initiating anti-tuberculous therapy. The presence of active urinary sediments, subnephrotic proteinuria and normal sized kidneys prompted performing a renal biopsy which showed interstitial inflammatory cell infiltration suggestive of acute interstitial nephritis, possibly drug induced. The reversal of renal impairment on cessation of rifampicin confirmed the diagnosis. As this is a reversible cause of acute kidney injury, awareness of this association and early identification is vital to prevent deterioration.

Key words: Rifampicin, acute kidney injury, acute interstitial nephritis, anti-tuberculosis treatment

Introduction

Rifampicin, a potent drug in anti-tuberculosis treatment (ATT) is a double-edged sword with strong side effects, namely hepatotoxicity. Rifampicin induced nephrotoxicity is an uncommon but noteworthy occurrence, attributed to an immune mediated mechanism more commonly associated with its intermittent use. However, there have been reports associated with its continuous use as well, as in this instance.(1)

Our patient, a 65-year-old with diabetes, was newly diagnosed with Category 1 tuberculosis. She developed a hypoglycemic episode and an acute kidney injury of unknown etiology during the second month of intensive phase treatment. Evaluation of the etiology of her acute kidney injury by investigations including a renal biopsy helped to narrow down the differentials. Early withdrawal of rifampicin enables good recovery of renal functions with the use of corticosteroids in more severe cases. (2) The permanent withdrawal of a potent drug like rifampicin from the treatment regime may be a setback in achieving a faster cure of tuberculosis, yet this is certainly outweighed by the renal benefits.

Case presentation

A 65-year-old woman with chronic cough for three weeks and constitutional symptoms, had been diagnosed with Category 1 smear-positive pulmonary tuberculosis (++) one month before her admission to us and was initiated on the standard fixed drug combination (FDC4) at that time. She had been prescribed 4 tablets of FDC4 daily, based on her body weight (55kg). This consisted of Rifampicin 600 mg, Isoniazid 300 mg, Pyrazinamide 1600 mg and

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Ethambutol 1100 mg, along with Pyridoxine 12.5 mg daily. She was incidentally diagnosed with uncomplicated diabetes mellitus at that time and notably she had normal renal functions (S.Cr 1 mg/dL, eGFR 63). Her glycemic control had been satisfactory with gliclazide 40 mg twice daily.

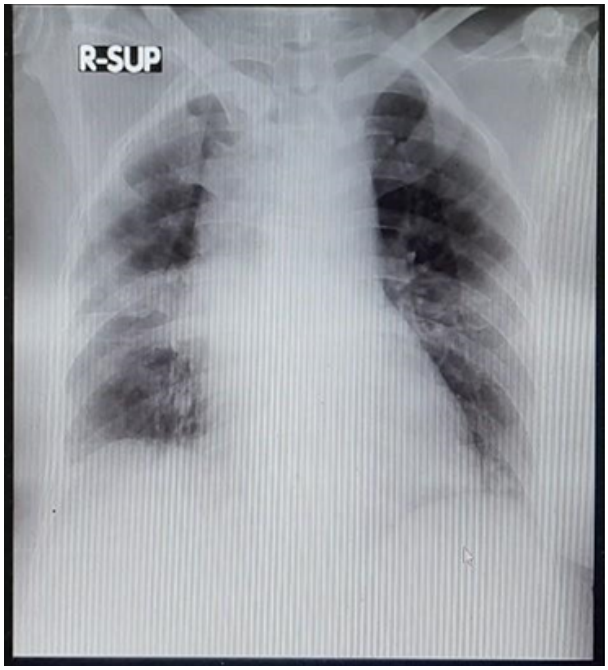

Figure 1 -Chest X ray: Right hilar prominence, small focal patchy nodular opacities in right middle lobe and left lower lobes, which are representative of diagnosed tuberculosis with residual changes.

During the second month of the ATT intensive phase, she developed a prodrome of nausea, reduced appetite and urine output in the weeks preceding her admission. This culminated in a state of unresponsiveness with which she was admitted and was diagnosed to have had a major hypoglycemic episode.

On examination, she was pale and had bilateral pitting pedal oedema. She also had right middle and left lower zone crepitations. She was anicteric with no features of liver failure. She was hemodynamically stable with no buccal or palmar pigmentation. Fundoscopy showed no diabetic retinopathy changes.

Her serum creatinine had risen from the baseline of 1 mg/dL to 8.8 mg/dL over one month. The hypoglycaemia was attributed to the development of a new onset acute kidney injury (AKI), further aggravated by sulphonylurea use. As she did not have any recurrent hypoglycemic episodes after omitting gliclazide or complaints of postural giddiness, the possibility of tuberculous adrenalitis precipitating an Addisonian crisis following initiation of ATT as a cause of hypoglycaemia was considered unlikely.

Urinary sediments were active- pus cells 15-20, red cells 15-20 / HPF. Though urine for dysmorphic red cells was negative, it did not completely exclude a glomerular pathology as the test has a low sensitivity. She had a subnephrotic range proteinuria. Urine eosinophil testing was not available at the hospital during that time.

She had elevated uric acid (9.5 mg/dL) and phosphate (7 mg/dL) levels. Ultrasonically, kidney sizes were normal with acute parenchymal changes. As her renal impairment coincided with the initiation of ATT, drug induced AKI was considered and she underwent a renal biopsy. Her biopsy showed 8 viable and 2 globally sclerosed glomeruli. Mild tubular atrophy with focal epithelial degeneration was present. The interstitium showed mild fibrosis with mixed inflammation including eosinophils. The overall biopsy features favored drug induced acute interstitial nephritis.

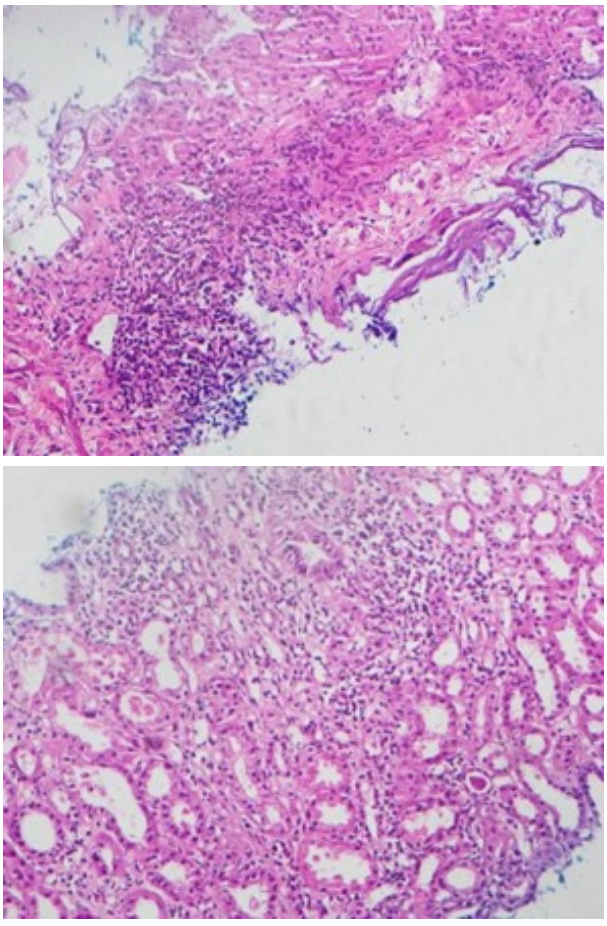

Figure 2 -Renal biopsy showing interstitial inflammatory cell infiltration

Table 1 - Summary of investigations

Investigation	Result	Reference range
White Blood Cell Count	7.91* 10^9/L No eosinophilia	4 – 10
Hemoglobin	7.91 g/dL	11-16
Red cell indices	MCV 86.1 fL	80 – 100
	MCH 30 pg	27-34
	MCHC 33 g/dL	32-36
	RDW-CV 12%	11-16
Platelet	231 * 10^9/uL	100 - 300
C Reactive Protein	10.4 mg/L	<6
Aspartate Transaminase	21 IU/L	5-34
Alanine Transaminase	13 IU/L	0-55
Alkaline Phosphatase	104 IU/L	44-147
Total bilirubin	0.4 mg/dL	0.2 - 1.2
Serum Albumin	3.8 g/L	34-54
International Normalized Ratio	1.04	0.8-1.1
Serum Creatinine	8.8 mg/dL	0.55 - 1.02
Serum sodium	138 mmol/L	136 -145
Serum potassium	5.5 mmol/L	3.5 - 5.1
Serum Calcium	8.4 mg/dL	8.6 -10.3
Serum phosphate	7 mg/dL	2.8 - 4.5
Serum uric Acid	9.5mg/dL	3.5 - 7.2
Blood picture	Normocytic normochromic red cells Moderate anemia of chronic disease	

Rifampicin was withheld. An alternate regime of isoniazid, pyrazinamide, levofloxacin and amikacin was commenced. Creatinine dropped from 8 to 2.38 mg/dL over two weeks, without requiring hemodialysis. She was discharged with nephrology follow-up arranged.

Discussion

In our patient the initiation of ATT correlated temporally with the development of AKI. She scored 5 on the Naranjo's Algorithm for adverse drug events, suggesting a drug-induced etiology, as opposed to other causes of AKI.(3) She denied using other medication or Ayurvedic treatment.

Renal impairment soon after diagnosis of diabetes, rapid 7-fold creatinine increase over 1 month and the absence of diabetic retinopathy were against diabetic nephropathy. Genitourinary tuberculosis by direct invasion of the bacilli, and tuberculosis-induced post infectious glomerulonephritis (4) were unlikely being one month into the ATT intensive phase and with the biopsy findings.

Rifampicin has varied renal side effects including acute interstitial nephritis, papillary and cortical necrosis, and minimal change disease (5), and proliferative glomerulonephritis.(6) Rapidly progressive crescentic glomerulonephritis and Fanconi Syndrome (7) have also been reported. There is an increased risk in those previously treated with rifampicin.(2)

Rifampicin binds to proteins which induce anti-rifampicin antibodies.(1) By a type II or III hypersensitivity reaction, the immune complexes in the glomerulus and renal interstitium trigger an inflammatory cascade resulting in nephritis.(1)

Only 10% have the classical triad of fever, rash, eosinophilia.(8) Subnephrotic proteinuria and elevated urine eosinophils are although suggestive of acute interstitial nephritis can also be present in urinary tract infections, hence non-specific.(9) The definitive diagnosis is by renal biopsy.

The role of corticosteroids, both oral prednisolone and pulse methylprednisolone in the management is still being researched on. Corticosteroids may hasten recovery (2) with cautious use due to risk of disseminated tuberculosis. In one study conducted, patients were initiated on steroids if there was no recovery of renal functions within one week of cessation of the drug.(10) Studies have shown that there was a better return of renal functions to baseline in those initiated on steroids within two weeks of withdrawal of the offending agent as compared to one month after.(11) Our patient recovered spontaneously without steroids.

Conclusion

This case illustrated the multi-disciplinary considerations in evaluating a new onset acute kidney injury involving the nephrology, respiratory and general medical teams. The diagnosis was established by histology and a clinically satisfactory response to treatment. Recommendations include diagnostic improvements such as testing for rifampicin induced autoantibodies in the blood, which may be less invasive and quicker in establishing the diagnosis, although not readily available. Secondly, guideline recommendations on the indications to initiate steroids in such situations based on further reports would be useful.

Authors' contribution
All authors were involved in the management of this patient

Declarations

Conflicts of interest
None

Consent for publication
Obtained from the patient and family. The authors also give consent for publication.

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CASE REPORT

Iron overload leading to cirrhosis in a patient with hereditary spherocytosis and heterozygosity for H63D mutation in the HFE gene

Madurapperuma MCP[1]*, Dulanjalie RBAT[1], Thennakoon TMHM[1], Gunawardena KW[2], Jayanaga WWLA[1], Dissanayake VHW[2]

Abstract

Hereditary spherocytosis (HS) refers to a group of autosomal dominantly inherited heterogeneous hereditary haemolytic anaemias (HHA). Significant iron overload in HS is uncommon. Iron overload has been described as a complication of HS when there is co-inheritance of hereditary haemochromatosis (HH). H63D mutation accounts for a minority of hereditary hemochromatosis cases and does not cause iron overload in an otherwise healthy heterozygous carrier state. We present a 64-year-old man , diagnosed with HS presenting with cirrhosis without significant on-going haemolysis. He had a markedly high serum ferritin and transferrin saturation. Magnetic Resonance Imaging for liver iron concentration revealed haemochromatosis of the liver. HFE genotyping showed heterozygosity for the H63D mutant allele. Haemolysis in HS does not usually result in clinically significant iron excess leading to haemochromatosis and the presence of H63D heterozygous mutation will increase the risk of clinically significant iron overload which can lead to hepatic iron deposition and fibrosis. Therefore, if a patient with H63D mutation demonstrates clinically significant iron overload, clinicians should search for other factors that increase iron excess such as on-going haemolysis, alcohol abuse and presence of metabolic syndrome.

Key words: Hereditary spherocytosis, Haemochromatosis, Cirrhosis, H63D mutation

Introduction

Hereditary spherocytosis (HS) refers to a group of autosomal dominantly inherited heterogeneous hereditary haemolytic anaemias (HHA). Clinical severity of HS is variable. Patients with a mild phenotype are often asymptomatic due to having a compensated haemolysis with mild anaemia. On the other end of the spectrum, patients with severe disease can have transfusion-dependent anaemia.

Iron overload in HHAs has been extensively studied in β-thalassemia.(1) However, data on the prevalence of iron overload in HS is limited.(1) Iron overload in patients in HHAs are usually due to recurrent blood transfusions and/or inappropriately high dietary iron absorption as a result of ineffective and increased erythropoiesis. Iron overload has been described as a complication of HS mostly when there is co-inheritance of hereditary haemochromatosis (HH). (2,3)

HH is an autosomal recessive condition and homozygosity for the C282Y variant in HFE is present in about 80% of individuals of European origin with the disease. A smaller proportion (5%) with

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compound heterozygosity for the C282Y/H63D mutations is observed . H63D mutation accounts for a minority of hereditary hemochromatosis cases. Patients who are homozygous or heterozygous for the H63D mutation are not at increased risk of developing clinical iron overload compared to those without this mutation, though they may still present with an elevation in transferrin saturation and serum ferritin levels.(4)

Here we present a 64-year-old patient with HS without significant haemolysis presenting with clinically significant iron overload. He was found to have H63D heterozygous haemochromatosis mutation.

Case presentation

A 64-year-old man , diagnosed with hereditary spherocytosis in 2008, presented to the National Hospital of Sri Lanka in October 2022, with progressively worsening lower limb and abdominal swelling associated with increased skin pigmentation for 4 months.

A month prior to presentation, he had also developed yellowish discolouration of the eyes without steatorrhoea, pruritus, or passage of tea-coloured urine. He did not have exertional dyspnoea, orthopnoea or paroxysmal dyspnoea. He denied loss of libido and erectile dysfunction, or joint pains. He had been a teetotaler with no history of alternative medicine use or long-term medications.

He was diagnosed with hereditary spherocytosis during family screening in 2008 when his daughter was diagnosed with the same disease. Since diagnosis, he had been followed up in the haematology clinic, and had maintained his haemoglobin levels between 9-10g/dL and a reticulocyte count between 6-7%. He had received only 4 units of red cell transfusions to date since the diagnosis. Five years ago, he underwent a laparoscopic cholecystectomy for symptomatic gallstones. Although a splenectomy was planned due to massive splenomegaly, it was deferred due to personal preference.

On general examination, his body mass index was 17 kg/m2, waist circumference was 76 cm and he had conjunctival pallor, icterus and generalised hyperpigmentation of skin. He had leukonychia, beau's lines and peripheral stigmata of cirrhosis such as spider naevi, loss of axillary and body hair and palmar erythema. There was pitting oedema up to the mid-calf level. Abdominal examination revealed a distended abdomen with a massive splenomegaly, spanning 9 cm from the left costal margin, and tense ascites. He had mild bilateral pleural effusions. Cardiovascular and neurology examinations were unremarkable.

Full blood count revealed mild neutrophil leukocytosis ($11.84x10^9$/L; neutrophils 79%), normocytic normochromic anaemia (haemoglobin 8.8 g/dL) with normal mean cell volume (87 fL) and increased mean cell haemoglobin concentration (37 g/dL) and thrombocytopaenia (platelets – $101x10^9$/L). Reticulocyte count was 6.5%. His erythrocyte sedimentation rate (ESR) was 24mm/ 1st hour and C-reactive protein (CRP) was 9.5 mg/dL.

Liver profile revealed, aspartate transaminase (AST) of 65 U/L, alanine transaminase (ALT) of 34 U/L, low albumin (2.5 g/dL) and globulin (2.8 g/dL), with a reversed albumin to globulin ratio, mild direct hyperbilirubinaemia (total 2.6 mg/dL; direct 1.2 mg/dL) and slightly elevated alkaline phosphatase (ALP) of 189 U/L and gamma-glutamyl transferase (GGT) of 80 U/L. Clotting profile revealed prolonged international normalised ratio (INR) 1.45, activated partial thromboplastin time (APTT) of 38s. Abdominal ultrasonography confirmed chronic liver cell disease with portal hypertension, massive splenomegaly (21cm) with gross ascites.

His serum ferritin was markedly high (1303 ng/mL), with elevated transferrin saturation (87.51%). Liver Magnetic Resonance Imaging (MRI) for liver iron concentration (LIC) via Signal intensity ratios (SIR) method based on T2*weighted imaging revealed low signal of T2*Gradient echo (GRE) compared to the erector spinae muscle (Liver/ Muscle ratio less than 0.9) confirming evidence of haemochromatosis of the liver (Figure 1). (5)

There were no other contributing factors for the iron overload such as long-term iron supplementation, or concomitant alcohol consumption. Serological tests for Hepatitis B and C viral infections, as well as inflammatory aetiologies such as primary biliary cholangitis, and autoimmune hepatitis were negative. HFE genotyping showed heterozygosity for the p.H63D mutant allele.

His upper gastrointestinal endoscopy (UGIE) showed grade 1 oesophageal varices. Diagnostic paracentesis revealed evidence of portal hypertension (Serum to ascitic albumin gradient; SAAG 1.5 g/dL; ascitic protein 1.2 g/dL) without spontaneous bacterial peritonitis.

Fasting plasma glucose was normal (87 mg/dL), lipid profile was normal (Total cholesterol 128mg/dL; LDL cholesterol 87 mg/dL; Triglycerides 98 mg/dL) with normal levels of follicular stimulating hormone (FSH), luteinizing hormone (LH) and testosterone.

Echocardiogram showed normal biventricular function and normal chamber sizes. Cardiac MRI facility was not available.

Iron chelation therapy was initiated as the patient would benefit from prevention of further deposition of iron. Phlebotomy was not considered in view of baseline moderate anaemia.

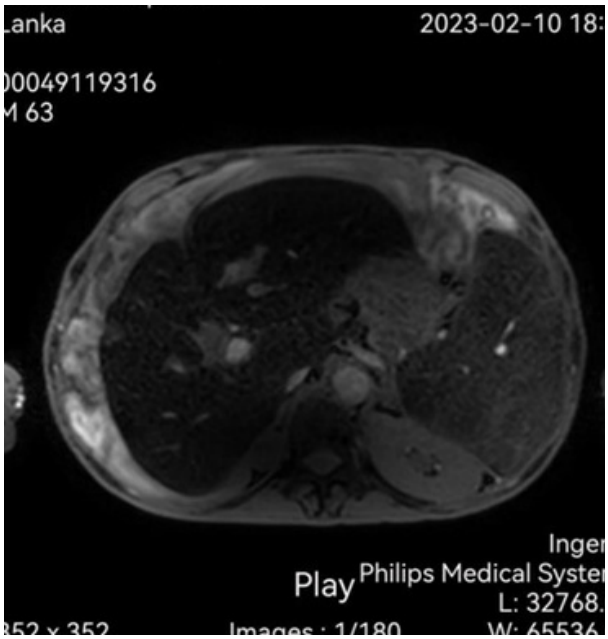

Figure 1 -T2* gradient axial echo slice of liver MRI - This demonstrates an abnormal low signal intensity of the liver compared to erector spinae muscle (L/M ratio <0.9).

Discussion

Index patient despite not having significant haemolysis ended with iron overload with organ dysfunction. Iron overload in patients with HS has mainly been reported with co-inheritance of HFE mutations.(6) This prompted us to look for coexistence of factors that would increase iron overload.

Most of the HFE-related hemochromatosis is associated with homozygosity for C282Y. The association of homozygosity for H63D with iron overload is debated. The H63D genotype might be considered a genetic variant that predisposes to slight alterations in iron parameters but not a disease-causing variant.(7)

However, other risk factors or other genetic causes of iron overload should be sought when patients with this genotype demonstrate iron excess. In combination with other acquired risk factors such as alcohol, metabolic syndrome, H63D is associated with a higher risk of mild iron overload.(8) In our patient, who is a teetotaler, risk factors for metabolic syndrome such as hypertension, diabetes, hyperlipidaemia and obesity were excluded. Hence, we can postulate that in our patient the presence of H63D mutation and concurrent haemolysis may have led to the profound iron excess.

C282Y/H63D compound heterozygosity may be a risk factor predisposing to mild or moderate forms of iron overload when in association with comorbidity factors, for example, alcohol or metabolic syndrome. (8,9) It is very rare for compound heterozygosity for C282Y/ H63D to be associated with a severe iron overload phenotype in the absence of acquired causes.(10)

We postulate that the following mechanisms might have contributed to the clinically significant iron overload in our patient.

1. Ineffective erythropoiesis and chronic haemolysis within the reticulo-endothelial system and the resultant erythropoietic drive may promote iron absorption via downregulation of hepcidin.
2. Heterozygous H63D mutation related increased risk of iron overload.

Our patient had clinically significant iron overload in the liver, he did not have clinical or echocardiographic evidence of myocardial iron overload or heart failure. We could not find literature supporting the preponderance of iron overload in the liver over myocardium in HS, in patients with non-transfusion dependent beta thalassemia. However, it has been observed that iron overload differentially affects the liver rather than the myocardium.(11)

It is also worth noting that this patient has a massive splenomegaly (21cm) which is not usually expected to be observed in HS. This may be due to a combination of chronic haemolysis induced extramedullary haemopoiesis, cirrhosis induced portal hypertension and iron deposition.

In patients without homozygosity for p.C282Y as in the index case, in the presence of additional risk factors for hepatic iron overload, such as the metabolic syndrome and chronic alcohol excess, non-invasive quantification of liver, spleen, pancreas and cardiac iron can guide diagnosis and management.

Conclusion

This case illustrates that although haemolysis in HS does not usually result in clinically significant iron excess leading to haemochromatosis, the presence of H63D heterozygous mutation will increase the risk of clinically significant iron overload which can lead to hepatic iron deposition and fibrosis. If a patient with H63D mutation demonstrates clinically significant iron overload, clinicians should search for other factors that increase iron excess such as on-going haemolysis, alcohol abuse and presence of metabolic syndrome.

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CASE REPORT

Autoimmune hepatitis overlapping with subacute cutaneous lupus erythematosus: A case report

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Abstract

Autoimmune hepatitis (AIH) is an autoimmune liver disorder which rarely coexists with systemic lupus erythematosus (SLE) and presents as an overlap syndrome affecting multiple organs. Herein, we report a case of a 35-year-old healthy male who was evaluated for bilateral leg oedema and was diagnosed with AIH 5 years back. Four years later he developed fever and multiple photosensitive skin rashes, worsening leg oedema and proteinuria to which a diagnosis of coexisting SLE was made. He was diagnosed with the rare entity of AIH subacute cutaneous lupus erythematosus overlap syndrome. He was medically managed with immunosuppressive medication to which he responded.

Key words: Autoimmune hepatitis, subacute cutaneous lupus erythematosus, systemic lupus erythematosus

Introduction

Autoimmune hepatitis (AIH) is a chronic necrotizing inflammatory disorder of unknown aetiology. It is characterised histologically by a heavy infiltrate of lymphocytes and plasma cells in the portal tract and serologically by the presence of circulating autoantibodies, and high serum gamma-globulin.(1) Patients with AIH may develop other autoimmune diseases. Systemic lupus erythematosus (SLE) is an autoimmune disease characterised by the production of antibodies to components of the cell nucleus in association with multiple organ involvement.(2)

Cutaneous lupus erythematosus (CLE) encompasses a wide range of dermatologic manifestations, which may or may not be associated with the development of systemic disease.(3) Three recognized subtypes of cutaneous lupus erythematosus (LE) are acute cutaneous LE (ACLE), subacute cutaneous LE (SCLE), and chronic cutaneous LE (CCLE). Patients presenting with SCLE skin lesions tend to have milder systemic disease and are less likely to have systemic disease activity.(4)

AIH and SCLE are two distinct autoimmune diseases that can present with overlapping clinical features. Although AIH primarily affects the liver and SCLE predominantly affects the skin, both conditions are characterised by autoantibody production and T-cell activation. Due to these similarities, the coexistence of AIH and SCLE can lead to diagnostic challenges and treatment complexities. In this case report, we describe the clinical presentation, diagnostic process, and management of a male patient with AIH-SCLE overlap.

Case presentation

A 35-year-old man was evaluated 5 years back when he presented with persistent bilateral leg oedema, fatigability, jaundice, and pruritic rash for one-month. He has no personal or family history of liver disease or connective tissue disorders. He denies alcohol

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consumption, history of blood transfusions or recent intake of hepatotoxic drugs. Following initial investigations, he was found to have chronic liver cell disease (CLCD), but despite extensive workup, no aetiology could be found. Immunological testing showed raised Immunoglobulin G (IgG) levels and liver biopsy showed interface hepatitis with bridging fibrosis which was consistent with AIH. The patient was started on prednisolone 50 mg mane and azathioprine 50 mg daily dose to which he partially responded. The same dose of prednisolone was maintained for 2 months while increasing the azathioprine dose to 100 mg daily to which the patient showed a satisfactory response. From the next month onwards, prednisolone was tapered off gradually and he was maintained on prednisolone 10 mg mane along with azathioprine 100 mg daily until he presented this time with the current symptoms.

Four years after the initiation of therapy he presented to the routine clinic with a fever and multiple photosensitive skin rashes on his arms, chest, back, and abdomen. It was a sudden onset, low-grade continuous fever which was not associated with chills and rigours. The onset of the skin rash was on the same day as the fever and it started from the chest and spread centrifugally. No other systemic manifestations were noted by the patient. As the symptoms progressively worsened over time the patient sought medical advice around 2 -3 weeks after the onset of symptoms.

On examination, he was febrile with a temperature of 38.0°C. He was not pale, not icteric, and no malar rash on his face was noted. There was no generalised lymphadenopathy. Bilateral pitting ankle oedema was present. There was a symmetrical erythematous maculopapular eruption predominantly distributed along the upper chest, abdomen, and lower back sparing the face and scalp. He had a blood pressure of 120/80 mmHg and a regular pulse of 84 beats per minute. Abdominal examination revealed a moderately distended abdomen with free fluid. His cardiovascular, respiratory and neurological examinations were unremarkable.

His investigation findings are mentioned in Table 1.

During our evaluation, the possible differential diagnoses which were considered for the rash were cutaneous drug eruption, SCLE and an allergic reaction as a part of DRESS syndrome. But with the characteristic findings in the skin biopsy report diagnosis of SCLE was confirmed. Hence, the patient was started on hydroxychloroquine and topical steroids which led to improvement in his skin lesions.

During the course of his illness, he has had multiple hospital admissions due to worsening bilateral leg oedema, abdominal distention & fatigability. During those admissions, he was detected to have nephrotic range proteinuria along with microscopic haematuria which was not seen in the current presentation.

Based on the clinical findings in the current presentation, a provisional diagnosis of hepatorenal syndrome was made by excluding other possibilities (obstructive uropathy, sepsis, nephrotoxic drugs, absent haematuria and non-significant proteinuria, poor response to volume expansion with intravenous albumin 1g/kg/day for 48 hours).

Furthermore, during the current presentation, his haemoglobin levels were found to be 6.5 – 7.2 mg/dL with a normochromic normocytic blood picture requiring multiple blood transfusions to maintain his haemodynamic stability. Despite low haemoglobin levels, no apparent bleeding manifestations or evidence of haemolysis was detected during the clinical examination. However, there were small varices with portal gastropathy in the upper gastrointestinal endoscopy and it was presumed to be the reason for the low haemoglobin in the background of anaemia of chronic disease.

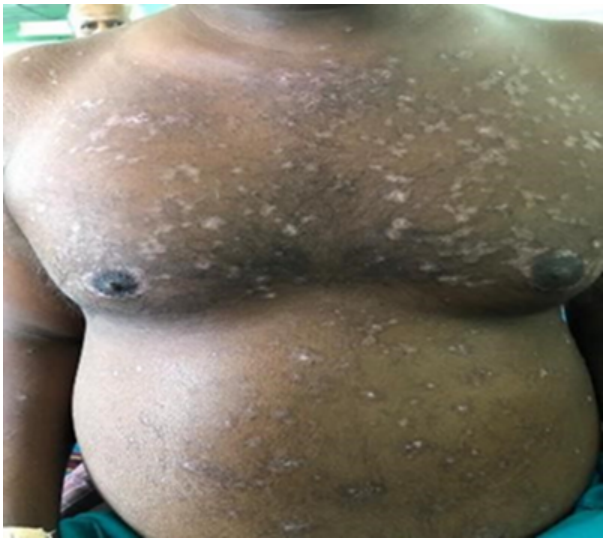

Figure 1 -Symmetrical erythematous maculopapular eruption predominantly distributed along the upper chest, abdomen, and lower back sparing the face and scalp

Furthermore, the other haematological manifestations were attributed to ongoing chronic liver cell disease and the absence of significant haematuria and proteinuria excluded the diagnosis of lupus nephritis. Multidisciplinary team input was

Table 1 - Summary of investigations

Investigation		Result		Reference range
		Day 01 of illness	Current presentation (5 years later)	
Full Blood Count	White Blood Cells	5.11 * 10^9/L	8.74* 109/L	4.5 – 11
	Haemoglobin	12.3 g/dL	7.2 g/dL	11-13
	Platelets	142 * 10^9/L	80* 109/L	150 – 400
Liver Biochemistry	Aspartate aminotransferase (AST)	136 IU/L	72 IU/L	10–35
	Alanine aminotransferase (ALT)	75 IU/L	53 IU/L	12–33
	Alkaline phosphatase (ALP)	92 IU/L	85 IU/L	300–500
	Total bilirubin	12.4 mg/dL	8.8 mg/dL	< 1.1
	Total Protein	-	8.5 g/dL	64 – 82
	Serum Albumin	-	2.7 g/dL	34 – 50
	Serum Globulin	-	5.8 g/dL	2-3.5
	Gamma GT	-	101U/L	5-40
Serum Creatinine		-	1.3 mg/dL	<1.2
Lipid Profile	Total Cholesterol	269 mg/dL	-	< 200
	Triglycerides	298 mg/dL	-	< 150
	HDL	39 mg/dL	-	35-65
	LDL	170.4 mg/dL	-	<100
Diabetes Screening	HbA1C	5.8%	-	< 6.5%
Iron Studies	Serum Iron	-	72.2 µ/dL	60 – 180
	Total Iron Binding Capacity	-	171.1 µ/dL	291 – 430
	Transferrin Saturation	-	42.19%	15 – 50%
	Serum ferritin	-	268 ng/mL	28 – 365

Table 1 - Summary of investigations continued..

Investigation		Result		Reference range
		Day 01 of illness	Current presentation (5 years later)	
Clotting Profile	Prothrombin Time	-	12 seconds	10 – 13
	INR (International Normalizing Ratio)	-	2.3	<1
Other Investigations	UPCR (Urinary protein to creatinine ratio)	-	48 mg/mmol	>300 – 350 nephrotic range
	Serum ceruloplasmin	34.6 mg/dL	-	20 – 60
Immunological Screening	Immunoglobulin (Ig) G	3526.5 mg/dL	-	700–1600
	dsDNA (Double Stranded DNA)	-	>150 IU/mL	<46.1
	Antinuclear antibody (ANA)		Positive	
	Anti-smooth muscle antibody		Positive	
	Anti-LKM Ab		Negative	
	Anti-Nuclear Factor		Positive	
Infection Screening	Hepatitis B Surface Antigen		Negative	
	Hepatitis B Antibody		Negative	
	Hepatitis C Antibody		Negative	
	Hepatitis A IgG antibody		Reactive	

Table 1 - Summary of investigations continued..

Investigation		Result (current presentation 5 years later)
Imaging Studies	Ultrasound scan Abdomen	CLCD with small amount of free fluid in pelvis.No portal hypertensionVarices present
	2D Echocardiography	Ejection Fraction – 60% Right Atrial & Right ventricular dilation present
	Upper gastrointestinal endoscopy	Very small oesophageal varices. No fundal varices.
	CECT Abdomen(Contrast Enhanced Computed Tomography)	Mild Hepatosplenomegaly with prominent left lobe. Portal/ hepatic veins normal
	Ultrasound guided Liver biopsy	CLCD with mild splenomegaly Interface Hepatitis with bridging fibrosis Fibrosis scoring 4.Portal tracts show ductular proliferation with lymphoplasmacytic infiltrate

obtained from the gastroenterology and haematology teams and the diagnosis of SCLE over SLE was entertained. He was started on a routine liver failure regimen while the 10 mg prednisolone dose was increased up to 60 mg mane to which he responded satisfactorily.

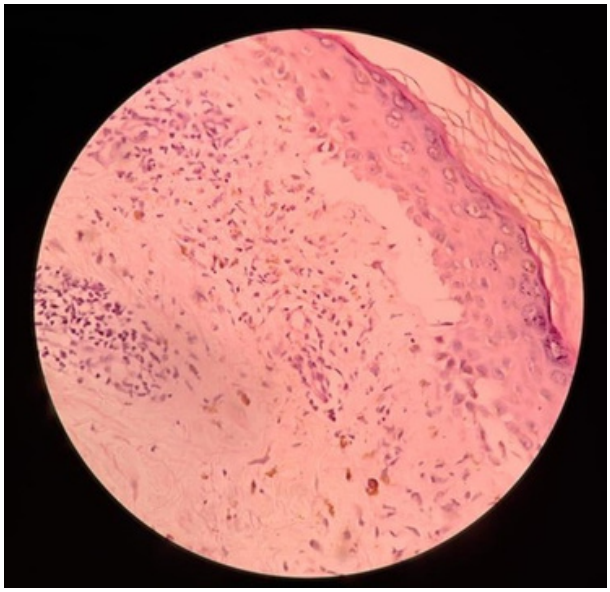

Figure 2 - Microscopic Features of Subacute Cutaneous Lupus Erythematosus. Interface dermatitis with vacuolization of basal keratinocytes and superficial lymphoid infiltrates

Discussion

SCLE represents a widespread, photosensitive, nonscarring, nonindurated form of lupus erythematosus (LE)-specific skin disease.(5) In contrast, AIH is an unresolved liver inflammation marked by hypergammaglobulinemia and autoantibodies in the blood.(1)

Concurrent autoimmune diseases are common in patients with AIH and mirror the full range of known autoimmune diseases. Therefore, an extended diagnostic screening for accumulating autoimmune diseases seems reasonable in patients with AIH.(6) The co-occurrence of autoimmune hepatitis (AIH) and SLE are deemed rare, with only a few case reports published thus far.(6) According to Runyon et al., 1980, liver disease was noted as early as four years before the diagnosis of SLE and as late as five years after its onset. Forty-five percent of the patients were noted to have liver disease and SLE in the same year. (7) Jablonska et al., 1998 suggested that patients with SCLE vary significantly from those with SLE in terms of cutaneous and visceral involvement, immunologic findings, photosensitivity, disease course, and therapy needs.(8) Subacute lesions are more common in patients with SCLE not fulfilling the ACR criteria for SLE but may be found in patients with SLE. (9)

Despite our patient being diagnosed with AIH based on histological findings in liver biopsy samples and

the presence of ANA and hypergammaglobulinemia, and SCLE based on clinical and cutaneous histopathology evidence, our patient did not fulfil the American College of Rheumatology criteria for SLE.

In our case, there is an overlap between AIH and SCLE, although there could still be an overlap between AIH and evolving SLE.

Conclusion

AIH and SCLE overlap is a very rare entity hence, co-occurrence of AIH and SCLE can pose a diagnostic and therapeutic challenge for clinicians. A high index of suspicion and a multidisciplinary approach is essential for the timely diagnosis and management of these overlapping autoimmune disorders.

Declarations

Conflicts of interest
None

Funding
None

Consent for publication
Written informed consent was obtained from the patient for publishing this case report

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CASE REPORT

Posterior reversible encephalopathy syndrome as the first presentation of a connective tissue disorder: A case report

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Abstract

Posterior Reversible Encephalopathy Syndrome (PRES) is a clinical-radiological diagnosis. Although hypertension is the main cause of this condition several secondary causes have been identified. Here we discuss a 53-year-old woman with a history of hypertension who presented with sudden onset of headache, seizures, and bilateral cortical blindness. MRI was suggestive of PRES. She had minimal blood pressure fluctuations. Antinuclear antibodies were significantly positive and a history of symmetrical polyarthritis was revealed. As the criteria for a particular connective tissue disorder were not fulfilled, the diagnosis of an undifferentiated connective tissue disease was made. In the presence of classical symptoms and imaging, PRES should be suspected even amongst patients without blood pressure fluctuations. Secondary causes should be identified and corrected in such patients.

Key words: Posterior Reversible Encephalopathy Syndrome, PRES , connective tissue disorder

Introduction

Posterior Reversible Encephalopathy Syndrome (PRES) is a condition that manifests with headache, seizures, altered higher mental functions and visual disturbances. Since its first description in 1996 by Hinchey et al.(1) it has been increasingly diagnosed due to the wide availability of neuroimaging.

Although it is often attributed to hypertension there are many etiologies including sepsis, solid organ and bone marrow transplantation, eclampsia and preeclampsia, renal failure, and malignancy (solid organ and haematological). Autoimmune disorders such as rheumatoid arthritis, Crohn's disease and systemic lupus erythematosus have also been implicated. Other causes are toxins including recreational drugs, poisons and immunosuppressive medications.(2) Patients may have a wide range of presentations such as encephalopathy states in 50-80%, seizures in 60-75%, headache in 50%, visual disturbances in 33% and focal neurologic deficits in 10-15 %.(3)

In most reported cases, blood pressure fluctuation is often noted.(4) This patient is unique as she had no major blood pressure fluctuations. Evaluation for secondary causes was suggestive of an evolving connective tissue disorder. This case report highlights the importance of recognising PRES as an initial presentation of connective tissue disease.

Case presentation

A 53-year-old woman with well-controlled primary hypertension for 5 years presented with a generalised headache for two days. This was followed by three generalised tonic-clonic seizures. She also complained of sudden onset bilateral painless loss of vision.

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On examination she was afebrile. There were no features of meningism. Her vision was reduced to just the perception of light in both eyes. The rest of the neurological examination was unremarkable.

Her blood pressure on admission was 130/80 mmHg in both arms. The maximum recorded blood pressure was 140/100 mmHg and the minimum was 130/80 mmHg. Her blood pressure variations are illustrated in Figure 1. On admission, she had one further episode of generalised tonic-clonic seizure that subsided spontaneously. However, she did not have any seizures after commencing on anti-epileptics.

A summary of her biochemical investigations, septic and autoimmune screening are shown in Table 1.

MRI brain T2 FLAIR showed multiple focal high signal intensities in the bilateral occipital lobes, parietal lobes, frontal lobes and left cerebellar hemisphere without diffusion restriction or blooming (Figure 2).

EEG showed generalised persistent attenuations and intermittent generalised low voltage delta waves. A clinical-radiological diagnosis of Posterior Reversible Encephalopathy Syndrome (PRES) was made. Evaluation for secondary causes revealed a history of an inflammatory type of small joint polyarthritis involving bilateral hands. She did not meet the ACR/EULAR classification criteria for rheumatoid arthritis. The autoimmune screening revealed a positive antinuclear antibody (ANA) level with a titre of 1:1000 and a mitotic pattern. The extractable nuclear antigen (ENA) Panel was positive only for Anti-Ro/SSA antibodies. Other antibodies including Rheumatoid factor and Anti dsDNA antibodies were negative. However, she did not meet the classification criteria for any defined connective tissue disease. A diagnosis of early undifferentiated connective tissue disease (UCTD) was made.

Her blood pressure was managed with oral anti-hypertensive drugs Losartan and amlodipine titrated to keep the blood pressure below 140/90 mmHg. Due to the recurrent seizures by the time of admission, she was started on oral Levetiracetam 500 mg twice a day. She had no further seizures after commencing on this anti-epileptic drug.

She had a complete recovery from her neurological symptoms within four days of symptom onset. She was discharged with a plan to follow up closely for the development of possible features of defined connective tissue disease.

Discussion

Posterior Reversible Encephalopathy Syndrome is a clinical-radiological diagnosis made in a patient with typical neurological signs and MRI findings. Imaging shows vasogenic oedema prominent in the posterior circulation.(5) These lesions are mostly seen in the occipital and parietal lobes. This patient also had bilateral occipital and parietal lesions. In addition, she also had lesions in the frontal lobe which are less commonly seen.

The exact pathophysiology of PRES remains

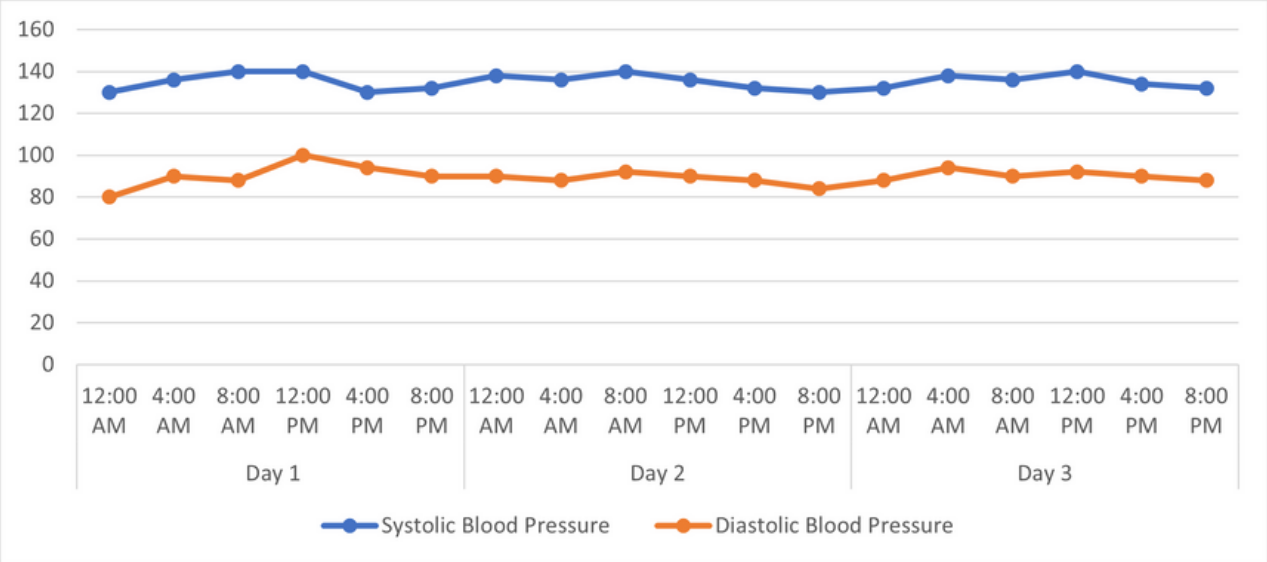

Figure 1 - Blood pressure fluctuations during ward stay

Table 1 - Summary of biochemical investigations, septic and autoimmune screening

Test	Result	Reference range
Full Blood Count		
White Blood Cell count	4.84 $\times 10^9$/L	(4–11)
Haemoglobin	14.9 g/dL	(12–15)
Platelets	256$\times 10^9$/L	(150–400)
Biochemical parameters		
C-reactive protein	5 mg/dL	(<6)
Erythrocyte Sedimentation Rate	14 mm/1st hour	(<20)
Sodium	138 mEq/L	(135-145)
Potassium	5.3 mEq/L	(3.5-5.0)
Creatine	0.86 mg/dL	(0.6-1.1)
Septic Screening		
Blood culture	No growth	
Cerebrospinal fluid culture	No growth	
Cerebrospinal fluid Full Report		
Protein	30 mg/dL	(15-45)
Glucose	83 mg/dL	
Random Blood Glucose	116 mg/dL	(70–140)
Cells	Nil	
Autoimmune Screening		
Antinuclear Antibody (ANA)	1:1000 (Mitotic pattern)	
Extractable Nuclear Antigen (ENA) Panel	Positive for Anti Ro/SSA antibodies	
Anti double stranded Deoxyribonucleic acid (ds-DNA) Antibodies	Negative	
Rheumatoid Factor	Negative	
Anti-cyclic citrullinated peptide (Anti CCP) Antibodies	Negative	

unknown. One of the most accepted theories is an increase in blood pressure above a level that can be compensated for by the autoregulatory mechanisms of the cerebral vasculature.(6)

Several cases that have had PRES with normal blood pressure have been reported.(7) Several other etiologies have been found in these patients. Immunosuppressive agents could break down the blood-brain barrier which causes vasogenic oedema. (8) PRES as the first presentation of an underlying autoimmune disease has been reported previously. (9)

Since our patient had both clinical and serological evidence of a connective tissue disease but did not meet the classification criteria for a connective tissue disorder, an undifferentiated connective tissue disease (UCTD) was suspected. However, she would need to be closely followed up for the development of features suggestive of defined connective tissue disease.

PRES should be managed with immediate control of blood pressure and the management of secondary causes. Although corticosteroids may reduce vasogenic oedema, they have no proven benefit in PRES.(10)

PRES may be the first clinical manifestation of an underlying connective tissue disease. This makes recognition of autoimmune diseases as a cause of PRES very crucial. This patient is unique as she had typical clinical and radiological features suggestive of PRES but had a close to normal blood pressure on admission and minimal fluctuations of blood pressure afterwards. She also had early signs of an evolving connective tissue disorder which was supported serologically. Although PRES can occur with established connective tissue disorders, it being the first presentation of an evolving connective tissue disorder is rare.

Conclusion

Posterior Reversible Encephalopathy Syndrome should be suspected in patients with acute onset headache, seizures and loss of vision and confirmed by neuroimaging. Although many secondary causes have been identified, the primary focus of the treating physician is to control the patient's blood pressure to ensure the prevention of persisting neurological damage. This case report highlights the importance of considering PRES amongst patients with minimal blood pressure fluctuations. It also highlights the need for clinical evaluation to exclude secondary causes of PRES in every patient as it may be the first presentation of an underlying connective tissue disorder.

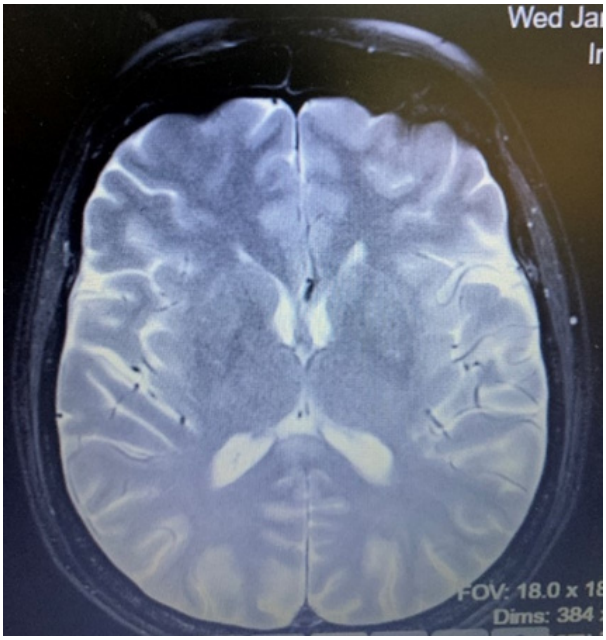

Figure 2 - MRI brain showing multiple focal T2 FLAIR high signal intensities in the bilateral occipital lobes, parietal lobes and frontal lobes

Declarations

Conflicts of interest
None

Consent for publication
Informed written consent was obtained from the patient to publish details regarding the patient's condition including photographic evidence

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Delayed pulmonary embolism occurring six months after a mild COVID infection: A case report

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Abstract

Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) is a globally impactful disease. Venous Thromboembolism (VTE), particularly pulmonary embolism is common in the acute stages. Occurrence after initial recovery remains rare. We report a 43-year-old man who was admitted following acute onset shortness of breath six months after mild SARS-CoV-2 infection. Computed Tomography Pulmonary Angiogram revealed a bilateral pulmonary embolism. No other risk factors for VTE were identified. This case report raises concern over a persistent pro-coagulopathy state caused by the SARS-Cov-2 virus even after recovering from the initial infection.

Key words: Pulmonary embolism, Pulmonary embolus, SARS-CoV-2

Introduction

COVID-19 is an infection caused by Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2). It made a significant global impact and caused significant morbidity and mortality all over the world.

Significant cardiovascular and respiratory complications have been reported to be associated with this infection.(1) Arterial and venous thrombosis have been reported with the latter being more common.(2) Increased frequency of complications was noted amongst patients receiving intensive care for Acute Respiratory Distress Syndrome (ARDS). Delayed pulmonary embolism following discharge amongst patients with moderate COVID-19 pneumonia, and not receiving intensive care, have only been occasionally reported.(3)

This case is unique in that the patient had only a mild infection managed at home. He then developed a bilateral pulmonary embolism almost six months later, leading to a cardio-respiratory arrest.

Case presentation

A 43-year-old previously healthy man presented with a sudden onset of severe shortness of breath. Following admission, he developed a cardio-respiratory arrest and underwent cardiopulmonary resuscitation. Return of spontaneous circulation was observed after five minutes. His post-arrest period was uneventful.

Retrospective history revealed that he had a SARS-CoV-2 infection six months back which had been confirmed using an oropharyngeal swab for PCR. He had no other significant past medical or surgical history. He had no history of prolonged immobility or trauma. He was unvaccinated for SARS-CoV-2.

After resuscitation, he was still tachypneic with a saturation of 93% on air. His blood pressure was 120/70 mmHg and he had a pulse rate of 110 bpm which was regular.

His blood investigations are listed in table 1.

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Table 1 - Summary of investigations

	Test	Result	Reference range
Full Blood Count	RBC	4.84×10^9/L	(3.80–4.80)
	Hb	14.9 g/dL	(11.8-14.8)
	Platelets	256×10^9/L	(150–400)
Biochemical parameters	D-dimer	1560 mg/dL	(<500)
	Highly sensitive Troponin I	0.012 ng/dL	(0.000–0.034)
	C-reactive protein	11.2 mg/dL	(<6)
	ESR	36 mm/1st hour	(<20)
	Partial thromboplastin time	33 sec	(30–40)
	Prothrombin time	10.6 sec	(10-14)
Arterial Blood Gas Analysis	pO2	75 mmHg	75-100
	pCO2	25 mmHg	35-45
	pH	7.47	7.35-7.45
	O2 saturation	91 %	
Occult cancer markers	Carcinoembryonic antigen	2.49	(0.0–5.0)
	Cancer antigen 19-9	7.8	(0.0–37.0)
	Alpha-fetoprotein	4.5	(<8.78)
	PSA	0.12	(<2.5)
Thrombophilia markers	Antithrombin III	96	(80–120)
	Factor V Leiden	Absent	
	Anti β2 GPI antibodies	Absent	
	Anticardiolipin antibodies	Absent	
	Lupus anticoagulant	Absent	
	Protein S	85	(75–130)
	Protein C	82	(70–140)

His chest X-ray was normal. ECG showed an "S1Q3T3" pattern with sinus tachycardia. Arterial Blood Gas revealed respiratory alkalosis. His Wells score for pulmonary embolism was 4.5. He underwent a CTPA which showed pulmonary embolism in bilateral second-order branching pulmonary arteries with small wedge infarcts in bilateral lower lobes (Figure 1). Bilateral lower limb Duplex scan was negative for Deep Vein Thrombi. Trans thoracic echo was normal with no right atrial or right ventricular dilation. There was no evidence of pulmonary hypertension. Tumour markers for occult malignancy were negative. He underwent a full body contrast-enhanced CT scan that revealed no malignancies. The thrombophilia screening done 3 months later was negative. His COVID antibodies were positive with a SARS-CoV-2 total antibody titre >45 (Reactive). Oropharyngeal and nasopharyngeal swab PCR for SARS-CoV-2 were negative.

He was treated with therapeutic doses of subcutaneous enoxaparin 1mg/kg twice a day. Warfarin too was started and adjusted to maintain INR between 2-3. He had satisfactory resolution of symptoms. He had a good follow up and warfarin was continued for 6 months and then stopped. He had no further complications of significance during the follow-up.

Discussion

There is sufficient data worldwide to support that SARS-CoV-2 could predispose patients to increased venous and arterial thrombosis.(4) Literature review reveals the incidence of pulmonary embolism up to 16.7% amongst patients managed for ARDS in certain studies.(5) Another study showed a 67% prevalence of peripheral VTE on screening duplex ultrasounds in 26 intensive care unit patients.(6)

Most of the studies show that VTE is prevalent in critically ill patients during the acute stage of infection.(7) In the few occasions that it has occurred in patients with mild SARS-CoV-2, the onset was within a few days after discharge.(8) Almost all reports of VTE were in the first 4 weeks following clearance of SARS-CoV-2.(9) Occurrences after the first 4 weeks were rarely encountered during the literature review.

Several theories have been postulated regarding the pro-thrombotic state of SARS-CoV-2 infection. Severe inflammation, endothelial dysfunction and stasis are possibilities.(7) Embolism of larger vessels is presumably due to inflammation, hypercoagulability and venous stasis in poorly mobilised patients.

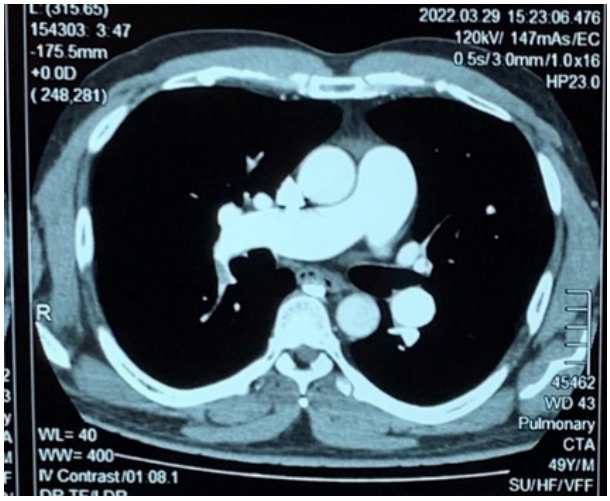

Figure 1 - Computed tomography pulmonary angiogram with arrow pointing to pulmonary embolus

This patient had residual systemic inflammation which was evident by the high inflammatory markers six months after the infection. This could explain the reason behind his prothrombotic state. Other immune-mediated diseases including myasthenia gravis (10) and autoimmune myocarditis (11) have been reported to occur late after SARS-CoV-2 infection.

Conclusion

SARS-CoV-2 infection both active and past should be considered a risk factor for both arterial and venous thrombosis. This case report highlights that an inflammatory state leading to a prothrombotic state may persist for as long as six months following infection with SARS-CoV-2. Thus clinicians should be aware that patients following covid infections could be at an increased risk of thromboembolic conditions.

Declarations

Conflicts of interest
None

Consent for publication
Informed written consent was obtained from the patient to publish details regarding the patient's condition including photographic evidence

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Recurrent Kounis syndrome due to amoxicillin: A case report

Soysa WLM[1]*, Sivagnanam FG[1]

Abstract

Kounis syndrome is the occurrence of acute coronary syndrome during an allergic reaction. It is thought to be due to mast cell activation and degranulation leading to coronary vasospasm. A 60-year-old gentleman presented with a cutaneous allergic reaction associated with tightening left-sided chest pain. This occurred 5 minutes after taking Amoxicillin. There were dynamic ECG changes with rising Troponin I. He had a similar episode following Amoxicillin four years ago. This case report highlights the importance of identifying Kounis Syndrome as an important differential diagnosis among patients presenting with chest pain.

Key words: Kounis syndrome, coronary vasospasm, acute coronary syndrome, anaphylaxis to amoxicillin

Introduction

Kounis Syndrome has been described as the occurrence of acute coronary syndrome during allergies, hypersensitivity, and anaphylactic or anaphylactoid insults.(1) Allergic angina and allergic myocardial infarctions, which are all associated with mast cell activation fall under the diagnosis of "Kounis Syndrome".(2) Three different mechanisms have been identified: Coronary vasospasm (Type 1), plaque erosion and rupture (Type 2) and stent thrombosis with histological infiltration by eosinophils and mast cells (Type 3).

Recognizing this syndrome as a separate clinical entity is crucial in clinical practice as its management differs from the standard management of acute coronary syndrome. Certain drugs used in acute coronary syndrome such as beta-blockers may be harmful in Kounis Syndrome.

This case report aims to highlight the importance of early recognition of this syndrome amongst patients presenting with chest pain, one of the commonest presentations to medical wards and emergency units.

This case report is unique in the fact that this patient had two episodes of allergic myocardial infarction due to the drug Amoxicillin. To the best of our knowledge recurrent acute coronary syndrome due to Kounis syndrome caused by the same agent is very limited in the literature.

Case presentation

A 60-year-old man presented with a sudden onset rash, swelling of face and lips and wheezing five minutes after taking amoxicillin for an infected wound. He also complained of severe tightening-type retrosternal chest pain. He is a smoker with a 17-pack-year history of smoking. His father died at the age of 65 due to acute coronary syndrome. He did not have hypertension, diabetes mellitus or dyslipidemia. He had a similar episode four years back, where he developed chest pain following an allergy to amoxicillin and was treated as an acute coronary syndrome.

On examination, he had facial and lip swelling with an erythematous maculopapular, pruritic rash over his face and arms. He had bilateral rhonchi on

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auscultation. His blood pressure was 90/60 mmHg and had a tachycardia of 110 bpm. Rest of the examination was unremarkable.

Initial ECG taken showed ST depressions in V1-V2, and subsequent ECG showed deepening T inversions from V1-V6 (Figure 1) This was before the administration of adrenaline. Troponin I was positive at 0.7 which was more than the 99th percentile. Subsequent 2D echo showed mild hypokinesia of the anterior wall with an EF of 50-55% and grade-I mitral regurgitation (MR).

A diagnosis of Kounis Syndrome was made with anaphylaxis to amoxicillin and concurrent allergic myocardial infarction (Non-ST elevation MI). He was managed for anaphylaxis.

The patient had an uneventful recovery. He was educated regarding his allergy to amoxicillin. The patient did not give consent for coronary angiogram.

Discussion

Kounis Syndrome was first described in 1991 by Kounis and Zavras. They described a disease entity among patients where there is an occurrence of chest pain during allergic reactions. Further clinical and laboratory findings of classical angina pectoris were observed in these patients. In 1995 Kovanen et al. published the results of a postmortem examination of 20 patients who died of myocardial infarction. Coronary artery specimens of these patients showed high levels of mast cell degranulation at the site of plaque rupture as compared to the adjacent or distant sites.(4) This raises significant concern that any allergic reaction can be a risk factor for plaque rupture.(5)

Various triggers have been reported to cause Kounis syndrome including drugs, food, and environmental agents such as insect and snake bites. Certain studies show that the most frequent drugs implicated are

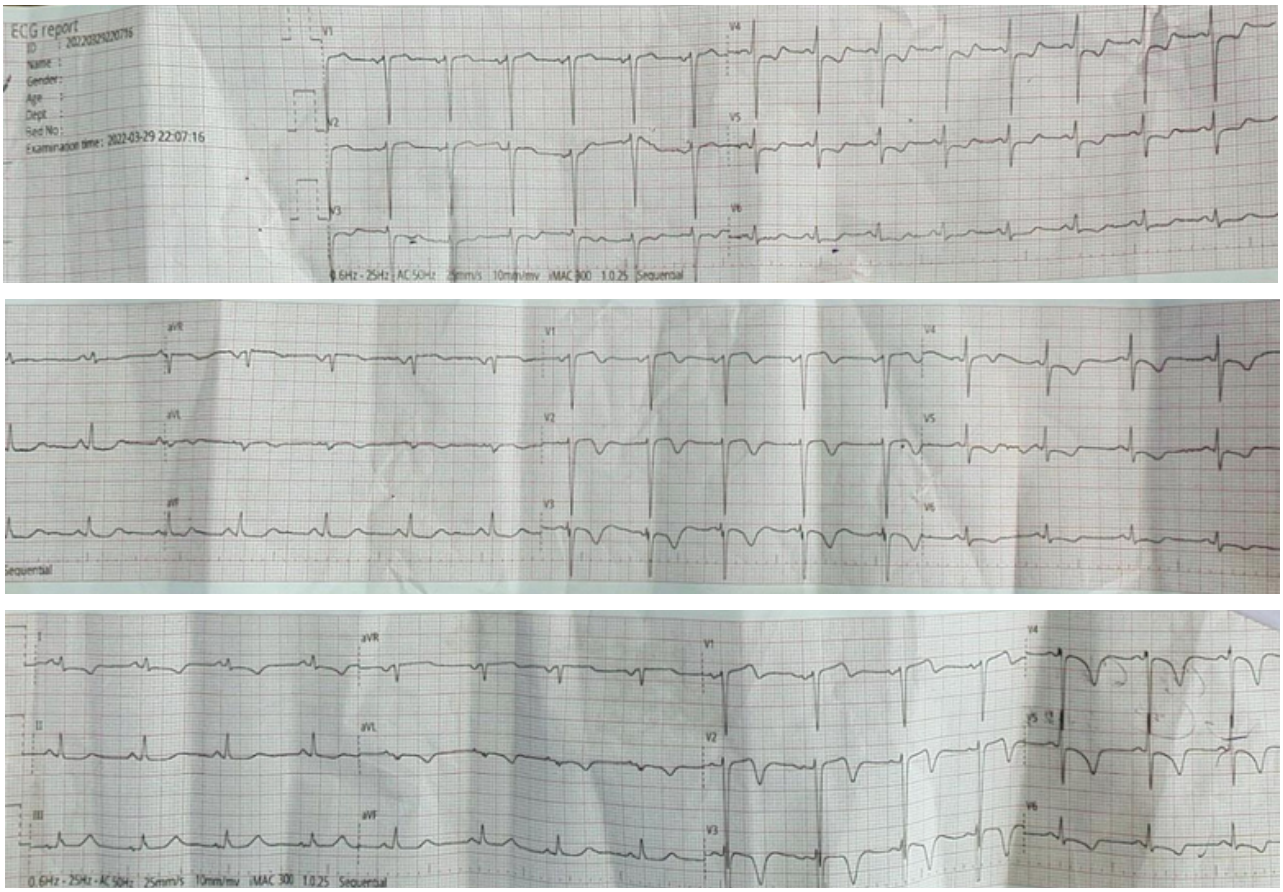

Figure 1 - Serial ECGs that were taken during admission every 15 minutes (in the order that they were taken from top to bottom).

nonsteroidal anti-inflammatory drugs (NSAID) (60.7%), drugs for cardiovascular disease (19.6%), antibiotics (17.6%), and anaesthetics (9.8%) (6,7,8) Amongst the antibiotics the commonest reported is amoxicillin/clavulanate.

Kounis syndrome can be diagnosed clinically based on a history of ischemic-type chest pain along with features of allergy following exposure to an allergen. It is thought to be due to the mast cell activation and degranulation which leads to inflammatory cascades and cytokine release which can trigger coronary vasospasm (Type 1), plaque erosion and rupture (Type 2) or stent thrombosis (Type 3), all leading to myocardial ischemia. Inflammatory mediators involved include histamine, tryptase and chymase.

Although the diagnosis is clinical, a coronary angiogram could be performed which is expected to show coronary artery vasospasm in the acute setting. Allergic reactions could be supported by high serum tryptase levels and eosinophilia in the blood. We did not perform tryptase levels as an obvious clinical diagnosis of anaphylaxis could be made in our patient with a history of allergy to amoxicillin. Eosinophilia was not observed in our patient.

Management will depend on the type of Kounis Syndrome. Type 1 will require only the management of the allergy/anaphylaxis while other types would additionally require the management as per regular acute coronary syndrome management guidelines with antiplatelets, statins and anticoagulation. Since an angiogram was not performed in the acute setting, we assumed the patient to have Type 2 Kounis syndrome due to multiple risk factors in this patient for coronary artery disease, such as age, smoking, and positive family history. We believed the patient had plaque erosion and rupture secondary to the allergic reaction.

There have been cases reported with acute coronary syndrome following adrenaline injection. This was thought to be unlikely as the patient was symptomatic with ECG changes before the administration of adrenaline. Secondly, only a therapeutic dose of adrenaline was used, which is unlikely to cause myocardial ischemia.

The literature review revealed multiple cases of Kounis syndrome reported from Sri Lanka.(9,10) However, to the best of our knowledge, this is the first case of recurrent Kounis syndrome with the same agent reported from Sri Lanka.

Conclusion

Kounis syndrome remains underdiagnosed in an emergency setting. This case report highlights the importance of emergency care doctors recognizing Kounis syndrome which is managed differently from standard management of acute coronary syndrome. It requires integration of the management of allergies/anaphylaxis with the management of acute coronary syndrome. It also highlights the need to add the management of Kounis syndrome to the management guidelines for acute coronary events.

Declarations

Conflicts of interest
None

Consent for publication
Informed written consent was obtained from the patient to publish details regarding the patient's condition including photographic evidence

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CASE REPORT

Autoimmune haemolytic anaemia secondary to COVID-19 infection presenting as anaemia-induced unstable angina

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Abstract

Autoimmune haemolytic anaemia (AIHA) is a condition characterised by antibody mediated haemolysis. COVID-19 infection has been associated with multiple extra pulmonary complications of autoimmune origin, including AIHA. We report a case of a 72-year-old man who presented with unstable angina induced by severe anaemia secondary to autoimmune haemolysis. His direct antiglobulin test was positive with IgG, C3d and IgM positivity denoting a mixed type AIHA. After exclusion of other known associations of AIHA, a possible diagnosis of COVID-19 infection presenting as mixed AIHA with severe symptomatic anaemia, was made. He was managed successfully with oral prednisolone and cautious blood transfusions.

Key words: Mixed autoimmune haemolytic anaemia, COVID-19, AIHA

Introduction

Autoimmune haemolytic anaemia (AIHA) is a condition characterised by autoantibodies directed against red blood cells causing extravascular or intravascular haemolysis. The reported global incidence is 1 to 3 per 100,000 / year. (1,2) AIHA can be divided into warm, cold, or mixed-type according to the type of autoantibodies present. Out of these, mixed-type accounts for 5% of all AIHA cases. (2) Nearly half of AIHA cases are primary, and the rest are secondary to another underlying disorder. COVID-19 infection, despite its primary target being the respiratory system, is known to cause a wide spectrum of extrapulmonary clinical manifestations. A considerable proportion of these manifestations has an underlying autoimmune process. One such rare association is AIHA. Here, we report a case of a 72-year-old man presenting with severe anaemia and anaemia-induced myocardial ischaemia following a mixed type AIHA in possible association with COVID-19 infection.

Case presentation

A 72-year-old man presented to medical casualty with acute onset constricting type central chest pain associated with nausea and sweating, lasting for approximately 30 minutes. This acute presentation was preceded by easy fatigability and exertional chest pain for four days. He gave a history of mild nonproductive cough and poor appetite during the past week. He denied any fever, and the rest of the systemic inquiry was unremarkable. His medical history included diabetes, stage 3 chronic kidney disease, dyslipidaemia and chronic coronary syndrome. He had undergone a coronary angiogram 12 years back which showed dual vessel disease with

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bridging collaterals. He was on optimum medical treatment at the time of evaluation. He was pale, mildly icteric, and haemodynamically stable. He was not in respiratory distress, and his lungs were clear on auscultation. He did not have hepatosplenomegaly or lymphadenopathy. Electrocardiograms showed partial right bundle branch block with inferior and lateral dynamic T inversions and ST segment depressions. Troponin levels were repeatedly negative. His initial blood investigations showed severe anaemia with a haemoglobin (Hb) level of 4.8 g/dL with an elevated mean corpuscular volume (MCV) of 102 fL. A diagnosis of anaemia-induced unstable angina was made, and the rest of the workup showed indirect hyperbilirubinaemia, elevated reticulocyte count and high LDH level supporting a haemolytic process with macrocytes and polychromasia in peripheral blood smear. The direct antiglobulin test (DAT) was positive, indicating an autoimmune aetiology. All 3 of IgG, C3d and IgM-cold-agglutinins were positive , further refining the diagnosis as mixed-type autoimmune haemolytic anaemia.

The results of the initial investigations are summarised in table 1.

Table 1 - Summary of initial investigations

Test	Result	Reference range
WBC	11240x10^6/L	4,500 - 10,000
Haemoglobin	4.8 g/dL	11-16
MCV	102 fL	80-100
MCH	32.2 pg	27-34
RDW	59.4 fL	35-56
Platelets	375,000 x10^6/L	150-450
Peripheral smear	Macrocytes with the appearance of granulocytic red cells and reduced RBC mass. neutrophilic leukocytosis with toxic changes. Platelets are normal.	
Reticulocyte count	18.69%	0.3-3.0
LDH	522 U/L	125-220
Total bilirubin	4.4 mg/dL	0-1.5
Direct bilirubin	1.0 mg/dL	0-0.2
AST	46 U/L	10-35
ALT	36 U/L	10-40
DAT and DAT profile	Positive with IgG, IgM and C3d positivity	
Serum creatinine	1.93 mg/dL	0.5-1.1
Chest x ray	Normal	
CRP	30 mg/L	< 5

WBC *- White blood cells,* ***MCV-*** *Mean corpuscular volume,* ***MCH-*** *Mean corpuscular haemoglobin,* ***RDW-*** *Red cell distribution width,* ***LDH*** *- Lactate dehydrogenase,* ***AST-*** *Aspartate transaminase,* ***ALT-*** *Alanine transaminase,* ***DAT-*** *Direct antiglobulin test*

Screening for causes of AIHA was done. He had a raised erythrocyte sedimentation rate (ESR) of 110 mm/ 1st hour. His anti-nuclear and anti-dsDNA antibodies were negative. The Contrast Enhanced CT chest, abdomen and pelvis showed no evidence of lymphoma. The peripheral blood smear was not suggestive of a haematological malignancy. Infections known to cause AIHA were screened for and hepatitis B, C, human immunodeficiency virus, epstein barr virus and mycoplasma infection were all negative. He denied any blood transfusions during the past three months and his medication did not reveal use of any drugs known to cause AIHA. As he complained of a mild cough and presented during the global pandemic of COVID-19 infection, we tested him for COVID. Even though his initial rapid antigen test was negative, the COVID PCR test became positive with a reactive COVID antibody titre suggestive of a recent infection. In the absence of other secondary causes and the clinical picture of mild cough followed by mixed-type AIHA, it was concluded that this was a case of mixed-type AIHA possibly secondary to COVID-19 infection.

He was transfused ABO, Rh and Kell compatible, indirect antiglobulin cross-matched, least incompatible leuko-depleted blood at 37°C. He was started on oral prednisolone 1mg/kg/day. His haemoglobin level gradually improved and stabilised at 9.7 g/dL over the next two weeks, followed by a reduction in indirect hyperbilirubinaemia and reticulocyte count. He was discharged on prednisolone and reviewed in 2 weeks, at which point he had a stable haemoglobin level.

Discussion

AIHA is diagnosed in the context of DAT positivity with ongoing haemolysis after excluding other alternatives. These include drug-induced haemolysis, recent blood transfusion within the past 3 months causing transfusion-related haemolysis, alloimmune haemolysis following organ or stem cell transplant and haemolytic disease of the newborn.(2) Warm AIHA is defined by the demonstration of DAT positivity for IgG alone or IgA + C3d, whereas cold agglutinin disease (CAD) is diagnosed by demonstrating the presence of a cold agglutinin, which is typically IgM.

Mixed-type AIHA is characterised by the presence of both a warm antibody and a cold agglutinin.(1,2) Our patient fulfilled all these criteria and was therefore diagnosed as mixed-type AIHA. Even in the presence of cold agglutinins, mixed AIHA does not typically show acrocyanosis or Raynaud's as in CAD.(2) The index patient lacked such symptoms. Mixed type has also been shown to cause more severe anaemia compared to other subtypes. In the GIMEMA study 63% of the severe anaemia cases were of mixed AIHA type.(3) This explains the degree of anaemia in our patient, which was severe enough to cause myocardial ischaemia.

As with other subtypes, mixed-type AIHA could be classified as primary or secondary. Shulman et al. described 144 patients with mixed-type AIHA, 50% of which were primary, whereas most secondary cases (42%) were associated with systemic lupus erythematosus (SLE).(4) One patient had mixed AIHA secondary to non-Hodgkin's lymphoma. In general, AIHA is known to be associated with other autoimmune conditions such as SLE, rheumatoid arthritis, autoimmune hepatitis, and scleroderma; infections such as EBV, hepatitis C, Hepatitis B, HIV, mycoplasma pneumonia and lymphoproliferative disorders such as chronic lymphocytic leukaemia or lymphoma.(1, 5, 6, 7) In our patient, we have excluded the above-known causes.

COVID-19 infection has been associated with multiple complications of autoimmune origin, such as Guillain-Barre syndrome, immune thrombocytopenia, vasculitis, autoimmune thyroid disease and AIHA. (8,9,10)

A systematic review described 50 cases of AIHA associated with COVID-19 infection, which appears to be a rare complication given the high disease prevalence.(11) However, it is important to recognise these patients early, as they reported a case fatality rate of 19%. Unlike other infections, which would typically predominantly cause one subtype of AIHA, COVID-19 infection was found to be associated with both cold (38%) and warm (28%) subtypes. Out of these 50 cases, only 3 showed mixed-type AIHA like our index patient. Most of these patients had one or more comorbidities, and only eleven patients had underlying lymphoproliferative disorders or other autoimmune conditions known to be AIHA triggers. (11) Lazarian et al. reported a case series of seven patients with COVID-19-associated AIHA.(12) Most of these patients had either moderate or severe disease. Authors observed that the onset of AIHA is compatible with the timing of cytokine storm, which may explain the pathophysiology behind the emergence of autoantibodies.(12) The proposed pathophysiology behind the occurrence of AIHA in COVID includes hyper stimulated immune response triggering autoimmunity and molecular mimicry.(13)

Treatment of AIHA consists of transfusions with least

incompatible blood for severe anaemia, immunosuppression, and treatment of the underlying disorder in secondary cases. In cases of mixed AIHA, caution must be taken to transfuse rewarmed blood at a temperature close to 37°C to avoid precipitating further haemolysis.

Management of mixed-type AIHA includes avoidance of cold exposure and glucocorticoids as first-line therapy, with good response rates to initial treatment. However, they typically progress to a chronic course with relapses. Second-line therapy recommended for mixed-type AIHA is similar to that of warm AIHA.(2) Rituximab is also now recommended as initial therapy as an adjunct to steroids or as a single agent by itself.(14)

Majority of the reported AIHA cases associated with COVID-19 have been treated with corticosteroids with good treatment response. In more severely ill patients, IVIG has been used as initial treatment in some case reports. Plasma exchange and rituximab have also been used as other treatment options. (11,15) Our patient responded well to initial treatment with oral prednisone reaching a haemoglobin target of 10 g/dL within one month.

Conclusion

Mixed-type AIHA is a rare complication associated with COVID-19 infection. It is important to beware of this condition as it can cause life-threatening haemolysis. Most such cases can be successfully treated with cautious blood transfusions and glucocorticoid therapy.

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Diabetic hand syndrome with scleredema diabeticorum, sclerodactyly and Dupuytren contractures

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A 57-year-old woman with poorly controlled hyperglycaemia (HbA1c of 8%) was admitted for glycemic control. She has had diabetes for 22 years with several micro and macro vascular complications. She had thickening of dorsum of her hands and fingers(sclerodactyly) with limitation of finger flexion. There were tapering of few fingers, indurated, waxy skin overlying the digits, Dupuytren contractures and healed scars from past bullous diabeticorum (Figure 1). Thickening of the skin of upper anterior chest wall (Scleredema) was noted (Figure 1). The history did not reveal any Raynaud phenomenon or inflammatory arthropathy. The other clinical features to suggest systemic sclerosis such as telangiectasia, calcinosis, speckled leucoderma were absent. There was normal nail fold capillaroscopy, and normal autoimmune markers which made the diagnosis of systemic sclerosis unlikely.

Diabetic hand syndrome, which is seen in longstanding poorly controlled diabetes, is a clinical entity characterized by several musculoskeletal and cutaneous manifestations including diabetic cheiroarthropathy, flexor tenosynovitis, Dupuytren contractures, diabetic sclerodactyly, carpal tunnel syndrome and Charcot (neuropathic) arthropathy.(1) Glycosylation of connective tissue proteins, microvascular injury, microvascular peripheral nerve damage, collagen deposition in cutaneous and periarticular structures are contributive.(1) The condition is an important cause of progressive deformity, disability, pain, poor quality of life of diabetic patients.(2) Potent topical and intralesional glucocorticoids, strict glycaemic control, low-dose methotrexate, prostaglandin E, colchicine, dimethyl sulfoxide, aminobenzoate and physiotherapy have been considered as potential management options. (3)

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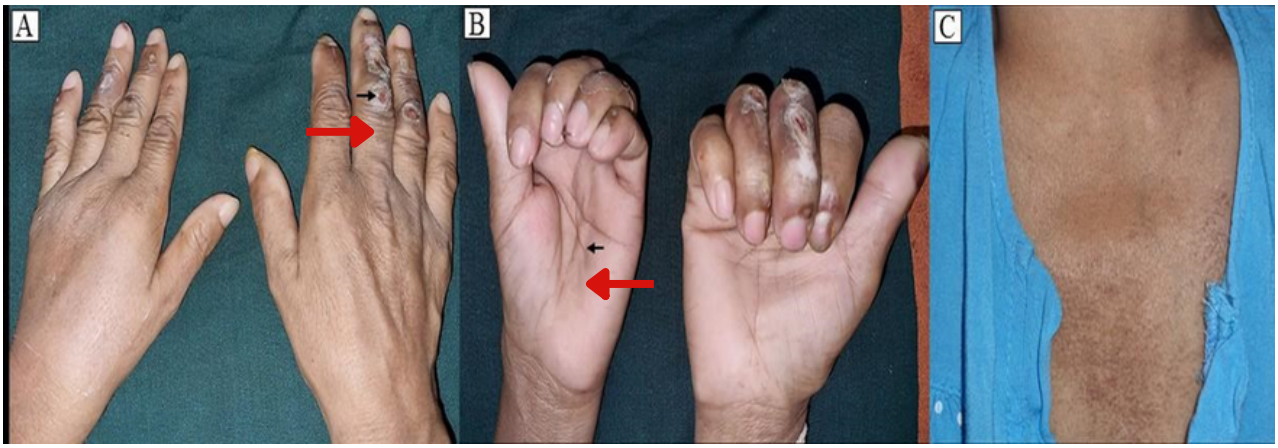

Figure 1 - **Panel A:** dorsum of hand with indurated waxy skin of digits, sclerodactyly and healed bullous diabeticorum (arrow); **Panel B:** sclerodactyly, tapering of fingers, limitation of finger flexion and Dupuytren contracture (arrow); **Panel C:** induration of skin of upper chest (diabetic scleredema)

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(1) Answer: D - Ice pack test

Picture A shows bilateral ptosis and picture B shows improvement of ptosis. Ice pack test is a popular bedside test carried out in suspected Myasthenia gravis to see the improvement of ptosis. Water on the face in picture B is evidence that the ice pack test is the test performed in this case.

(2) Answer: D - Tuberous sclerosis

The picture shows evidence of adenoma sebaceum and a shagreen patch on her face. The MRI shows a giant cell astrocytoma which is a benign tumour seen almost exclusively in young patients with tuberous sclerosis.

(3) Answer: B - Scleromyxedema

Scleromyxedema is a rare cutaneous mucinosis. It is characterised by symmetrical eruption of shiny firm papules and the papules may evolve to hardened plaques. Many other extracutaneous manifestations including cardiac, gastrointestinal and musculoskeletal are possible. Dysphagia is due to esophageal dysmotility. Paraproteinemia is associated with over 80% of patients.

(4) Answer: C -Bronchial carcinoma with multiple hepatic metastasis

The contrast CT scan of chest and abdomen show evidence of bronchial carcinoma with multiple liver secondaries. The appearances are not typical of abscesses (typical appearance of liver abscess includes hypodense mass with enhanced peripheral rim or capsule). Right sided infective endocarditis causes multiple lung abscesses.

(5) Answer: A -Bronchiectasis with superadded infection

Cystic bronchiectasis is shown in the image. Superadded infection is evident with the history of fever and appearance of air fluid levels. Tuberculosis needs to be excluded in this case.

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