VOLUME 4 | ISSUE 1

PRAXIS

UNDERGRADUATE MEDICAL RESEARCH JOURNAL

A Publication of
STUDENTS' SCIENTIFIC SOCIETY
of Armed Forces Medical College, Pune

PRAXIS

UNDERGRADUATE MEDICAL RESEARCH JOURNAL

VOLUME 4 | ISSUE 1

A Publication of
STUDENTS' SCIENTIFIC SOCIETY
of Armed Forces Medical College, Pune

PRAXIS
UNDERGRADUATE MEDICAL RESEARCH JOURNAL

Editorial Board

PRAXIS
UNDERGRADUATE MEDICAL RESEARCH JOURNAL

Index

PRAXIS
UNDERGRADUATE MEDICAL RESEARCH JOURNAL

EDITORIAL

Emerging and Re-emerging vector borne diseases

AVM Rajesh Vaidya[a] VSM

[a]Dean & Deputy Commandant, Armed Forces Medical College, Pune

The spectrum of infectious diseases is changing rapidly in conjunction with dramatic socioeconomic and ecological changes. There have been considerable advancements in achieving global goals, however, newer emerging and re-emerging infectious diseases pose a serious question as to our approach and the way ahead to tackle them. While emerging infectious disease are those whose incidence have increased in the last two decades or threatens to do so in the near future, re-emerging infections are those that have shown resurgence after a period of decline. These diseases impose an important global burden on public health, increasing health inequalities more so in tropical and subtropical countries like ours. [1]

Vector-borne emerging and re-emerging infections constitute a major public health concern. It is a known fact that not all vectors have equal significance with respect to disease transmission. Some vectors have had relatively more impacts than others, an aspect epitomized by mosquito-borne new and old diseases such as malaria, dengue, chikungunya, Zika virus, West Nile fever virus, Crimean-Congo hemorrhagic fever, Yellow fever, Japanese encephalitis etc. Among all, malaria and dengue have an enormous public health concern in Asia and Africa. There have been reports of altitudinal shift in incidence of malaria with the illness occurring more in higher altitudes at Ethiopia and Columbia during the warmer seasons. [2,3]

The effect of interaction between the changing vector ecology, pathogen evolution and human transmigration driving the emergence of disease is exemplified by dengue. There is an indication of increasing trends on epidemiological studies in endemic countries. Threatening nearly half a billion people worldwide, dengue has emerged as the most rapidly progressing arboviral illness. [4,5]

Chikungunya has gained new anthropophilic vectors and has been introduced in newer localities The several epidemics in the continents of Africa and Asia, particularly India has raised serious public health concerns. [6]

Vector-borne zoonotic diseases as compared to, as compared to directly transmitted ones are emerging at an alarming rate. Though the vector-borne illnesses form about 14% of infectious diseases in humans, the vector-borne zoonotic diseases account for a disproportionate 22% of the newly arising human diseases. Studies reveal that 60-80% of the newly arising infections have zoonotic origins with reservoirs in animals. [7]

With recent events across the world the burning question remains, why are these vectors borne diseases on a rise again. It is a complex interplay of multiple factors at ecological and population level. Global concerns of rapid population growth leading to uncontrolled urbanization, rampant poverty all are fertile breeding grounds for vector borne diseases. Ironically, the growing trade and tourism also enhances the potential for spread of newer diseases. Mutation in newer pathogens combined with vector resistance to insecticides provide newer pathways for maintenance of these. Also, one of the most important factors is the low priority and support given to preventive and public health services in many countries.

The uncertainty of introduction and propagation of emerging vector borne diseases will always be there. The only way a country can tackle this is to recognize them early and take rapid control and preventive measures. Strengthening national capability in the form of better epidemiological sciences and investment on public health. Intersectoral collaboration on a sociopolitical level such as health ministry with urban development, education, agriculture etc. will lead to better health policies. Rapid flow of disease surveillance and other relevant data from endemic countries will enable everyone to be better prepared and control an emerging disease. Role of private sector and NGOs in providing advanced services and education is the need of the hour.

With the rapid advancement of technology and access to literature, numerous emerging, re-emerging and stable vector borne diseases are better managed but the future efforts on blocking emergence of new diseases is uncertain. And this should be our cue to anticipate an uninterrupted fight with emerging vector borne diseases. Strengthening active surveillance techniques, timely and accurate diagnosis and effective case management has been of paramount significance. Molecular diagnostic techniques like whole genome sequencing and studies tracing the phylogenetic evolution can play a decisive part in precisely identifying the novel pathogens. [8]

References

1. Gubler DJ. The global threat of emergent/re-emergent vector-borne diseases. In: Atkinson PW, editors. Vector Biology, Ecology and Control. Dordrecht: Springer (2010).

2. Wilder-Smith A, Gubler DJ. Geographic expansion of dengue: the impact of international travel. Med Clin North Am. (2008) 92:1337–90.

3. Lambrechts L, Scott TW, Gubler DJ. Consequences of the expanding global distribution of Aedes albopictus for dengue virus transmission. PLoS Negl Trop Dis. (2010) 4:e646.

4. Bhatt S, Gething PW, Brady OJ, Messina JP, Farlow AW, Moyes CL, et al. The global distribution and burden of dengue. Nature. (2013) 496:504–7.

5. Brady OJ, Smith DL, Scott TW, Hay SI. Dengue disease outbreak definitions are implicitly variable. Epidemics. (2015) 11:92–102.

6. Burt FJ, Chen W, Miner JJ, Lenschow DJ, Merits A, Schnettler E. et al. Chikungunya virus: an update on the biology and pathogenesis of this emerging pathogen. Lancet Infect Dis. (2017) 17:e107–17.

7. Jones KE, Patel NG, Levy MA, Storeygard A, Balk D, Gittleman JL, et al. Global trends in emerging infectious diseases. Nature. (2008) 451:990–3.

8. Rabaan AA, Al-Ahmed SH, Sah R, Al-Tawfiq JA, Haque S, Harapan H, et al. Genomic epidemiology and recent update on nucleic acid- based diagnostics for COVID-19. Curr Trop Med Rep. (2020)

PRAXIS
UNDERGRADUATE MEDICAL RESEARCH JOURNAL

PERSPECTIVE ARTICLE

Silencing the Echoes...

Col (Dr) Jyoti Prakash[a]

[a]MD, MAMS, PGDM, PGDCA, PDC Child Psy, WHO Fellow (Johns Hopkins)

We are missing something...

This frequently happens in our practice. Over the years we have evolved professionally. From being mechanistic to humanistic. From 'seeing a person with a disease' to 'visualizing the person who has the disease'. We start thinking with feelings. Some call it a 'gut feeling'.

It was not adding up. Rohit was 18 years old. For the last two years, he had been having acute episodes of palpitation associated with anxiety, shortness of breath, and a choking sensation in the throat. He was initially shown to a physician who ruled out any organic etiology for his symptoms and referred him to us.

This is the reinforced myth still prevalent in medical science - that any sign or symptom for which we are unable to find any evidence with the available investigations, is non-organic and functional in nature. As if the mind were a separate entity from the brain and the body. Function exists without a structure. I don't foresee a day in the future when we can take the mind out from the brain, point out the pathology there and say, “that’s what I was saying...not organic”.

Well, we have to accept this myth. ICD 10 also believes it, and classifies accordingly.

Coming to Rohit… the symptoms were suggestive of panic attacks but he did not ascribe any specific reason/background for the same. The Resident had been meticulous. She had covered all facets of assessments based on the proforma they are regularly grilled on, and had come out content with a provisional diagnosis of panic disorder. But something was missing….

We are dealing with science here, however abstract it may be. We might not establish a cause-and-effect association but there needs to be a logic or rationale for the symptoms. There has to be a background in which these symptoms develop. Even chaos has an order.

“But Sir, I have asked him everything. He denies any stressor or problem on the socio-academic front”.

Let’s make the discussion less structured and more informal. Go with the story as he describes it. More open-ended questions. Let it flow. Let’s not ask, “What was the problem?”. Let’s ask him, “What could possibly have caused it? What was going on in the background? Anything not to his liking?”. A free conversation often helps people open up; when Rohit developed rapport, his subsequent narrative verified the extent of certainty in this fact.

Rapport has been a grossly mis-utilized word in psychiatry. Some perceive it as 'how systematically one has derived history as per existing protocol/proforma', others understand it as 'how friendly one has become'. This process of easing the communication between therapist and patient for fruitful exchange of information for a holistic intervention, is often underappreciated. But, like a reading glass, when used effectively, this also brings much more clarity to what earlier appeared as a blur.

"Let us call him", said I. Rohit came in, and we exchanged greetings. We talked about his life and his family members in general. I could see a gradual development of comfort in communication. He was able to communicate freely, but whenever he looked sideways to the Resident, I noticed him to be hesitant in conversation. I perceived there was some issue in the background, which probably was gender related, and he was embarrassed to talk.

Elicitation and appreciation of gender-specific cultural issues comes with experience. It was difficult for me too, initially.

I proceeded further with open-ended questions. During the course of the interview, I could see him developing further comfort in the conversation. He was talking more freely, even in the presence of the lady doctor, who by now was declared by his amenable mind to be a gender-neutral part of the whole team, led by me.

...and then we found out what was missing.

"Schoolmates used to make fun of me."

Elicitation is like straightening out a ball of wool. If you find one end of the thread, you can easily unfold the rest. With a nonjudgmental expression and unequivocal compassion, I gave a non-verbal empathic nod… "go on". He let it all out as if he were waiting for this moment to happen.

He had achieved puberty late and appeared less masculine than his contemporaries. While community bathing at a riverside picnic, he was made fun of by some classmate, for having a smaller symbol of masculinity. This became the talk of the class for a few days. The notion of reduced masculinity was ascribed to his every act, the way he walked… or talked.

For an adolescent, nothing is more adversely impacting than being doubted about his sexual readiness, right when he is venturing into adulthood. The whole process of life gets compromised, be it intimacy with the opposite gender, marriage, or procreation. The biochemical upheaval which goes on during the adolescent process adds further fuel to the insult.

Following one of these ridiculing episodes, with these thoughts in mind, he felt uncomfortable, suffocated and there it happened - a panic attack.

It was all clear. He also felt relieved after this ventilation of emotion. Many of our diagnostic conversations were therapeutic too. Sky was clearer. Road ahead looked better. We had found what was missing - the context. We had **"understood the person who had the illness"**.

It is always difficult to lay bare a person and visualize the malady in all its clarity. But if done so, the repair has always been easy. Years of experience, by now, have made this almost like a reflex to me.

I started with universalization. "Well, Rohit, though your experience is unique, it does happen to many an adolescent at your age. Let me start with the biology of…"

PRAXIS
UNDERGRADUATE MEDICAL RESEARCH JOURNAL

ORIGINAL ARTICLE

Exploring the knowledge and acceptance of reputed Authorship Criteria: A Pilot Study among medical researchers in India

Bhavik Bansal[a]

[a]Medical Student, All India Institute of Medical Sciences, New Delhi

Article Info

Article History:
Received: 29 June 2022
Accepted: 01 September 2022
Available: 18 November 2022

Keywords:
Research Ethics
Authorship
Honorary Authorship
Guest Authorship

bansalbhavik@aiims.edu
(Bhavik Bansal)

Abstract

Objectives: To determine knowledge and acceptance of authorship criteria among residents, PhD scholars and faculty involved in medical research in India.
Design: A cross sectional survey was performed via Google forms (a web-based platform).

Results: A total of 117 participants responded to the survey, of whom 66 (56%) were faculty/professors, 23 (20%) residents and 28 (24%) PhD scholars. 33% respondents had faced conflicts with their guide, 58% respondents have offered honorary authorship sometime in their careers. Only half of the respondents were aware of the ICMJE guidelines for authorship.

Conclusions: Gift Authorship and 'pressure to publish' are largely prevalent in bio medical research in India. Journals requiring author-contribution declarations, overlooking the number of publications as the sole source of offering academic promotions among others, are possible solutions to curb this problem.

Introduction

Research presents as a tool to add to the existing knowledge on any topic. A research report is a free communication by a scientist or a group of scientists informing their peers about a set of novel findings that either provide answers to puzzling problems or raise issues that are of academic or practical interest.

However, recently the idea of publishing papers has come to be driven by the increased chances of getting hired and getting academic promotions rather than the will to add to science itself. In medical research these days, the line between a credit-worthy contribution and the 'honor' of being a co-author is starting to fade. Institutional medical research in developing countries like India is seeing a rise in the tendency among authors to award authorship as a measure of one's respect towards a colleague (here, called a 'Guest Author'). The work of such a guest author is referred to as 'Honorary Authorship'.

As 'authorship' becomes a more sought-after tag, published papers are seeing an increase in the list of authors and hence the increasing prevalence of "honorary authorship" in recent years.1 The act of offering gift authorship is even more common among junior authors,2 who are commonly seen appending the name of the head of their labs/departments as co-authors on their papers for getting the required funds for their project and/or getting access to research subjects.

In addition to awarding authorship to a renowned name in the field to garner credibility, if the real contributors behind the work are hidden which may or may not be to prevent an impending conflict of interest, the scientific community is left with a lack of information behind this 'Ghost Author's' affiliations and ulterior motives. This practice is often called 'Omitted authorship'.3,4 The debate over order of authors as well as responsibilities too has drawn attention of many.

In this paper we have focused on the prevalence of malpractices surrounding authorship, and have tried to dig deep into the reasons for the same while evaluating factors that could possibly lead to it.

ICMJE guidelines

The International Committee of Medical Journal Editors (ICMJE) defines an author as an individual who has made substantial intellectual contributions to a scientific investigation and fulfills the following criteria:

1. *Substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work (Scholarship); AND*
2. *Drafting the work or revising it critically for important intellectual content (Authorship); AND*
3. *Final approval of the version to be published (Approval); AND*
4. *Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved (Agreement).*

In addition to being accountable for the parts of the work he or she has done, an author should be able to identify which co-authors are responsible for specific other parts of the work and have confidence in the integrity of the contributions of their co-authors.

As per the guidelines, those who do not meet the aforementioned criteria must be acknowledged in a separate section.[5]

Review of Literature

Authorship fraud is the most prevalent of research frauds, among others such as data fabrication, plagiarism, data falsification, authorship fraud, publication fraud, and grant fraud.6 A prevalence of honorary authorship ranging from 4% - 74% across various article types and high impact journals has been reported in literature.[7-10]

Gift authorship is often justified against the background of professional relationships that may have existed in the past or happen to exist in the present. It's not uncommon to find seniors or colleagues from the same department getting listed as co-authors on a paper.[11] Consequently, negative collaborative experiences are less commonly reported when the collaborators are from different universities as compared to those from the same university.[12]

The first author may find it harmless to offer authorship as they shall still bear the tag of being the first author while also looking self-righteous when all it would take is to add another name in the byline.[13] Authorship gifting behaviors may even arise out of career building reasons which continually impose a pressure to publish, colloquially called the 'Publish or Perish' principle. Order of authorship could only seldom predict the nature of contribution in papers published in leading biomedical journals.[15]

The fraction of articles, across various article types and study settings, with all co-authors fulfilling the ICMJE guidelines has been found to range between 64% - 68% in literature.[16-19] Self- reported awareness of the ICMJE guidelines was found to vary from 40% to 81.4%.[11,18,20-22] Even among the significantly small proportion of people who are able to specify all the three criteria, hardly few know that all criteria have to be met.[22,23] Among those who are not fully aware of the ICMJE guidelines, Statement 1 ("Substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work") was agreed to be a part of the ICMJE criteria and Statement 3 ("the final approval of the manuscript version to be submitted for publication is required for authorship") is least thought of as being a part of the criteria.[24]

Aims & Objectives

Primary Objective

1. To determine the prevalence of honorary authorship self-reported by medical researchers in India, separately for faculty, PhD scholars and residents.
2. To determine the prevalence of conflicts among co-authors and the principal investigator regarding authorship order
3. and/or inclusion.
4. To determine the awareness about reputed guidelines for author selection, like the ICMJE guidelines.

Secondary Objective

1. To gauge the broader reasons people believe it is justified to offer honorary authorship.
2. To determine if a correlation exists between education abroad with knowledge and acceptance towards good authorship selection practices.
3. To determine if a correlation exists between formal research ethics training with knowledge and acceptance towards good authorship selection practices.

Materials & Methods

The questionnaire was formulated after thorough literature review and consultation from relevant anonymized stakeholders - 2 Heads of Department (one in clinical and one in pre-clinical departments), 3 faculty, 3 residents and 3 PhD students. All these stakeholders rated the pooled questions based on relevance and clarity, questions with an average relevance score below 80% were dropped, and questions with sub-optimal clarity scores were rephrased in consultation with these stakeholders.

Section 1 of the questionnaire is related to demographic details of the respondent, which are anonymized, but identifies the respondent based on his/her experience in research. Section 2 builds more on prior experiences, including exposure to authorship guidelines, formal training in research ethics and part of education being abroad (defined as training lasting more than 6 months amenable to certification).

Section 3 focuses on the knowledge and views among respondents regarding currently accepted authorship guidelines. It comprises a 10-questions Likert type questionnaire asking for opinions on statements prevalent as myths regarding authorship guidelines. Each respondent is given a score between +10 and -10

(it has been called the Section 3 score in the manuscript) based on their (dis)agreement to a particular question. These scores are then analyzed in context of their demographics and prior experiences.

A web-based platform called Google Forms was used to gather data from the questionnaire. The data was collected over July-August 2021. The link to the form was disseminated through relevant groups, forums and mailing lists. The participants filled the form in an anonymized fashion, and therefore follow-up could not be performed. The sampling was performed through a convenience-based methodology. A sample size couldn't be calculated a priori as this study was a pilot study among this target population.

Results

Sample Characteristics
The study included 117 participants of whom 66 (56%) were faculty/professors, 23 (20%) residents and 28 (24%) PhD scholars. Faculty who responded to the questionnaire had a median experience of 14.5 years, and a median of 41.5 publications till date with 26% (n=17) having received formal training abroad, while residents and PhD scholars had more than a median experience of 5 years, and more than a median of 4 publications. (Table 1.1)

Authorship
33% respondents had faced conflicts with their guide regarding inclusion or order of co-authorship. 58% responders including 35 (53%) faculty, 14 (61%) residents and 19 (68%) PhDs admitted to having offered honorary authorship (Table 1.2) out of several reasons viz. seeking a proofreading from the person concerned as they are more experienced (n=67), as a token of respect/legacy (n=54), it kept the team motivated and helped maintain good relations (n= 48), the probability of publishing increased (n= 38), they bring funding for the research and more opportunities to the table (n=21), felt a pressure to publish (n= 15). (Table 2)

On being questioned on their current knowledge of authorship criteria and ICMJE guidelines, only 50% were fully aware of the ICMJE guidelines while the rest were either not aware they existed (24%) or had not read them (26%). Only 53% of the responders had had formal training on research ethics. (Table 1.3) Mentors/ guides were the source of information regarding authorship guidelines and research ethics for 43 (37%) of the respondents. (Table 1.4)

Current project
Of those currently working on a project, most respondents 73% (n= 93) reported to be involved in manuscript writing/editing. Residents and PhD scholars were more likely to be involved in data collection and data analysis (>70%), faculty were more likely to be involved in experimental design/innovation (62%). PhD scholars were actively involved in almost all areas of research work- data analysis (96%), data collection (75%), experimental design/innovation (75%), Manuscript writing (93%) and Lab work (68%) (Table 1.5).

Group Sample Characteristics	Faculty/Professor (N = 66)	Resident (N = 23)	Phd Scholar (N = 28)	Total (N = 117)
Frequency (% Total)	66 (56%)	23 (20%)	28 (24%)	117 (100%)
Experience - Median (IQR)	14.5 (10.0 - 23.5)	5.0 (1.0 - 8.0)	5.5 (3.25-7.75)	10.0 (5.0 - 20.0)
Number of Publications - Median (IQR)	41.5 (18.5 - 150.0)	4.0 (3.0 - 8.0)	4.5 (1.25 - 16.25)	17.0 (4.0 - 50.0)
Prior Experiences				
Formal training abroad	17 (26%)	0 (0%)	2 (7%)	19 (16%)
Conflict with guide regarding authorship	21 (32%)	9 (39%)	9 (32%)	39 (33%)
Offered honorary authorship	35 (53%)	14 (61%)	19 (68%)	68 (58%)
Formal Course on Research Ethics	42 (63%)	9 (39%)	11 (39%)	62 (53%)
Awareness about the ICMJE Guidelines				
Yes, I am aware	45 (68%)	9 (40%)	5 (18%)	59 (50%)
Not aware	9 (14%)	7 (30%)	12 (43%)	28 (24%)
I am aware they exist. (I have not read them)	12 (18%)	7 (30%)	11 (39%)	30 (26%)
Source of first exposure to authorship guidelines				
Mentor/Guide	25 (38%)	8 (35%)	10 (36%)	43 (37%)
Colleague	4 (6%)	0 (0%)	4 (14%)	8 (7%)
Internet	11 (17%)	5 (22%)	4 (14%)	20 (17%)
Formal Training	19 (29%)	1 (4%)	1 (4%)	21 (18%)
I don't have any prior exposure.	7 (10%)	9 (39%)	9 (32%)	25 (21%)
Role in current Project				
Data Analysis	29 (44%)	18 (78%)	27 (96%)	74 (63%)
Data Collection	25 (38%)	16 (70%)	21 (75%)	62 (53%)
Experimental Design/ Innovation	41 (62%)	9 (39%)	21 (75%)	71 (61%)
Manuscript Writing/ Editing	49 (74%)	18 (78%)	26 (93%)	93 (79%)
Clinical Intervention	27 (41%)	9 (39%)	7 (25%)	43 (37%)
Wet Lab Work	10 (15%)	5 (22%)	19 (68%)	34 (29%)

Table 1.1: Demographic characteristics of sub-groups; Table 1.2: Prior experiences among participants; Table 1.3: Awareness about the ICMJE Guidelines among participants; Table 1.4: Source of first exposure to authorship guidelines among participants; Table 1.5: Role in current projects of the participants

Reason for Honorary Authorship (n = 117)	
There is always a pressure to publish.	15 (13%)
They bring in money/opportunities.	21 (18%)
They help in proofreading because they have immense experience.	67 (57%)
Out of respect and/or legacy to do so.	54 (46%)
That way the probability of publishing increases.	38 (32%)
Motivates team/maintain relations.	48 (41%)

Table 2: Reasons for Honorary Authorship as reported by study participants.

Knowledge Score

The distribution of Section 3 scores was roughly a gaussian distribution centered at the mean of -0.07 with a standard deviation of 3.15. The score for sub-groups based on formal training abroad, formal training in research ethics and awareness about ICMJE guidelines showed a positive, yet not a significant change. (Table 3)

Sub-Groups based on:	Yes - Mean (Z value)	No - Mean (Z Value)
Formal training in research ethics	+ 0.72 (0.251)	- 1.08 (-0.321)
Education abroad	+ 2.1 (0.689)	- 0.53 (-0.146)
Aware about ICMJE Guidelines	+ 0.44 (0.162)	- 0.64 (-0.181)

Table 3: Knowledge Scores among subgroups classified as one who responded differently to questions as in different rows

Discussion

This survey was aimed at determining the prevalence of honorary authorship among residents, faculty and PhD scholars in India and gauging their awareness on the ICMJE authorship criteria. Honorary authorship was self-reported by 58% of our respondents of which maximum were PhD scholars (68%) and least were the faculty (53%). More than 40% based their offer of honorary authorship on the ground that their paper gets a proofread from a more experienced

person, out of respect and/or that it motivates the team and maintains relations. These results are in line with similar studies.

Literature highlights various other difficulties around the idea of authorship which include being forced to add an undeserving author,20 and exclusion from authorship when it was deserved.7,23 The results of our study show that conflicts among co-authors and the principal investigator regarding authorship order and/or inclusion are prevalent (>30% in each subgroup). Absence of a mechanism to decide the

order of authorship could be a reason behind this.20 The lack of awareness of the authorship criteria as a reason for these conflicts was debunked by Dhaliwal et. al.21 In our study, maximum negative collaborative experiences were reported by residents (39%) which could possibly be explained by their relatively less powerful position in academia.[12]

Only 50% of our respondents self-reported to be aware of the ICMJE criteria while 26% knew they existed but had not read them or were not aware of the guidelines at all (24%). These results fall in line with the existing literature. Source of first exposure often sets the bar for behaviors that are expected and rewarded in academic research. In India, graduate students get exposed to research mostly via a guide in their university. However, these guides rarely make an effort to make students able to recognize and deal with ethical issues.[25,26]

The question persisted, how significant an impact a targeted training would make, even if undertaken. In our study neither formal training abroad nor formal courses on research ethics were found to make a significant impact on the knowledge of the authorship guidelines. Similar results have been reported in previous studies.[25] This low level of awareness among medical researchers possibly poses a challenge on ethical practices of authorship and has been used to explain the much prevalent misconduct in the scientific community in recent times.[11, 27]

However, studies show that the level of awareness of the authorship criteria has little influence on the practice of authorship, and that more latent issues like the highly competitive environment and the absence of a check-and-report system in most institutions demand redressal.[7,21] Some researchers consider the guidelines rigid with regards to the practical barriers and the restrictive nature of the three listed criteria. This has brought in criticism for the ICMJE which in turn has been used to justify the scientific misconduct with many authors debunking them entirely.[23] Authors have even reported contributions that could not be matched by any ICMJE criterion.[27] This has sparked a debate in academia, with many authors coming forward to support the ICMJE and calling the criticisms unjustified.[28]

Strengths and Limitations

Our results might not be generalizable due to the small sample size (n= 117) of our study, restricted due to the timed nature of the project and compliance among participants being lower than expected. Subjective nature of the scoring done in Section 3 could serve a gray area for our study. A study like ours, in the context of medical researchers in India, wasn't found in literature, which makes it a pilot study, therefore a sample size couldn't be calculated pre-emptively. The sampling was done through a convenience-based system, with a possible skewed distribution towards researchers in tertiary centers in Northern India.

The questionnaire was derived from subjective statements, although well-established in literature and consulted with expert stakeholders, the statements used were not part of a previously validated questionnaire. The questionnaire was administered among varied strata of medical researchers, while maintaining complete anonymity by ensuring that no question asked can trace the participant or their workplace/guide. This kind of anonymity encourages participants to be more open about their experiences regarding conflicts and disagreements with their superiors and colleagues.

This study therefore serves towards the initial efforts to bring attention towards the inconspicuous problem of authorship conflicts and publication pressure, encouraging further studies on these issues, particularly so in the context of medical researchers in India.

Conclusion

Over the past couple years, research misconduct has gained substantial attention. Our study adds to it by having separate analyses for all the three subgroups

involved (Residents, Faculty and PhDs scholars) of medical researchers in India. Differences were evident among the three groups. It reinforces that gift authorship is prevalent in the scientific community.

Honorary authorship not only affects academic growth by invalidating records of indexing and citation tracking services but also releases certain crucial safeguarding checks on data reliability.[29] It puts a question mark on the accuracy and integrity of the new research papers being published. As this directly poses a threat to sound clinical decision making and policy formation, the problem needs prompt and a proper redressal mechanism.

Supportive attention and prompt, detailed feedback may help circumvent many ethical problems.26 Getting a signed statement of justification for authorship/specifying their contributions in the paper and having a fixed-credit system could curb the prevalence of gift authorship, though some studies show non-significant effects of such systems already in place.[8]

Efforts should be made to reduce the 'pressure to publish' on medical researchers. Abolishing the practice of valuing a doctor's or an institution's quality in terms of its research output, and judging their research performance using a mere numerical value as h-index is needed.[30] We predict that with the ongoing heated debate within the scientific community could eventually lead to a common solution that is agreeable to all.

Acknowledgments

We would like to thank Dr. Nalin Mehta (Professor, Department of Physiology, AIIMS Delhi) for mentoring in this ICMR-STS project. We would also like to thank Bhavya Kensal, who gave insightful comments to the manuscript drafting process.

References

1. Paper authorship goes hyper [Internet]. [cited 2021 Aug 29]. Available from: https:// www.natureindex.com/news-blog/paper-authorship-goes-hyper

2. Eisenberg RL, Ngo L, Boiselle PM, Bankier AA. Honorary Authorship in Radiologic Research Articles: Assessment of Frequency and Associated Factors. Radiology. 2011 May 1;259(2):479– 86.

3. Gasparyan AY, Ayvazyan L, Kitas GD. Authorship problems in scholarly journals: considerations for authors, peer reviewers and editors. Rheumatol Int. 2013 Feb;33(2):277–84.

4. Zimba O, Gasparyan AY. Scientific authorship: a primer for researchers. Reumatologia. 2020;58(6):345–9.

5. ICMJE | Recommendations | Defining the Role of Authors and Contributors [Internet]. [cited 2021 Jul 16]. Available from: http://www.icmje.org/recommendations/browse/roles-and- responsibilities/defining-the-role-of-authors-and-contributors.html

.

6. Reisig MD, Holtfreter K, Berzofsky ME. Assessing the perceived prevalence of research fraud among faculty at research-intensive universities in the USA. Account Res. 2020 Oct;27(7):457–75.

7. Schroter S, Montagni I, Loder E, Eikermann M, Schäffner E, Kurth T. Awareness, usage and perceptions of authorship guidelines: an international survey of biomedical authors. BMJ Open. 2020 Sep 21;10(9):e036899.

8. Wislar JS, Flanagin A, Fontanarosa PB, Deangelis CD. Honorary and ghost authorship in high impact biomedical journals: a cross sectional survey. BMJ. 2011 Oct 25;343:d6128.

9. Bates T, Anić A, Marusić M, Marusić A. Authorship criteria and disclosure of contributions: comparison of 3 general medical journals with different author contribution forms. JAMA. 2004 Jul 7;292(1):86–8.

10. McClellan JM, Mansukhani N, Moe D, Derickson M, Chiu S, Kibbe MR, et al. Courtesy Authorship in Academic Surgery Publications. JAMA Surg. 2019 Dec 1;154(12):1110–6.

11. Bonekamp S, Halappa VG, Corona-Villalobos CP, Mensa M, Eng J, Lewin JS, et al. Prevalence of honorary coauthorship in the American Journal of Roentgenology. AJR Am J Roentgenol. 2012 Jun;198(6):1247–55.

12. Tsai C-C, Corley EA, Bozeman B. Collaboration experiences across scientific disciplines and cohorts. Scientometrics. 2016 Aug 1;108(2):505–29.

13. Sokol DK. The dilemma of authorship. BMJ. 2008 Mar 1;336(7642):478.
14. Ladouceur R. Publish or perish. Can Fam Physician. 2019 Feb;65(2):86.

15. Shapiro DW, Wenger NS, Shapiro MF. The Contributions of Authors to Multiauthored Biomedical Research Papers. JAMA. 1994 Feb 9;271(6):438–42.

16. Goodman NW. Survey of fulfillment of criteria for authorship in published medical research. BMJ. 1994 Dec 3;309(6967):1482.

17. Hwang SS, Song HH, Baik JH, Jung SL, Park SH, Choi KH, et al. Researcher contributions and fulfillment of ICMJE authorship criteria: analysis of author contribution lists in research articles with multiple authors published in radiology. International Committee of Medical Journal Editors. Radiology. 2003 Jan;226(1):16–23.

18. Hoen WP, Walvoort HC, Overbeke AJ. What are the factors determining authorship and the order of the authors' names? A study among authors of the Nederlands Tijdschrift voor Geneeskunde (Dutch Journal of Medicine). JAMA. 1998 Jul 15;280(3):217–8.

19. Ghajarzadeh M. Guest authors in an Iranian journal. Dev World Bioeth. 2014 Apr;14(1):15–9.

20. Reinisch JF, Li W-Y, Yu DC, Walker JW. Authorship Conflicts: A Study of Awareness of Authorship Criteria among Academic Plastic Surgeons. Plast Reconstr Surg. 2013 Aug;132(2):303e.

21. Dhaliwal U, Singh N, Bhatia A. Awareness of authorship criteria and conflict: survey in a medical institution in India. MedGenMed Medscape Gen Med. 2006 Dec 12;8(4):52.

22. Jawaid M, Jawaid SA. Faculty Member's Views, Attitude and Current Practice As Regards International Committee of Medical Journal Editors Criteria for Authorship. Iran J Public Health. 2013 Oct;42(10):1092–8.

23. Bhopal R, Rankin J, McColl E, Thomas L, Kaner E, Stacy R, et al. The vexed question of authorship: views of researchers in a British medical faculty. BMJ. 1997 Apr 5;314(7086):1009– 12.

24. Alshogran OY, Al-Delaimy WK. Understanding of International Committee of Medical Journal Editors Authorship Criteria Among Faculty Members of Pharmacy and Other Health Sciences in Jordan. J Empir Res Hum Res Ethics JERHRE. 2018 Jul;13(3):276–84.

25. Authorship Not Taught and Not Caught in Undergraduate Research Experiences at a Research University | SpringerLink [Internet]. [cited 2021 Aug 23]. Available from: https://link.springer.com/article/10.1007%2Fs11948-02000220-6

26. Anderson MS, Louis KS, Earle J. Disciplinary and Departmental Effects on Observations of Faculty and Graduate Student Misconduct. J High Educ. 1994 May;65(3):331–50.

27. Ivaniš A, Hren D, Marušić M, Marušić A. Less work, less respect: authors' perceived importance of research contributions and their declared contributions to research articles. PloS One. 2011;6(6):e20206.

28. Ali MJ. ICMJE criteria for authorship: why the criticisms are not justified? Graefes Arch Clin Exp Ophthalmol. 2021 Feb 1;259(2):289–90.

29. Baerlocher MO, O'Brien J, Newton M, Gautam T, Noble J. Data integrity, reliability and fraud in medical research. Eur J Intern Med. 2010 Feb;21(1):40–5.

30. Aulakh R. Mandatory publication in India: setting quotas for research output could encourage scientific fraud. BMJ. 2016 Sep 15;354:i5002.

PRAXIS
UNDERGRADUATE MEDICAL RESEARCH JOURNAL

REVIEW ARTICLE

Immunotherapy – Its relevance in current times

Lt Col (Dr) Mahima Lall[a], Suyash Singh[b], Gurmukh Varandani[b], Ankur Jha[b]

[a] Professor, Department of Microbiology, Armed Forces Medical College, Pune

[b] Medical Student, Armed Forces Medical College, Pune

Article Info

Article History:
Received: 13 September 2022
Accepted:12 October 2022
Available: 18 November 2022

Keywords:
COVID-19
Corona
YouTube
Prevention
WHO

ankur28jha@gmail.com
(Ankur Jha)

Abstract

A huge proportion of annual mortality, morbidity and healthcare associated costs are still attributable to infectious diseases, both in the developed as well as the developing nations. This problem is greatly compounded by emerging drug resistance and immunocompromised states. In this scenario, there is a renewed interest in exploring novel immunotherapeutic approaches for infectious diseases. This article tries to bring together the important active and passive immunotherapeutic modalities currently under consideration for various viral, bacterial, fungal and parasitic diseases. Also, the use of convalescent plasma therapy for COVID-19 has been discussed in the light of the ongoing coronavirus pandemic. The relevant guidelines pertaining to the use of the immunotherapeutic agents have been briefly summarized.

Introduction

Infectious diseases have been known to haunt mankind since time immemorial. Immunotherapy dates back to the pre-antibiotic era almost by a century when vaccination was popularized by Jenner in 1796. A century later, following the discovery of the diphtheria toxin, von Behring and Kitasato in 1890s developed the concept of passive immunotherapy and administered toxin-antiserum to patients with diphtheria.[1] In the coming decades, serum therapy was used as a treatment for pneumococcal pneumonia, diphtheria, scarlet fever and meningococcal meningitis.[2] Passive immunotherapy was the only known lifesaving intervention available for many infections before the advent of antibiotics.[3,4]

The first real victory in defeating infections was achieved with the development of "Salvarsan" for syphilis by Paul Ehrlich in 1909.[5] The serendipitous discovery of Penicillin by Fleming in 1945 ushered the antibiotic era. The rapidity with which antimicrobial resistance (AMR) is developing and the slow rate of new drug development indicates that we might soon run out of our armamentarium of effective antibiotics, making infections difficult to treat and eradicate.[6,7]

The key to victory over infections, is not merely using newer and more potent antimicrobial agents, but also in making the immune system of the host competent enough to successfully target and eliminate the infectious agent, without altering the normal physiology.[8] This is the basis of immunotherapy which can be defined as the use of naturally occurring agents or drugs to modify the body's immune response to certain antigens, thereby providing a possible modality to prevent or treat infectious diseases.[9]

In recent times, there has been a resurgence of interest in immunotherapy, both active and passive, for both therapeutic and prophylactic use in the treatment of infections. This can be partly ascribed to the changing dynamics of infectious diseases, and partly to the great success which immunotherapy has shown in the arena of oncology.[10] Up-regulation of immune checkpoint molecules, such as Programmed death ligand (PD-1) and cytotoxic T-lymphocyte (CTLA4) on immune cells occurs during acute infections, newer approaches and recent success of immune checkpoint blockade in cancer therapy suggest that targeting these pathways could also be effective for preventing and treating a range of infectious diseases. Future prospects are being investigated for bacterial, viral, fungal and parasitic diseases.[11] Recently a global pandemic of SARS-CoV-2 caused by coronavirus causing COVID-19 disease has become a health concern across the world.[12,13] The use of convalescent plasma therapy (CPT) has shown promise even as antiviral therapy did not show benefit over standard care.[14,15] This article will try to outline the various immunotherapeutic approaches used currently in the treatment of infectious diseases including COVID-19.

Immunotherapeutic approaches for viral diseases

Convalescent plasma immunotherapy has a special role in the management of viral diseases.[16] It was used for treating patients during the outbreak of severe acute respiratory syndrome (SARS) and the Middle East respiratory syndrome (MERS).[17] As there is no specific antiviral agent for most viruses and because of the ability of the viruses to play with the host's immune mechanism leading to immune mediated tissue destruction, treating viral infections becomes challenging. Viruses may cause immune suppression as in case of human immunodeficiency virus (HIV).[18]

Immunotherapy for Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)
The most recent example of a successful trial is the use of immunotherapy during the ongoing COVID-19 pandemic.[19,20] The pathology of COVID-19 has been speculated to be an inflammatory storm known as the cytokine storm.[21] However, this is different from that seen in sepsis. In a study, administering CPT in the dosage of 200-2400 mL, with neutralizing antibody titers >1:640 showed declining viral load (VL) and better patient outcome, observed as normalization of temperature, resolution of lung lesions, acute respiratory distress syndrome (ARDS) and weaning off from the ventilator.[22] Despite having limitations, the study has brought immunotherapy to the forefront; however, the findings are yet to be translated into clinical guidelines. The cytokine storm and the proposed hypothesis and anecdotal evidence of treating this with anti-inflammatory therapies directed at reducing interleukin-6 (IL-6), IL-1 and tumor necrosis factor α (TNFα) with some beneficial effects have shone light on possible immunotherapeutic modalities for COVID-19.[23] Anti-IL-6 has been shown to be effective in chimeric antigen receptor T (CAR-T) and cytokine response syndrome (CRS).

Tocilizumab (TCZ) a recombinant human IL-6 monoclonal antibody has shown efficacy in COVID patients.24 A dysregulated host immune response leading to pulmonary inflammation secondary to IL-6, a pro-inflammatory cytokine produced by T- and B-cells, monocytes and fibroblasts, has been found to be the cause of alveolar damage. Clinical studies have shown that IL-6 receptor antagonist TCZ in a dose of 8 mg/kg, by binding IL-6 receptors and preventing it from exerting its pro-inflammatory effects, is effective in treating COVID-19 patients with extensive bilateral lung lesions.[25,26]

Glucocorticoids such as dexamethasone and their role in salvaging patients on ventilatory support has come from the initial yet unpublished reports of the RECOVERY (Randomized Evaluation of COVID-19 Therapy).[27] The trial declares overall mortality benefit in ventilated and oxygen requiring patients who received dexamethasone in a dose of 6 mg a day for 10 days. Potent anti-inflammatory action and cytokine storm amelioration are mediated at many levels, involving direct action on both T and B lymphocytes, inhibition of immunoglobulin synthesis and stimulation of lymphocyte apoptosis.

Hydroxychloroquine (HCQ), a drug used in Malaria, Rheumatoid Arthritis and autoimmune connective tissue disorders is also evoking interest as a prophylactic and therapeutic option in COVID-19. It is believed to impair the terminal glycosylation of ACE2 receptor which is the binding site for the envelope spike glycoprotein of the SARS-COV-2.[28]

The angiotensin converting enzyme (ACE2) receptors which have been proposed as the entry point for the SARS-COV-2 may allow invasion and entry into host cells through endocytosis, these receptors are widely present on cells in the heart, kidney, blood vessels, and the alveolar epithelial cells. Baricitinib, a JAK and AAK1 inhibitor (Adapter-associated protein kinase 1; regulates endocytosis of virus cells), is a possible candidate for treatment of COVID-19. Therapeutic dosage with either 2 mg or 4 mg once daily was sufficient to reach the plasma concentration of inhibition. However, the concern about JAK inhibitors is that they can inhibit other inflammatory cytokines including interferon alfa (INF-a), which has an important role in virus clearance.

Immunotherapy for Ebola virus disease (EVD)
World Health Organization (WHO) in its interim guidelines on treatment of early Ebola Virus disease, has considered CPT as an "efficacious and biologically plausible" therapy. It allows transfusion of 400-500 mL of ABO-Rh compatible convalescent whole blood/plasma in two doses of 200-250 mL, and at the dose of 10mL/kg for pediatric patients.[29] When viewed in light of previous findings, as in case of SARS, CPT holds promise for EVD as an empirical trial in case of newly emerging infections.

Immunotherapy for Hepatitis B virus (HBV) and Hepatitis C (Hep C)

Hepatitis B virus (HBV) is a highly prevalent viral infection that is the leading cause of liver cirrhosis, end-stage liver disease and hepatocellular carcinoma (HCC) throughout the world.[30] It has been a successful candidate of immunotherapy for a long time, because of its non-cytopathic nature and peculiar immunopathogenesis, wherein it displays several immune evasion tactics. The acute self-limited hepatitis, which is usually controlled by the polyclonal T-cell response, may evolve into a chronic infection due to early suppression of innate immune response. This suppression can be partly due to the large amounts of antigens presented by HBV which causes exhaustion of T-cells and PD-1 receptor mediated dysfunction of antigen presenting cells (APCs). PDL-1 blockade and infusion of HBV-specific TCR T-Cells for HCC is a potential immunotherapeutic approach under investigation.[31]

Pegylated interferon-α2a (PEG-IFN) is an immunomodulator with weak anti-viral properties that targets sustained remission of disease in chronic HBV although this is seldom achieved in more than 30-40% patients. For chronic HBV, the American association for the study of liver diseases (AASLD) recommends that PEG-IFN along with entecavir/tenofovir can be used as an initial therapy for patients of immune active disease (ALT>2xULN/significant histologic liver disease plus elevated HBV DNA above 2,000 IU/mL for HBeAg negative patients or above 20,000 IU/mL for HBeAg positive patients). A dose of 0.5 mL of HBIG is to be administered intramuscularly, along with Hep B vaccine (3 doses; 0.5 mL within 7 days, 1 month and 6 months respectively), to a neonate born to an HBsAg positive mother. Use of IFN-α has been the backbone for Hep C therapy for more than two decades, which served to boost the innate immunity response.[32]

Immunotherapy for Human papillomavirus (HPV) induced Cutaneous warts

Cutaneous warts are a common skin problem worldwide, with estimates ranging from a prevalence of 5-30% in children and young adults. They are caused by the infection of epidermal keratinocytes by human papillomaviruses (HPV) which can easily spread from person to person through contact. Immunotherapeutic treatment options for cutaneous warts, Imiquimod is widely used as a topical therapy for the treatment of anogenital warts.[33] It is a Toll like receptor-7 (TLR7) agonist. Imidazoquinolinone compound activates macrophages and natural killer (NK) cells to release various cytokines. Another approach is the use of contact immunotherapy with Diphenylcyclopropenone (DCP) or Squaric acid dibutyl ester (SADBE) which triggers immunity by inducing a delayed type hypersensitivity reaction. Measles, mumps, rubella (MMR) and Bacillus Calmette Guerin (BCG) vaccines have also been applied intralesionally and topically, respectively, to provide contact immunotherapy.

Immunotherapy for Varicella Zoster virus (VZV)

Immunotherapy, as Varicella Zoster Immunoglobulin (VARIZIG®) is recommended in immunocompromised children, adults, pregnant women and premature infants for post-exposure prophylaxis within 96 hours, at the doses of 0.6-6mL (62.5-625 IU as per weight) IM.

Immunotherapy for Rabies virus

Human Rabies Immunoglobulin (HRIG) is recommended for the post-exposure prophylaxis of Rabies in previously unvaccinated individuals.[34] 20 IU/kg body weight of the immunoglobulin is infiltrated as much as possible around the site of animal bite, and the remaining dose administered intramuscularly. HRIG administration should be carried out as soon as possible after the animal bite, up to a maximum of 7 days, but not later than that.

Immunotherapy for Measles virus
Immunoglobulins (IGs) are also recommended for post-exposure prophylaxis in diseases like measles and rubella.[35] CDC recommends administration of immunoglobulin 0.5mL/kg IM to children less than 12 months of age and 400mg/kg IV to pregnant women exposed to measles, who are unimmunized or their immunization status is doubtful. Infants 6-11 months old may receive an MMR vaccine instead of IG, if administered within 72 hours of exposure.

Immunotherapy for Dengue, Chikungunya and Zika virus
Arboviral infections occur every year in the developing world, causing high morbidity and mortality. Immunotherapy as anti-chikungunya virus hyperimmune immunoglobulin (CHIKVIg) is under investigation for the prevention of transmission to neonates from viremic mothers.[36] IVIg has been strongly recommended by WHO for the management of Guillain-Barre Syndrome which complicates Zika virus infection.

Immunotherapeutic approaches for bacterial diseases

Before the advent of antimicrobial agents, passive immunotherapy was greatly in vogue for the management of bacterial disease. They might be the sole treatment options for the newly emerging pan-drug resistant superbugs.

Immunotherapy for Tuberculosis (TB)
IFN-γ augments the host immune response against intracellular pathogens like mycobacteria, leishmania, rickettsia, legionella, chlamydia. Administration of interferon-γ as an adjuvant can help us tackle multidrug resistant tuberculosis (MDRTB) which is now emerging as a major public health problem.[37] Administering 2 million IU of aerosolized IFN-γ thrice a week for six months to six patients, along with antitubercular therapy (ATT) showed radiological improvement with reduced size of cavitary lesion in five.38 Similarly, administration of aerosolized IFN-γ and BCG has shown to be effective for patients with advanced Mycobacterium Avium Complex.[39-41]

Immunotherapy for Leprosy
The physical manifestation of the debilitating disease leprosy can lie anywhere along a spectrum from tuberculoid to lepromatous, depending upon the host immune response. Any variation in the host immune status can result in lepra reactions.42 Thalidomide has been used for several decades for the treatment of type 2 lepra reaction, erythema nodosum leprosum (ENL).[43] It has the ability to suppress inflammation by inhibiting TNF-α production by monocytes.

Immunotherapy for Streptococcal infection
Ranging from mild diseases like impetigo and pharyngitis, to the deadly toxic shock syndrome, the burden of infection by group-A β-hemolytic streptococcus increasing. The necrotizing soft tissues infections caused by it are mediated by the hyperstimulation of immune response by the superantigens.[44] Although IVIg has been tried for its treatment for about 20 years now, the advantage conferred by it has not been replicated in placebo controlled randomized trials. An investigational drug Reltecimod (AB103), which mimics the superantigen in binding to the costimulatory CD28 molecule, is in trials.

Immunotherapy for Staphylococcal infection
Various novel strategies have been investigated for the management and prevention of staphylococcal infection which may manifest in the form of sepsis, toxic shock syndrome, necrotizing pneumonia, etc. Passive immunotherapeutic options like Pagibaximab (anti-Lipoteichoic acid chimeric antibody), Aurograb (antibody against Staph ABC Transporter), and Altastaph (polyclonal antibodies derived from sera of treated individuals), have been evaluated but their efficacy has not been proven in clinical trials.

In a Cochrane review, pentoxifylline when used as an adjunct to antimicrobials, was found to be effective in reducing mortality and duration of hospital stay in case of neonates.[45]

Immunotherapy for Clostridium difficile Infection (CDI)
Clostridium difficile continues to be the most prevalent hospital acquired infection in the developed world. Toxin A (TcdA) and toxin B (TcdB) are the most important virulence factors of C. difficile. Bezlotoxumab is an FDA approved antibody that can be used to prevent recurrent CDI in persons 18 years or older, at a single dose of 10 mg/kg infused intravenously over 60 minutes. Another such antibody is Actoxumab. Concurrent administration of both the antibodies has been found to be more effective in animal experiments. IVIG products also contain anti-toxin A antibodies, hence are proposed as an adjunct treatment for CDI.

Immunotherapy for Tetanus and Diphtheria
Passive immunotherapy is used very commonly for bacterial diseases like tetanus and diphtheria. 250 IU (500 IU if more than 24 hours have elapsed) of tetanus immunoglobulin (TIG) is recommended to be administered in case of all tetanus prone wounds.[46] TIG should be given in instances in which a person has received less than 3 doses of tetanus vaccine or is uncertain of own immunization status, or in case of immunocompromised children. Diphtheria has seen resurgence in recent times. Equine diphtheria antitoxin along with antimicrobial drugs is the preferred treatment. The recommended dose of antitoxin is of 40000-100000 IU.

Immunotherapeutic approaches for fungal diseases

Immunotherapy commands a special significance in fungal infections because most of them occur mostly in states of deranged immunity. Antifungal drug choices are relatively limited, and species such as non-albicans candida are inherently resistant to most antifungals. Innate immune responses play an important role in the severity of fungal infections, as can be seen in the phagocyte NADP Oxidase deficiency (Chronic granulomatous disease) where trivial fungal infections can become life threatening.

Administration of recombinant cytokines and growth factors tailored according to the genetic defect in the host leading to the fungal infection can greatly improve patient outcomes.[47] INF-γ has been found to be an effective adjunct in the treatment of cryptococcal meningitis, invasive candidiasis, chronic granulomatous disease etc. It exerts its effect probably by favoring the protective Th1 immunity and by directly activating the effector cells such as macrophages and microglia.

Vitamin D3 was shown to restrict the Th2 response by Aspergillus fumigatusin in-vitro experiments. Studies have shown that daily supplementation of 4000 IU of Vit D3 over a period of 24 months, diminished the IL-13 responses from peripheral CD4+ T cells and Aspergillus-specific IgE levels in patients of cystic fibrosis, who presented with a history of allergic bronchopulmonary aspergillosis.

Immunotherapy in Oncology

Immunotherapy has proven to be a game changer in cancer treatment. The approval of the immune checkpoint inhibitors (ICI) was a landmark in this regard.

Currently, several immune checkpoint inhibitors and 2-chimeric antigen receptor T-cell [CAR-T] products have been approved for treating more than 15 types of malignant diseases. Some of them from the long list are Pembrolizumab approved for melanoma, non-small cell lung cancer, Hodgkin's lymphoma, hepatocellular carcinoma, Nivolumab for Renal Cell Carcinoma, Melanoma, Urothelial Carcinoma both of which target PD-1. Other drugs being investigated include Atezolizumab, Durvalumab, Avelumab targeting PD-L1 and Toripalimab, Sintilimab, Camrelizumab, Tislelizumab for Hodgkin's lymphoma.[48]

Taking the example of colorectal cancer, the research on immunotherapy in metastatic colorectal, cancer and various treatment modalities include Ipilimumab, Nivolumab (checkpoint inhibitors), autologous peptide cancer vaccines, chimeric antigen receptor T-cell therapy (adoptive cell transfer), oncolytic herpes simplex virus NV 1020 (oncolytic virus therapy), Epacadosate and Indoximod (ID-O1 inhibitor and Anti-OX40 agonist) are under trial and immunotherapy is being explored in these patients.[49]

A key challenge in the broad implementation of immunotherapies for cancer remains the controlled modulation of the immune system as these therapeutics have serious adverse effects including autoimmunity, non-specific inflammation and immune related adverse events (IRAEs) including inflammatory arthritis, sicca syndrome, myositis, vasculitis, renal adverse effects etc.[50]

Understanding how to increase the response rate to various class of immunotherapy is key to improving efficacy and controlling these adverse effects.

Advanced biomaterials and drug delivery systems such as nano particles and the use of T-cells to deliver therapies, could effectively harness immunotherapy and reduce its side effects.[51]

Conclusion

Immunotherapy, is an efficacious therapeutic option for infectious diseases. It can be applied at all levels of disease management, from primary prevention, treatment to secondary prevention. It has the potential to tackle even refractory infections and bridge the gap due to both bacterial and host factors such as drug resistant organisms and immune suppression. Revisiting CPT during COVID-19 pandemic highlights the promise this age-old therapeutic method holds.

References

1. Manohar A, Ahuja J, Crane JK. Immunotherapy for infectious diseases: past, present, and future. Immunol Invest. 2015;44(8):731-737. doi:10.3109/08820139.2015.1093914

2. Hey A. History and Practice: antibodies in infectious diseases. Microbiol Spectr. 2015;3(2):1-15. doi:10.1128/microbiolspec.aid-0026-2014

3. Dobosz P, Dzieciątkowski T. The intriguing history of cancer immunotherapy. Front Immunol. 2019;10(December). doi:10.3389/fimmu.2019.02965

4. Barney S. Graham Donna M. Ambrosino. History of passive antibody administration for prevention and treatment of infectious diseases. Curr Opin HIV AIDS. 2015;10(3):129-134. doi:10.1016/j.physbeh.2017.03.040

5. Taylor GSRWM. Salvarsan in the treatment of Syphilis. Lancet. 1911;iii:1412-1416.

6. Aslam B, Wang W, Arshad MI, Khurshid M, Muzammil S, Rasool MH, Nisar MA, Alvi RF, Aslam MA, Qamar MU, Salamat MK. Antibiotic resistance: a rundown of a global crisis. Infection and drug resistance. 2018;11:1645.

7. Casadevall A. Crisis in infectious diseases: 2 decades later. Clin Infect Dis. 2017;64(7):823-828. doi:10.1093/cid/cix067

8. Wykes MN, Lewin SR. Immune checkpoint blockade in infectious diseases. Nat Rev Immunol. 2018;18(2):91-104. doi:10.1038/nri.2017.112

9. Keller MA, Stiehm ER. Passive immunity in prevention and treatment of infectious diseases. Clin Microbiol Rev. 2000;13(4):602-614. doi:10.1128/CMR.13.4.602-614.2000

10. Naran K, Nundalall T, Chetty S, Barth S. Principles of immunotherapy: implications for treatment strategies in cancer and infectious diseases. Front Microbiol. 2018;9(December):1-23. doi:10.3389/fmicb.2018.03158

11. Zumla A, Rao M, Wallis RS, Kaufmann SH, Rustomjee R, Mwaba P, Vilaplana C, Yeboah-Manu D, Chakaya J, Ippolito G, Azhar E. Host-directed therapies for infectious diseases: current status, recent progress, and future prospects. The Lancet Infectious Diseases. 2016 Apr 1;16(4):e47-63.

12. Wang C, Horby PW, Hayden FG, Gao GF. A novel coronavirus outbreak of global health concern. Lancet. 2020;395(10223):470-473. doi:10.1016/S0140-6736(20)30185-9

13. Zhou P, YANG X, wANG XG, HU B. ZHANG w. Si Hr, zHu y, li B, HuanG cl, cHen HD, cHen J, luo y, Guo H, JianG rD, liu MQ, cHen y, SHen Xr, WanG X, zHenG XS, zHao K, cHen QJ, DenG F, liu ll, yan B, zHan FX, WanG yy, Xiao GF, SHi zl. A pneumonia outbreak associated with a new coronavirus of probable bat origin. Nature. 2020;579:270-3.

14. Guan WJ, Ni ZY, Hu Y, Liang WH, Ou CQ, He JX, Liu L, Shan H, Lei CL, Hui DS, Du B. Clinical characteristics of coronavirus disease 2019 in China. New England journal of medicine. 2020 Apr 30;382(18):1708-20.

15. Chen L, Xiong J, Bao L, Shi Y. Convalescent plasma as a potential therapy for COVID-19. Lancet Infect Dis. 2020;20(4):398-400. doi:10.1016/S1473-3099(20)30141-9

16. Mair-Jenkins J, Saavedra-Campos M, Baillie JK, Cleary P, Khaw FM, Lim WS, Makki S, Rooney KD, Convalescent Plasma Study Group, Nguyen-Van-Tam JS, Beck CR. The effectiveness of convalescent plasma and hyperimmune immunoglobulin for the treatment of severe acute respiratory infections of viral etiology: a systematic review and exploratory meta-analysis. The Journal of infectious diseases. 2015 Jan 1;211(1):80-90.

17. Arabi YM, Alothman A, Balkhy HH, et al. Treatment of Middle East Respiratory Syndrome with a combination of lopinavir-ritonavir and interferon-β1b (MIRACLE trial): Study protocol for a randomized controlled trial. Trials. 2018;19(1):1-13. doi:10.1186/s13063-017-2427-0

18. Rouse BT, Sehrawat S. Immunity and immunopathology to viruses: What decides the outcome? Nat Rev Immunol. 2010;10(7):514-526. doi:10.1038/nri2802

19. Chiappelli F, Khakshooy A, Greenberg G. CoViD-19 Immunopathology & Immunotherapy. Bioinformation. 2020;16(3):219-222. doi:10.6026/97320630016222

20. Remy KE, Brakenridge SC, Francois B, Daix T, Deutschman CS, Monneret G, Jeannet R, Laterre PF, Hotchkiss RS, Moldawer LL. Immunotherapies for COVID-19: lessons learned from sepsis. The Lancet. Respiratory Medicine. 2020 Apr 28.

21. Zhou Y, Fu B, Zheng X, Wang D, Zhao C. qi Y, Sun R, Tian Z, Xu X, Wei H. Pathogenic T cells and inflammatory monocytes incite inflammatory storm in severe COVID-19 patients. Natl Sci Rev. 2020.

22. Rajendran K, Narayanasamy K, Rangarajan J, Rathinam J, Natarajan M, Ramachandran A. Convalescent plasma transfusion for the treatment of COVID-19: Systematic review. J Med Virol. 2020;(April):1-9. doi:10.1002/jmv.25961

23. Zhang W, Zhao Y, Zhang F, Wang Q, Li T, Liu Z. The use of anti-inflammatory drugs in the treatment of people with severe coronavirus disease 2019 (COVID-19): the experience of immunologists from China. Clin Immunol. 2020;10.

24. Fu B, Xu X, Wei H. Why tocilizumab could be an effective treatment for severe COVID-19? J Transl Med. 2020;18(1):1-5. doi:10.1186/s12967-020-02339-3

25. Toniati P, Piva S, Cattalini M, Garrafa E, Regola F, Castelli F, Franceschini F, Focà E, Andreoli L, Latronico N, Research BI. Tocilizumab for the treatment of severe COVID-19 pneumonia with hyperinflammatory syndrome and acute respiratory failure: A single center study of 100 patients in Brescia, Italy. Autoimmunity reviews. 2020 May 3:102568.

26. Xu X, Han M, Li T, Sun W, Wang D, Fu B, Zhou Y, Zheng X, Yang Y, Li X, Zhang X. Effective treatment of severe COVID-19 patients with tocilizumab. Proceedings of the National Academy of Sciences. 2020 May 19;117(20):10970-5.

27. Group RC. Effect of Dexamethasone in Hospitalized Patients with COVID-19 – Preliminary Report. Published online 2020.

28. Schrezenmeier E, Dörner T. Mechanisms of action of hydroxychloroquine and chloroquine: implications for rheumatology. Nat Rev Rheumatol. 2020;16(3):155-166. doi:10.1038/s41584-020-0372-x

29. Garraud O. Use of convalescent plasma in Ebola virus infection. Transfus Apher Sci. 2017;56(1):31-34. doi:10.1016/j.transci.2016.12.014

30. Popping S, Bade D, Boucher C, van der Valk M, El-Sayed M, Sigurour O, Sypsa V, Morgan T, Gamkrelidze A, Mukabatsinda C, Deuffic-Burban S. The global campaign to eliminate HBV and HCV infection: International Viral Hepatitis Elimination Meeting and core indicators for development towards the 2030 elimination goals. Journal of virus eradication. 2019 Jan;5(1):60.

31. Fuller MJ, Callendret B, Zhu B, Freeman GJ, Hasselschwert DL, Satterfield W, Sharpe AH, Dustin LB, Rice CM, Grakoui A, Ahmed R. Immunotherapy of chronic hepatitis C virus infection with antibodies against programmed cell death-1 (PD-1). Proceedings of the National Academy of Sciences. 2013 Sep 10;110(37):15001-6.

32. Ashfaq UA, Javed T, Rehman S, Nawaz Z, Riazuddin S. An overview of HCV molecular biology, replication and immune responses. Virol J. 2011;8(Figure 1):1-10. doi:10.1186/1743-422X-8-161

33. Kumar P, Dar L, Saldiwal S, Varma S, datt Upadhyay A, Talwar D, Sharma VK, Verma KK, Dwivedi SN, Raj R, Gupta S. Intralesional injection of Mycobacterium w vaccine vs imiquimod, 5%, cream in patients with anogenital warts: a randomized clinical trial. JAMA dermatology. 2014 Oct 1;150(10):1072-8.

34. Gogtay NJ, Munshi R, Ashwath Narayana DH, Mahendra BJ, Kshirsagar V, Gunale B, Moore S, Cheslock P, Thaker S, Deshpande S, Karande S. Comparison of a novel human rabies monoclonal antibody to human rabies immunoglobulin for postexposure prophylaxis: A phase 2/3, randomized, single-blind, noninferiority, controlled study. Clinical Infectious Diseases. 2018 Jan 18;66(3):387-95.

30. Arciuolo RJ, Jablonski RR, Zucker JR, Rosen JB. Effectiveness of measles vaccination and immune globulin post-exposure prophylaxis in an outbreak setting - New York City, 2013. Clin Infect Dis. 2017;65(11):1843-1847. doi:10.1093/cid/cix639

31. Couderc T, Khandoudi N, Grandadam M, Visse C, Gangneux N, Bagot S, Prost JF, Lecuit M. Prophylaxis and therapy for Chikungunya virus infection. The Journal of infectious diseases. 2009 Aug 1;200(4):516-23.

32. Tomioka H. Adjunctive Immunotherapy of Mycobacterial Infections. Curr Pharm Des. 2005;10(26):3297-3312. doi:10.2174/1381612043383232

33. Koh WJ, Kwon OJ, Suh GY, Chung MP, Kim H, Lee NY, Kim TS, Lee KS. Six-month therapy with aerosolized interferon-γ for refractory multidrug-resistant pulmonary tuberculosis. Journal of Korean Medical Science. 2004 Apr 1;19(2):167-71.

34. 39.Hoft D, Abate G. Immunotherapy for tuberculosis: future prospects. ImmunoTargets Ther. Published online 2016:37. doi:10.2147/itt.s81892

35. 40.Abate G, Hamzabegovic F, Eickhoff CS, Hoft DF. BCG vaccination induces M. Avium and M. Abscessus cross-protective immunity. Front Immunol. 2019;10(FEB):1-10. doi:10.3389/fimmu.2019.00234

36. 41.Chatte G, Panteix G, Perrin-Fayolle M, Pacheco Y. Aerosolized interferon gamma for Mycobacterium avium-complex lung disease. Am J Respir Crit Care Med. 1995;152(3):1094-1096. doi:10.1164/ajrccm.152.3.7663788

37. Silva PHL, Santos LN, Mendes MA, Nery JAC, Sarno EN, Esquenazi D. Involvement of TNF-Producing CD8+ effector memory T Cells with immunopathogenesis of erythema nodosum leprosum in leprosy patients. Am J Trop Med Hyg. 2019;100(2):377-385. doi:10.4269/ajtmh.18-0517

38. Teo SK, Resztak KE, Scheffler MA, Kook KA, Zeldis JB, Stirling DI, Thomas SD. Thalidomide in the treatment of leprosy. Microbes and infection. 2002 Sep 1;4(11):1193-202.

44. Miranda D, Bulger EM. Novel immune therapies in the management of streptococcal sepsis and necrotizing soft tissue infections. Surg Infect (Larchmt). 2018;19(8):781-784. doi:10.1089/sur.2018.225

45. Pammi M, Haque KN. Pentoxifylline for treatment of sepsis and necrotizing enterocolitis in neonates. Cochrane Database Syst Rev. 2015;2015(3). doi:10.1002/14651858.CD004205.pub3

46. The Immunisation Advisory Centre. Guidelines for the management of tetanus-prone wounds. 2018;(November):2018. https://www.immune.org.nz/sites/default/files/resources/Written Resources/AdministrationTetanusFlowChartImac20181130V01Final.pdf

47. Lofgren SM, Abassi M, Rhein J, Boulware DR. Recent advances in AIDS-related cryptococcal meningitis treatment with an emphasis on resource limited settings. 2018;15(4):331-340. doi:10.1080/14787210.2017.1285697.Recent

48. Pan C, Liu H, Robins E, Song W, Liu D, Li Z, Zheng L. Next-generation immuno-oncology agents: current momentum shifts in cancer immunotherapy. J Hematol Oncol. 2020 Apr 3;13(1):29. doi: 10.1186/s13045-020-00862-w. PMID: 32245497; PMCID: PMC7119170

49. Wrobel P, Ahmed S. Current status of immunotherapy in metastatic colorectal cancer. Int J Colorectal Dis. 2019 Jan;34(1):13-25. doi: 10.1007/s00384-018-3202-8. Epub 2018 Nov 21. PMID: 30465238

50. Cappelli LC, Shah AA, Bingham CO 3rd. Immune-Related Adverse Effects of Cancer Immunotherapy- Implications for Rheumatology. Rheum Dis Clin North Am. 2017 Feb;43(1):65-78. doi: 10.1016/j.rdc.2016.09.007. Epub 2016 Oct 22. PMID: 27890174; PMCID: PMC5127444

51. Riley RS, June CH, Langer R, Mitchell MJ. Delivery technologies for cancer immunotherapy. Nat Rev Drug Discov. 2019 Mar;18(3):175-196. doi: 10.1038/s41573-018-0006-z. PMID: 30622344;

PRAXIS
UNDERGRADUATE MEDICAL RESEARCH JOURNAL

CASE REPORT

Dermatological manifestations in Polycythemia Rubra Vera after long-term hydroxyurea therapy

Meghanshi Rajput[a]

[a]Medical Student, Lady Hardinge Medical College, New Delhi

Article Info

Article History:
Received: 15 June 2022
Accepted: 06 October 2022
Available: 18 November 2022

Keywords:
Dermatomyositis
Hydroxyurea
Polycythemia
Skin

meghanshi.rajput@gmail.com
(Meghanshi Rajput)

Abstract

Hydroxyurea (HU) is an antitumor drug, chemically a derivative of hydroxylated urea. HU is used in the treatment of several hematological diseases and myeloproliferative disorders. With its prolonged use, various dermatological lesions are manifested by the patient, suggestive of toxic effects of hydroxyurea. Here, we reported a case of a 67-year-old lady with a diagnosis of Polycythemia Rubra Vera who presented with dermatological side effects after 13 years of primary treatment.

Introduction

Hydroxyurea (HU) is an antineoplastic drug, chemically a hydroxylated urea derivative. As a chemotherapeutic agent, HU is used in the treatment of several hematological diseases, such as myeloproliferative disorders. Hydroxyurea is usually well tolerated, but numerous skin changes have been associated with the prolonged HU therapy, such that there is an increased occurrence of dermatomyositis-like eruptions, xerosis, hyperpigmentation, ichthyosis, atrophic and ulcerative lesions.[1,2]

Here, we reported a case of a 67 years old lady with a diagnosis of Polycythemia Rubra Vera that in 13 years of treatment with hydroxyurea has developed many muco-cutaneous lesions. The aim of this case report is to emphasize cutaneous manifestation after prolonged treatment of hydroxyurea in the patient of polycythemia rubra vera.

Case Report

In May of 2008, a 67-year-old lady of Asian race was referred to the hematology centre because of her abnormal blood tests, splenomegaly and facial plethora. There were no lymphadenopathy or hemorrhage signs. Peripheral smear revealed polymorphonuclear leukocytosis. The bone marrow aspiration from iliac crest showed hypercellularity with M:E ratio of 7:1. The bone marrow biopsy showed hypercellular marrow with predominance of granulocytes series, normoblastic erythroid series, no increase in blasts and normal megakaryocytes, interpreting a myeloproliferative disorder. No signal for BCR-ABL transcript was detected in leukocytes of the peripheral blood. The diagnosis of Philadelphia negative myeloproliferative disorder, probably polycythemia rubra vera was made and the treatment was started with hydroxyurea adjusted to between 0.5 and 1.0g/day, according to hematological parameters. After thirteen years of treatment, the patient has numerous skin lesions that appeared gradually over 5 years: diffuse skin hyperpigmentation, oral ulcers, atrophic lesions on forearms, melanonychia of the nails, diffuse cutaneous xerosis, and ichthyosis on legs.

The patient has been followed by both dermatology and hematology departments, it was decided to maintain therapy with hydroxyurea associated with photoprotection and topical care for the skin lesions by emollient lotions.

Tapering the daily dose of the drug from 1g/day to 0.5g/day reduced the lesions. Withdrawal of the drug generally leads to spontaneous healing of these lesions. The patient is continuing regular follow up.

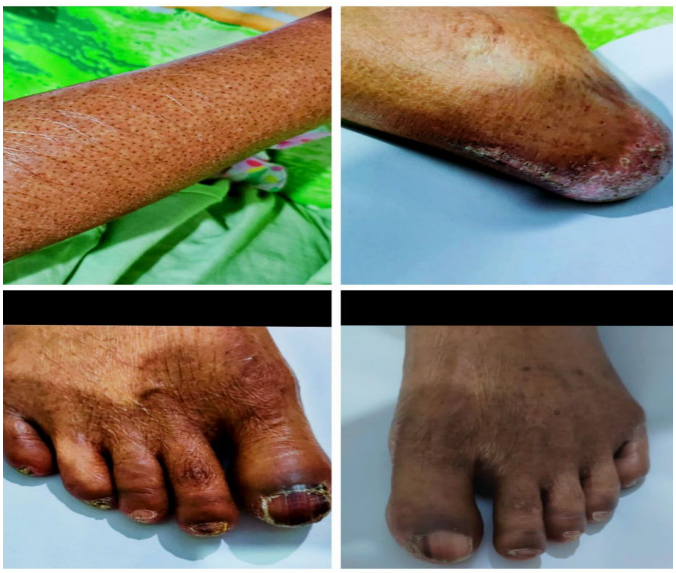

Figure 1: Cutaneous xerosis of lower leg, atrophic lesion over Achilles tendon area, melanonychia with longitudinal bands on foot, and decrease of melanonychia on foot after suspension of hydroxyurea

Figure 2: Hyperpigmentation of both hands with atrophic lesions and melanonychia of nails and ichthyosis of forearm

Discussion

Hydroxyurea (HU) is an antineoplastic drug, chemically a hydroxylated urea derivative which acts as a metabolic inhibitor of ribonucleotide reductase and a potent non alkylating myelosuppressive agent. This chemotherapeutic agent inhibits the conversion of ribonucleotides into deoxyribonucleotides when it inhibits M2 subunit of ribonucleotide reductase. Thus, interfering in DNA synthesis of proliferative cells, leading them to death in the S phase of cell cycle.[5] HU is used in treatment of many hematological disorders, mainly for Philadelphia chromosome-negative myeloproliferative syndromes and sickle-cell disease.[4] HU is usually a well-tolerated drug, but several mucocutaneous adverse effects have been observed on prolonged treatment with it, resulting in pain and discomfort. There is involvement of all three mucocutaneous areas (skin, nails, and mucosa) resulting in dermatomyositis like eruptions, diffuse hyperpigmentation, xerosis, ichthyosis, alopecia, facial erythema, nail alterations, keratosis of palms & soles, stomatitis, aphthous ulcers in oral cavity and various atrophic and ulcerative lesions.[6,7]

Multiple ulcers are associated with long term hydroxyurea therapy, though the pathogenesis is still not clear. It is proposed that various theories that could be responsible include DNA inhibition theory, thrombokinesis, and microcirculation rheology theory. [8]

The other skin alterations such as xerosis, ichthyosis, and diffuse hyperpigmentation are quite common on prolonged treatment with HU. Nail alterations include longitudinal bands, transverse bands with diffuse pigmentation, which may occur simultaneously in the same patient. For these cutaneous lesions, photoprotection and topical care by emollient lotions may be administered. These lesions regress on withdrawal of the medication, thus indicating these lesions are drug induced toxicity.

Hydroxyurea is categorized as an essential drug by WHO and is commonly prescribed for indefinite period in treatment of several hematological diseases such as polycythemia vera, and essential thrombocytosis. Care providers often tend to show insufficient awareness of cutaneous side effects, and often miss diagnosis or diagnosis is made late. Therefore, regular dermatologic screening should be performed on hydroxyurea-treated patients.

Conclusion

The patients on long term hydroxyurea therapy need regular dermatological follow-up for the early diagnosis and selection of appropriate treatment for cutaneous lesions.

Conflict of Interest: None declared
Financial Support and Sponsorship: No external funding.

References

1. França ER, Teixeira MAG, Matias KF, Antunes DECM, Braz RA, Silva CEF. Cutaneous adverse reactions after prolonged use of hydroxyurea in Polycythemia Vera. An Bras Dermatol. 2011;86(4):751-4.

2. Cantisani C, Kiss N, Naqeshbandi A.F, Tosti G, Tofani S, Cartoni C, Carmosino I, Cantoresi F. Nonmelanoma skin cancer associated with Hydroxyurea treatment: Overview of the literature and our own experience.

3. Oskay T, Kutluay L, Ozyilkan O. Dermatomyositis-like eruption after long-term hydroxyurea therapy for polycythemia vera. Eur J Dermatol. 2002 Nov-Dec;12(6):586-8. PMID: 12459535.

4. Quattrone F, Dini V, Barbanera S, Zerbinati N, Romanelli M. Cutaneous ulcers associated with hydroxyurea therapy. J Tissue Viability. 2013 Nov;22(4):112-21. doi: 10.1016/j.jtv.2013.08.002. Epub 2013 Aug 28. PMID: 24050921.

.

5. Bohn J, Hansen J.P.H, Menné T. Ulcerative lichen planus-like dermatitis due to long term hydroxyurea therapy. Journal of the European Academy of Dermatology and Venereology.

6. Ferrari A, Carobbio A, Masciulli A, Ghirardi A, Finazzi G, Stefano V.D, Vannucchi A.M, Barbui T. Clinical outcomes under hydroxyurea treatment in polycythemia vera: a systematic review and meta-analysis. Haematologica. 2019 Dec; 104(12): 2391–2399.

7. Mendonça R, Gueiros LA, Capellaro K, Pinheiro VP, Lopes MA. Oral lesions associated with hydroxyurea treatment. Indian J Dent Res 2011;22:869-70

8. Xu Y., Liu J., Hydroxyurea-induced cutaneous squamous cell carcinoma: A case report. World J Clin Cases. 2019 Dec 6; 7(23): 4091–4097.

PRAXIS
UNDERGRADUATE MEDICAL RESEARCH JOURNAL

IMAGES IN CLINICAL MEDICINE

Nail Changes following Chemotherapy

Ashvin Varadharajan[a]

[a] Medical student, Armed Forces Medical College, Pune

Article Info

Article History:
Received: 12 August 2022
Accepted: 10 September 2022
Available: 18 November 2022

Keywords:
Chemotherapy
Leukonychia
Chromonychia
Mees
Muerkhe
Beau

ashvinv2510@gmail.com
(Ashvin Varadharajan)

Case Report

This 56-year-old lady was diagnosed with metastatic carcinoma colon when she presented with weight loss and pain abdomen. She was started on multi-agent chemotherapy with following drugs every 2 weeks: 5-Fluorouracil, Leucovorin and Oxaliplatin. She responded initially after six cycles but progressed after twelve cycles of the regime. She was started on second-line therapy with 5-Fluorouracil, Leucovorin and Irinotecan. She continues to be on the regime with partial response.

Anticancer chemotherapy has been found to induce a variety of upsetting side effects, among which are chemotherapy-induced nail changes. These include Mees' lines (true leukonychia), Muerkhe's lines (apparent leukonychia), Beau's lines, and chromonychia (nail pigmentation). Mees' lines are white transverse non-blanchable bands running across the entire nail-bed, parallel to the lunula, which migrate with nail growth.1 They result from onychocytes parakeratosis in ventral nail plate, as an outcome of drug-induced toxic insult to nail matrix. Mees' lines may also be seen in arsenic poisoning, Hodgkin's lymphoma, SLE, and even COVID-19.[2] Muerkhe's lines are fainter than Mees' lines, do not migrate with nail growth, and disappear upon nail compression. These occur due to chemotherapy-associated vascular congestion leading to nail-bed edema or abnormal nail attachment.[3] They may also be seen in severe hypoalbuminemia.[4]

Beau's lines are transverse depressions on the proximal nail bed, resulting from interruption of mitotic activity. This interruption, in extreme cases, can involve the entire depth of nail matrix leading to shedding of nails (onychomadesis). They may also occur in Raynaud's disease and nail infections.

Anti-cancer chemotherapy may also lead to brownish-black, characteristically transverse bands of pigmentation known as melanonychia. These occur due to melanocyte activation and proliferation in nail matrix. Other causes of melanonychia include infections (Trichophyton, Pseudomonas, HIV), subungual keratosis, psoriasis, friction, endocrine disorders (Addison's disease, Cushing's disease, hyperthyroidism), phototherapy and X-ray exposure.[5]

Figure 1:
Mees' line (yellow arrow) and Melanonychia (yellow star)

References

1. Huang T-C, Chao T-Y. Mees lines and Beau lines after chemotherapy. C Can Med Assoc J = J l'Association medicale Can. 2010 Feb;182(3):E149.

2. Fernandez-Nieto D, Jimenez-Cauhe J, Ortega-Quijano D, Diaz-Guimaraens B, Dominguez-Santas M, Martinez-Rubio J. Transverse leukonychia (Mees' lines) nail alterations in a

3. Gupta A, Parakh A, Dubey AP. Chemotherapy induced nail changes. Indian J Dermatol. 2008;53(4):204–5.

4. Alzahrani MF, AlJasser MI. Nail Changes during Chemotherapy. N Engl J Med. 2018 Oct;379(16):1561.

5. Singal A, Bisherwal K. Melanonychia: Etiology, Diagnosis, and Treatment. Indian Dermatol Online J. 2020;11(1):1–11.

PRAXIS
UNDERGRADUATE MEDICAL RESEARCH JOURNAL

IMAGES IN CLINICAL MEDICINE

A rare case of Pachydermoperiostosis

Satyabrata Singha[a]

[a] Medical student, Armed Forces Medical College, Pune

Article Info

Article History:
Received: 14 August 2022
Accepted: 03 September 2022
Available:18 November 2022

Keywords:
Hypertrophic osteoarthropathy
Touraine-Gole-Solente
Cutis verticis gyrate
Pachydermoperiostosis

satyabrata112200@gmail.com
(Satyabrata Singha)

Case Report

A 26 year old male presented with asymptomatic swellings of the distal parts of all the fingers & toes since last 20 years which was gradually progressive for the initial 15 years & pain over the right knee joint of 2-week duration. On clinical examination there was grade IV clubbing in all the fingers & toe nails. X-ray examination showed periostitis of both the hands, feet & leg bones. Rest of the dermatological examination & ECG was within normal limits.

Based on these findings, a diagnosis of primary pachydermoperiostosis was made.

Pachydermoperiostosis or hypertrophic osteoarthropathy, also known as Touraine-Gole-Solente is an autosomal dominant disorder characterized by clubbing and periosteal new bone formation that involves distal extremities.[1] Clinical features include clubbing of digits, hyperhidrosis and thickening of skin especially face and forehead, cutis verticis gyrata, arthralgia and limited joint movement.

Primary Pachydermoperiostosis should be differentiated from secondary hypertrophic osteoarthropathy (HOA) by radiography of digits which shows exuberant new bone formation and a smooth undulating surface whereas primary HOA has irregular periosteal surface.

Three forms of this disease were described: classic or complete form, presented with skin and skeletal changes; incomplete form, with skeletal changes but no dermal findings; and forme fruste with dermal changes but no skeletal findings.

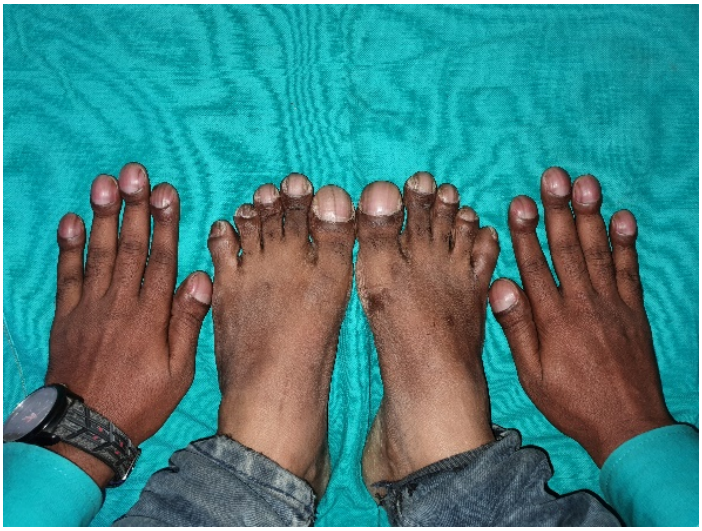

Figure 2: Bilateral clubbing of finger and toes

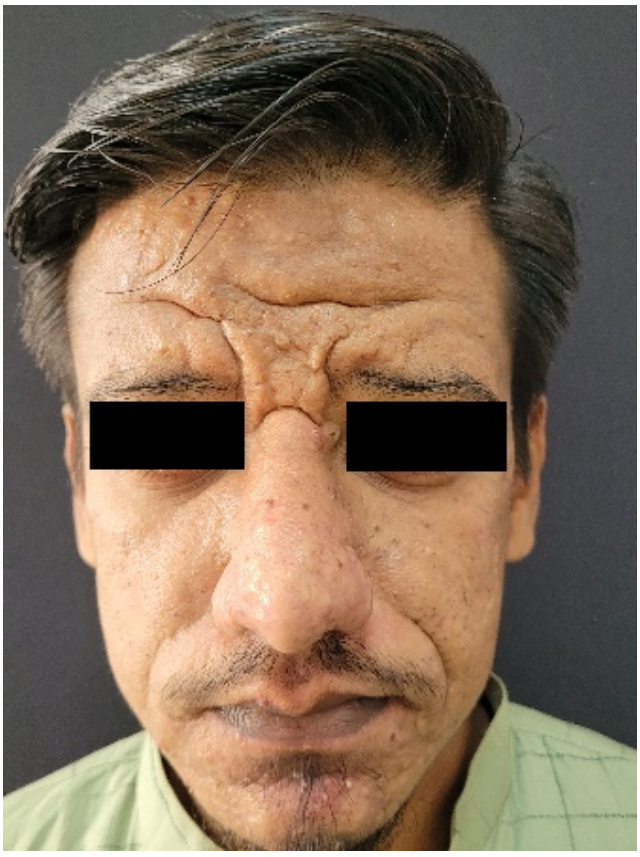

Figure 1: Coarse thickened skin with furrows on forehead and deep nasolabial folds

No specific treatment exists; however, in most cases, PDP tends to stabilize over time. The therapeutic options for the control of symptoms consist of aspirin, nonsteroidal anti-inflammatory drugs (NSAID), systemic corticosteroids, and colchicine.[2] Plastic surgery is reserved for those patients with significant eyelid ptosis or those with severe aesthetic problems.[3]

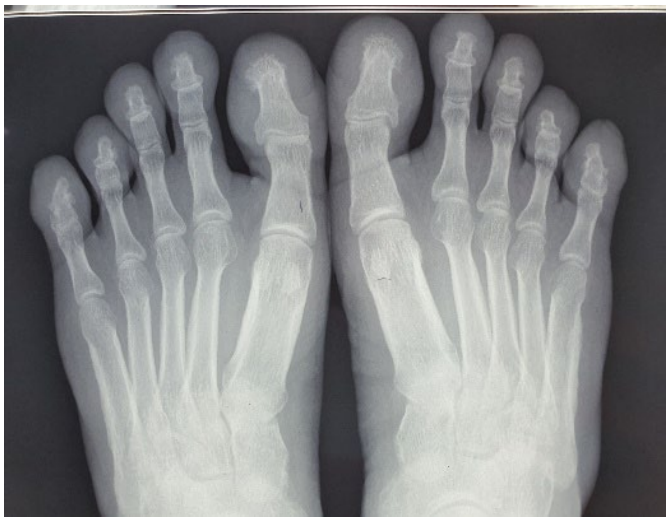

Figure 2: Periostitis in the great toe and distal pharynx

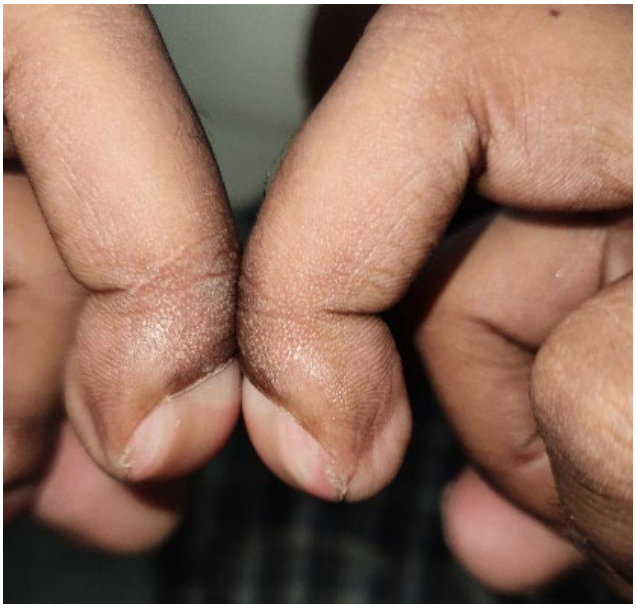

Figure 3: Grade IV clubbing (Drumstick appearance)

References

1. Jajic Z, Jajic I, Nemcic T. Primary hypertrophic osteoarthropathy: clinical, radiologic, and scintigraphic characteristics. Archives of medical research. 2001 Mar 1;32(2):136-42

2. Zhang H, Yang B. Successful treatment of pachydermoperiostosis patients with etoricoxib, aescin, and arthroscopic synovectomy: Two case reports. Medicine. 2017 Nov;96(47).

3. Taichao D, Fuling L, Hengguang Z. Comprehensive surgical strategies for the management of pachydermoperiostosis. Facial Plastic Surgery. 2018 Jun;34(03):330-4.

PRAXIS
UNDERGRADUATE MEDICAL RESEARCH JOURNAL

IMAGES IN CLINICAL MEDICINE

A case of Malignant Melanoma

Ashi Anand[a]

[a] Medical student, Armed Forces Medical College, Pune

Article Info

Article History:
Received: 16 August 2022
Accepted: 03 October 2022
Available:18 November 2022

Keywords:
Superficial spreading melanoma
Nodular melanoma
Lentigo maligna melanoma
Acral lentiginous melanoma

ashianand786@gmail.com
(Ashi Anand)

Case Report

This 47 years old lady presented with complaints of dark raised lesions on the skin of the abdomen in the last two months. There was no history of any associated complaints. Dermatological examination revealed multiple black coloured papules and nodules on abdomen. They were non tender and non-ulcerated with no bleeding on touch. Histopathology from one of the nodules revealed features of melanoma. According to ABCDE's of melanoma it was diagnosed to be malignant melanoma.

Malignant melanoma is a malignancy of pigment-producing cells (melanocytes), which are located primarily in the skin, but also found in the ears, gastrointestinal tract, eyes, oral and genital mucosa and leptomeninges. Based on clinical and pathological findings there are 4 types of melanoma: superficial spreading melanoma, which is the most common type, characterized by being a flat lesion with irregular borders and various types of pigmentation; nodular melanoma , the most aggressive, showing a vertical growing pattern, black–blue colour and presents a tendency to bleed and/or ulcerate; lentigo maligna melanoma, shows as a flat pigmented lesion with dark coffee colour, acral lentiginous melanoma, the least frequent type that predominates in black and mixed–race people, it´s observed in the palm of the hands, soles or the nail bed.[1]

Melanoma treatment usually consists of surgical removal of the tumour with a portion of the surrounding normal skin. Alternatively, a surgical biopsy of the lymph nodes could be necessary to rule out dissemination of cancer close to the primary lesion.

Surgery as the only method of treatment is realized in small and superficial melanomas. In case of the lesion doesn´t have this characteristics, radiotherapy, chemotherapy and immunotherapy are recommended. If the depth of the lesion is more than 4mm or if the conclusion of the lymph nodes biopsy is positive, a high risk of dissemination to other organs exists. Interferon–α is recommended in these cases after surgery. In patients who melanoma spreads to other organs apart from skin and lymph nodes, treatment is more complex and generally doesn´t have a cure, being palliative care the treatment of choice. In this cases chemotherapy and use of interferon–α o interleukin–2 could be considered.

Malignant melanoma is a malignant neoplasia which represents a high rate of mortality and bad prognosis due to lack of early diagnosis. Therefore, periodical screening of suspicious lesions and early detection of this entity allow a timely treatment which enable complete cure of the disease in most cases.[2]

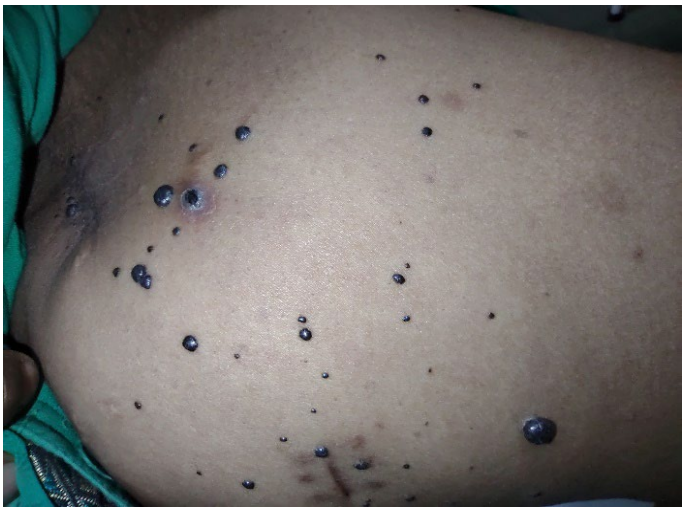

Figure 1: Dark raised lesions on the skin of the abdomen

References

1. McCourt C, Dolan O, Gormley G. Malignant melanoma: a pictorial review. Ulster Med J. 2014 May;83(2):103-10.

2. Mosqueira JR, Gomez E, Bravo F, Vega JD, Soto L. Malignant melanoma: Case report and review of the literature. Open Access J Trans Med Res. 2017;1(2):00008.

PRAXIS
UNDERGRADUATE MEDICAL RESEARCH JOURNAL

IMAGES IN CLINICAL MEDICINE

Skin features of Tuberous Sclerosis Complex

Aditya Jayapalan[a]

[a] Medical student ,Armed Forces Medical College, Pune

Article Info

Article History:
Received: 08 August 2022
Accepted: 06 September 2022
Available:18 October 2022

Keywords:
Tuberous sclerosis
Bourneville disease
Köenen tumors
Shagreen patches

adijmenon110302@gmail.com
(Aditya Jayapalan)

Case Report

A 25-year-old male visited the skin OPD with complaints of skin coloured raised lesion on the face, brown coloured patch on the face, a patch on the back of upper trunk, and fair raised skin lesion on lower back. No discharge associated with the skin lesions. On general examination multiple brown sessile nodular growths were noted on the nose and cheeks in a characteristic “butterfly pattern” – angiofibromas. Hypermelanotic Café-au-lait patch was noted on the right cheek of the patient. Similar sessile and nodular growths were noted in the upper and lower extremities, suggestive of periungual fibromas or Köenen tumors. On the lower back an orange peel appearance, is examined, indicative of shagreen patch. Hypomelanotic macules of variable size and shape were also noted in the lower trunk’s posterior region. Vital signs were found to be within satisfactory limits. According to the diagnostic criteria of International Tuberous Sclerosis Complex Consensus Conference 2012 with more than two major features, the case was diagnosed to be of Tuberous Sclerosis Complex (TSC).[1]

Tuberous sclerosis complex (TSC), also known as Bourneville disease, is a genetic multisystem disorder with an autosomal dominant inheritance pattern, with prominent skin involvement that frequently occurs in early childhood, occurs with a frequency of about 1:5800 to 1:12300 births.

Dermatological manifestations are the earliest to occur thus helping in early diagnoses of the condition if identified in time. The main dermatological manifestations are hypomelanotic macules (ash- leaf spots), facial angiofibromas, shagreen patches (collagenomas), fibrous cephalic plaques, periungual fibromas and multiple café-au-lait spots. Although these skin lesions usually do not lead to severe complications but can be disfiguring and can cause severe psychological issues for TSC patients and their families.[2]

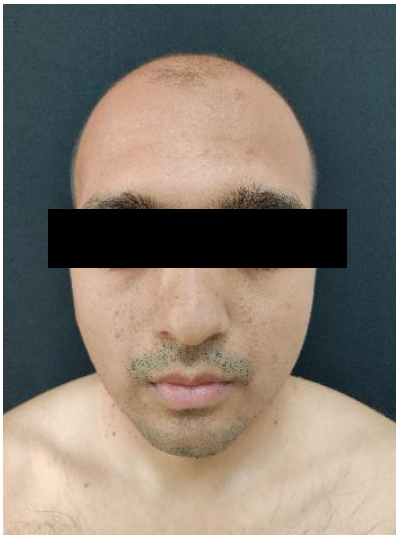

Figure 1: Facial angiofibromas - skin-coloured papules involving the malar region in butterfly distribution Mees' line (yellow arrow) and Melanonychia (yellow star)

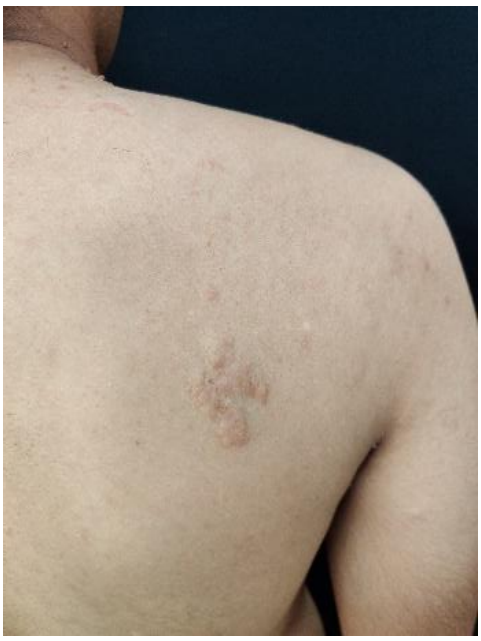

Figure 3: Shagreen patch on the upper back

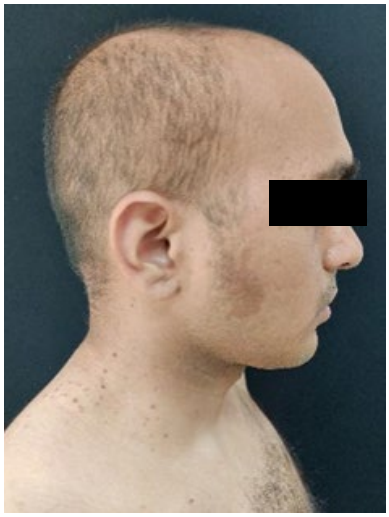

Figure 2: Café-au-lait patch on the face

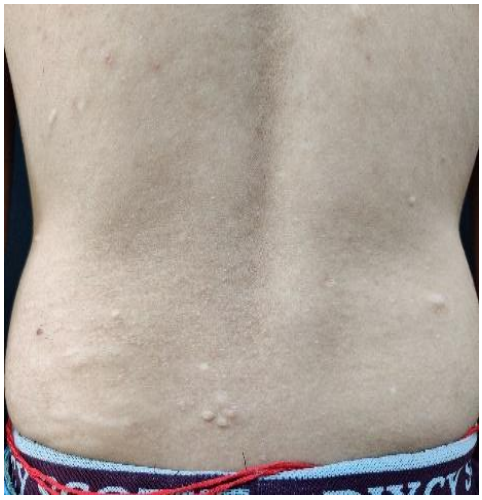

Figure 4: Hypomelanotic macule and several plaques with variable size and shape located on the lower back

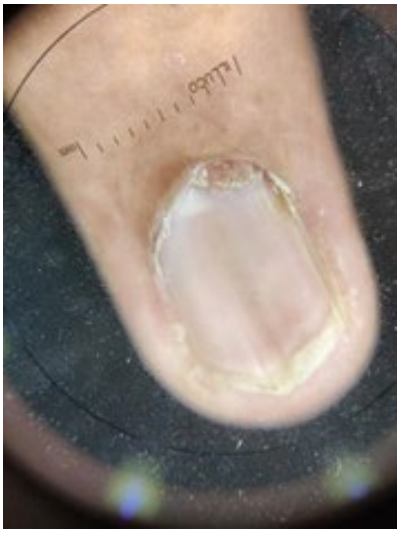

Figure 5: Periungual fibroma- a nodular sessile growth near the nail on the nail bed

References

1. Northrup H, Krueger DA, Roberds S, Smith K, Sampson J, Korf B, Kwiatkowski DJ, Mowat D, Nellist M, Povey S, de Vries P. Tuberous sclerosis complex diagnostic criteria update: recommendations of the 2012 International Tuberous Sclerosis Complex Consensus Conference. Pediatric neurology. 2013 Oct 1;49(4):243-54.
2. Ebrahimi-Fakhari D, Meyer S, Vogt T, Pföhler C, Müller CS. Dermatological manifestations of tuberous sclerosis complex (TSC). JDDG: Journal der Deutschen Dermatologischen Gesellschaft. 2017 Jul;15(7):695-700.

PRAXIS
UNDERGRADUATE MEDICAL RESEARCH JOURNAL

LETTER TO THE EDITOR

Impact of Online Classes and Risk of Computer Vision Syndrome During COVID-19 Pandemic

Victor Ghosh[a], Lakshmi Deepak Bethineedi[a], Tarun Kumar Suvvari[b]

[a] Medical Student, Andhra Medical College, Vishakhapatnam

[b] Medical Student, Rangaraya Medical College, Kakinada

The COVID-19 outbreak has impacted everyone's life and daily activities. The education system is the one that has been hit the most. It shifted traditional classroom sessions to a digital platform. As a result, students' screen time on digital gadgets increased. In the long run, this will raise the risk of vision problems and ocular pathologies associated with symptoms such as tiredness, straining of eyes and redness leading to blurred or double vision.[1] Computer vision syndrome (CVS), often known as digital eye strain (DES),[2] is one of the common pathologies to consider.

CVS patients present with a range of ocular and visual symptoms. Many millions of people of all ages are at risk of DES as a result of the huge rise in digital gadget usage in recent years. While the symptoms are typically transitory, the illness can cause severe and recurring discomfort for patients, as well as major economic repercussions for those who work with computers on a regular basis.[2,3] Symptoms include eye strain, headaches, blurred vision, dry eyes and pain in the neck and shoulders. Prolonged exposure to low intensity light from digital devices is also a probable risk factor for disruption of the melatonin secretion cycle from pineal gland and thereby interrupting circadian sleep cycles.[2]

The education system has become virtual and online as a result of the Covid 19 epidemic. This pushed students to utilize digital gadgets for longer timeframes. The long-term effects of this continuous use might lead to DES or CVS.[4] Continuously staring at a screen might lower the natural blink rate of the eyelids, increasing the risk of dry eye. Eye exercises and taking regular pauses between sessions might help to alleviate the issue to some extent. "20-20-20" rule is used to alleviate the strain by relaxing the eyestrain after every 20 minutes of work by fixing vision at 20 feet distant object for 20 seconds. This helps in relaxation of intraocular muscles and decrease further defect causation. The time and distance are not specific and can be approximated according to person comfort.

Amit Mohan Et al studied children aged 10 to 17 who had recently developed asthenopic symptoms.[5] During the COVID-19 epidemic, they subjectively assessed the degree of visual fatigue in children attending online classes, as well. Online classes lasting more

than 4 hours were shown to be more harmful to abnormal binocular vergence and accommodation parameters than online Balsam Alabdulkader conducted a questionnaire-based study on usage of digital devices and associated DES symptoms during home isolation and curfew times.[6] This survey showed that the symptoms are associated with the duration of digital devices usage and also to occupation type they are involved in.[7]

DES or CVS can be prevented by positioning computer screens 22 to 28 inches away from eyes, maintaining a distance of about 4 to 5 inches, and tilting the screen back about 10 to 20 degrees.[8] Blinking often will help keep eyes hydrated, minimizing dry eyes; lowering computer glare can help to some extent lessen eye strain; wearing blue light-blocking eyewear; using lubricating eye drops; and adhering to the 20-20-20 rule will help to prevent CVS.[9] With a change in lifestyle, CVS symptoms resolve on their own. But one should see a doctor if they experience symptoms such as rapid changes in vision, flashes in the eyes, eye pain or redness, or dry eyes that are resistant to eye drops and continue to worsen.[10]

In conclusion, classes lasting more than four hours may be more harmful to the eyes. Aside from classrooms, the growing use of digital gadgets across all occupations has had a significant impact on the eye. Regular eye examinations by health professionals, a reduction in screen time, taking breaks between sessions, and including eye exercises and massage techniques in daily routine can all help diagnosing and decreasing the impact of the disease at an early stage. Ophthalmic associations like All India Ophthalmological Society (AIOS), American Academy of Ophthalmology and others should consider digital eye strain (DES)/ computer vision syndrome (CVS) as a significant problem. More studies are required to assess the problem and there is a need to find out an effective solution.

References

1. Blehm C, Vishnu S, Khattak A, Mitra S, Yee RW. Computer vision syndrome: a review. Surv Ophthalmol. 2005 May-Jun;50(3):253-62. doi: 10.1016/j.survophthal.2005.02.008. PMID: 15850814.

2. Sheppard AL, Wolffsohn JS. Digital eye strain: prevalence, measurement and amelioration. BMJ Open Ophthalmol. 2018 Apr 16;3(1):e000146. doi: 10.1136/bmjophth-2018-000146. PMID: 29963645; PMCID: PMC6020759.

3. Suvvari TK, Kumar Kandula VD. Ocular symptoms and clinical profile associated with COVID-19. Pan Am J Ophthalmol 2021;3:11

4. Mohan A, Sen P, Shah C, Jain E, Jain S. Prevalence and risk factor assessment of digital eye strain among children using online e-learning during the COVID-19 pandemic: Digital eye strain among kids (DESK study-1). Indian J Ophthalmol. 2021 Jan;69(1):140-144. doi: 10.4103/ijo.IJO_2535_20. PMID: 33323599; PMCID: PMC7926141.

5. Mohan, Amit, et al. "Binocular Accommodation and Vergence Dysfunction in Children Attending Online Classes During the COVID-19 Pandemic: Digital Eye Strain in Kids (DESK) Study-2." J Pediatr Ophthalmol Strabismus. 2021;58(4):224–231

6. Alabdulkader B. Effect of digital device use during COVID-19 on digital eye strain. Clin Exp Optom. 2021 Aug;104(6):698-704. doi: 10.1080/08164622.2021.1878843. Epub 2021 Feb 22. PMID: 33689614.

7. Al Tawil L, Aldokhayel S, Zeitouni L, Qadoumi T, Hussein S, Ahamed SS. Prevalence of self-reported computer vision syndrome symptoms and its associated factors among university students. Eur J Ophthalmol. 2020 Jan;30(1):189-195. doi: 10.1177/1120672118815110. Epub 2018 Nov 26. PMID: 30474390.

8. Rosenfield M. Computer vision syndrome: a review of ocular causes and potential treatments. Ophthalmic Physiol Opt. 2011 Sep;31(5):502-15. doi: 10.1111/j.1475-1313.2011.00834.x. Epub 2011 Apr 12. PMID: 21480937.

9. Gowrisankaran S, Sheedy J. Computer vision syndrome: A review. Work. 2015;52(2):303-314.

10. Bogdănici C, Săndulache D, Nechita C. Eyesight quality and Computer Vision Syndrome. Rom J Ophthal. 2017;61(2):112-116

PRAXIS
UNDERGRADUATE MEDICAL RESEARCH JOURNAL

The Editorial Team...

Left to Right

Med Cdt Aditya Jayapalan : Associate Editor (Student Division)
Med Cdt Shivam Singh: Technical Editor (Student Division)
Med Cdt Ashvin Varadharajan: Editor-in-Chief (Student Division)
Gp Capt (Dr.) TVSVGK Tilak: Deputy Editor and Officer-in-Charge
Med Cdt Ritwik Johari: Associate Editor (Student Divison)
Med Cdt Satyabrata Singha: Associate Editor (Student Division)
Med Cdt Ashi Anand: Associate Editor (Student Division)


PRAXIS
An Undergraduate Medical Research Journal