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Training for Translation – The Physician Scientist's Career Path

Siobhan V. Glavey,[1] Ilyas Sahin,[1] Francisco J. Bonilla-Escobar,[2] Juliana Bonilla-Velez[3]

"Translational research transforms scientific discoveries arising from laboratory, clinical, or population studies into clinical applications to reduce cancer incidence, morbidity, and mortality"

Translational Research Working Group NCI.[1]

The terms "translational research" or "bench-to-bedside" have become buzzwords in the last ten years and are used to refer to the process of transfer of knowledge from the basic sciences to its application in the clinical and community based setting.

The "translation" of scientific discovery into clinical outcomes may seem like a fluid process but in reality is met with major stumbling blocks related to challenges faced in science, medicine and public health. Although this process has been a natural part of the advancement of medical and scientific knowledge, since their emergence, it has gained increased focus in the last number of years for a variety of reasons. Major advances in scientific research have been made in many fields at an unprecedented pace in the last decade. One such example in the genomic field has been the human genome project and the subsequent deep sequencing data that continues to emerge from this.[2] This has resulted in a plethora of new data emerging in the life sciences with the knock on effect in the translational field being that high-throughput mechanisms are needed to bring benefits to patients in an effective and timely manner. This translation is, increasingly, being carried out by highly skilled individuals in the translational field who are capable of bridging the gap between science and medicine. Many of those with an interest in these fields in recent years have opted to pursue this path in a coordinated manner through dual training with doctorate degree in medicine and science, often as a formal MD/PhD program.

Since 2005, the National Institute of Health (NIH) in the United States has focused on funding translational research with an increasing focus on the biomedical field and collaboration between clinicians and scientists. In 2006, they launched the Clinical and Translational Science Award program with the stated goals of accelerating the process of translating laboratory discoveries into treatments for patients, to engage communities in clinical research efforts, and to train a new generation of clinical and translational researchers.[3]

This is however not a new concept, but recognition of an increasing and unmet need. Many of the major discoveries in clinical medicine that have benefited patients all over the world have been led by physician scientists who were able to formulate scientific hypothesis based on clinical observations. Physician scientists work in a dual capacity in both fields where they can act as catalysts for discovery and innovation on both sides. However, gaining a strong background in both clinical medicine and basic science remains a challenge. This pathway traditionally begins with attending medical school and gaining clinical expertise as a physician. It is not always possible to acquire significant experience in laboratory-based research during this time, with most students learning the basics in taught courses and some electing to spend summer months in laboratory rather than clinical settings.

This has been addressed in recent years in the United States and other countries with several academic institutions now offering MD/PhD programs aimed at highly competitive candidates who are interested in dual training in medicine and science. The American Association of Medical Colleges has a detailed list of the available programs in the United States on their website. (Available from: https://www.aamc.org/students/research/mdphd/applying_md-phd/61570/mdphd_programs.html, updated 2010 Oct 1; cited 2013 Sept 18) These programs provide mentorship and training in a coordinated and focused manner and prepare individuals for becoming independent physician scientists. In Europe and Asia several programs are also being developed to train physician scientists and in Latin America there are now two countries offering MD/PhD programs, Mexico and Brazil (Available from: http://www.itesm.edu/wps/wcm/connect/snc/portal+informativo/por+campus/monterrey/institucion/n200013654789, cited 2013 Sept 18).[4-6] It will take time for more of these programs to become established, as the curricula and objectives of such newly developed programs evolve, but the impetus and incentive for universities to offer these programs is increasing.[7] Such programs are usually designed to allow a more time-efficient track to the completion of training, as the length of the traditional non-integrated path can be a major deterrent for many individuals.

Outside of these programs students who wish to pursue a career as a physician scientists should be guided by their mentors and, most importantly, by their own research interests. Encouragement at this level is vital in early career development of physician scientists and can lead to life-long collaborations. Strong mentorship can help students to avoid compartmentalization of research training and practice from their clinical training, this is one of the main road blocks in the development of early physician scientists who often see these as distinct areas and have difficulty merging progress in both.

Following completion of an MD/PhD, candidates are likely to be

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highly competitive for residency programs in their chosen field. Ideally this path would see them continue their dual training by having protected time for research throughout, however this is often not feasible due to the high clinical commitment during this time. To address this, growing number of residency programs in the United States have established research track programs that are specifically aimed at MD/PhDs or those aiming to become physician scientists, which allow them to develop their clinical expertise while continuing to make advances in their chosen scientific field (Available from: https://freida.ama-assn.org/Freida/user/viewProgramSearch.do, updated individually by programs; cited 2013 Sept 18. Available from: http://www.physicianscientists.org/search/custom.asp?id=776, updated continuously; cited 2013 Sept 18).

Outside of the US this is also increasingly the case with investigators and funding agencies alike recognizing the importance of addressing the need for funding and support to translational research. Several public sector organizations, modeled on the NIH Center for Advancing Translational Sciences in the USA, are being developed and funding agencies in developed and developing countries are making specific funding available to the translational research sector.[8] In Europe, several initiatives have been established to promote translational research centers, such as the European research infrastructure (EATRIS) or the UK National Institute of Health Research Biomedical Research Units and Centres.[6,9,10] This is also being addressed by international societies and meetings which aim to promote translational research initiatives and foster collaborations.[10] This coordinated approach aids the development of physician scientists to becoming principal investigators by again avoiding compartmentalization and de-skilling in either area.

Following this many physician scientists will complete further post-graduate training or a fellowship in their chosen field before becoming faculty members at universities, medical schools and research institutes. The major challenge faced at this point is attainment of funding for research. This is often facilitated at the early physician scientist stage by the wonderful national and international collaborations that have developed between medicine and science. This can aid physician scientists to becoming independent principal investigators with the support of senior colleagues. Through this, physician scientists are in a position to enhance care of patients both directly and indirectly. While there remain several obstacles in the career development path of physician scientists there is no doubt that this is a highly rewarding career track, which is in the midst of an exciting era.

It is clear that medicine and science are now moving at an unprecedented pace and alongside this there is inevitably an increasing demand for experts who have the ability to translate between these two exciting areas. To achieve this early opportunities for students to engage in both disciplines should be encouraged and mentorship provided through this challenging but immensely rewarding process.

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Original Article

Prevalence and Side Effects of Energy Drink Consumption among Medical Students at Umm Al-Qura University, Saudi Arabia

Naif A. Bawazeer,[1] Najmah A. AlSobahi[1]

Abstract

Background: Energy drinks are freely available at markets and shops on the university campus without regulation or proper education regarding its side effects. The caffeine amount within energy drinks is high and could become an addictive substance or cause intoxication. Therefore, this study aims to assess the prevalence of energy drink consumption and its reported side effects among medical students. **Methods:** A total number of 257 medical students from Umm Al-Qura University completed a questionnaire about energy drinks that was administrated electronically from September through November, 2012. **Results:** Out of the 257 participants, 27.2% (n=70) reported consuming at least one energy drink per month, with 61.5% (n=48) being males. Males consume significantly more energy drinks than females (p=0.0001). The students consumed energy drinks to get energy in general (32.8%) and while studying for exams or finishing a project (31.4%). Other reasons given include, lack of sleep (12.8%), just to be like friends (11.4%), or driving (8.5%). Heart palpitations are the most common side effect in our sample (20%), followed by insomnia (10%), headache and tremors (5.7%), nausea and vomiting (4.2%) and nervousness (2.8%). **Conclusion:** Energy drinks consumption is common practice among medical students and the main reason cited for consumption is the need for energy during general activities. Approximately one-third of the consumers manifested some side effect after consumption. We recommend the need to create public awareness about energy drinks. Further studies are recommended to assess the educational level of students consuming energy drinks, about the dangerous side effects.

Keywords: Energy Drinks, Caffeine, Adverse effects, Medical Students (Source: MeSH-NLM)

Introduction

Energy drinks started in 1997 when RedBull® was first released, and followed by many others trade names. With time, energy drinks became more than just drinks, the young population consumed them to indicate they have an athletic and modern lifestyle, while others to increase their cognitive function, especially before exams or an assignment deadlines.[1] Hence, more than 500 new energy drinks had been launched worldwide by 2006 and beverage companies were reaping the financial rewards of the 5.7 billion dollar energy drink industry.[2]

The literature shows that energy drinks give consumers some energizing effects when compared to placebo, as the advertisements claim.[3] Caffeine is the primary compound responsible for these effects and it is absorbable by all body tissues. Caffeine is structurally similar to adenosine, and its amount in 8 ounces of energy drinks is about 80 to 141 mg.[4] In addition, previous studies have revealed that high caffeine amounts are able to induce diuresis, insulin resistance and increase mean arterial blood pressure.[5] Also, high contents of carbohydrates, guarana, taurine, ginseng and creatine play an important role in the energy boosting process.[6] Furthermore, caffeine can fulfill all the criteria for being an addictive substance, namely dependence, tolerance, and withdrawal.[7] The symptoms of caffeine withdrawal include nervous irritability, tremors, muscle twitching, sensation disturbances, tachypnea, palpitation, flushing, arrhythmias, diuresis, gastrointestinal disturbances and patients may have generalized anxiety or depression.[8]

Previous studies showed that caffeine has side effects and may reach intoxication levels; studies show that almost every organ system is affected when caffeine is taken in large quantity.[9] Caffeine intoxication presents with nausea and vomiting, which can be difficult to control, along with agitation, nervousness, headache, tremors, and sleep disturbances.[10] More serious side effects include tachycardia and arrhythmias, in addition to electrolyte imbalances such as hypokalemia, hypomagnesaemia and hypophosphatemia. Seizures can result from the increased serum lactate, which is preceded by hyperglycemia and metabolic acidosis.[12] These conditions could result in a medical emergency. The clinical presentation typically resolves between 4 to 6 hours after intoxication.[11] On the other hand, the severity of symptoms has been reported to be less than that resulting from intoxication induced by caffeine directly from medications.[9]

Energy drinks are usually stored next to sport drinks in supermarkets and people may confuse them. In fact, sports drinks

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are beverages that aim to replace water and electrolytes lost through sweating during exercise, while energy drinks aim to induce performance-enhancing effects with nonnutritive stimulants that actually result in more dehydration.[15]

Energy drinks are freely available at markets and shops in university campus without regulation or proper education for its side effects for the general public, and more studies are needed to investigate the safety profile among consumers.[13,14] Therefore there is a great concern about energy drink consumption, especially among the young adult population. Previous studies conducted worldwide among college students and medical school students demonstrated that energy drink consumption is a common practice. However, all of them were observational studies that reflect the pattern and frequencies of consumption only. Moreover, in Saudi Arabia there are no previous studies exploring this uprising problem in the general public or among medical students.

The primary aim of this study was to estimate prevalence of energy drink consumption among Umm Al-qura University medical students and report the side effects present in this population. In addition, the study investigated reasons promoting the use of energy drinks and the beneficial effects after consumption.

Methods

In this study, 257 Umm Al-Qura University (Makkah, Saudi Arabia) medical students from different stages of the clinical years (4th, 5th and 6th years) participated in this cross-sectional survey, from September to November, 2012. The medical school at Umm Al-Qura University is from the public sector and students are enrolled from all over the country. A self-administered questionnaire was used to collect the data. We distributed the questionnaire electronically as a Google form© through social media website groups which covered all students from the clinical years. Invitation requests reached all 750 clinical years students, but there is no guarantee that all reviewed the invitation within the study period. Only 257 out of 750 clinical year students in Umm Al-Qura University completed the survey, for a response rate of 34.3%. The questionnaire was designed after reviewing selected related papers.[13-15]

The questionnaire can be found in the Appendix. Firstly, students were asked their gender, study year, and if they are consuming energy drinks. If they answered affirmatively, they would be prompted with the rest of the questionnaire. The questionnaire evaluated when they started consuming energy drinks, consumption pattern (frequency, quantity and type of energy drinks), reasons for consuming such drinks, if they feel more alert when having these beverages, if they experienced side effects and of which type: heart palpitations, headaches, crash episodes, insomnia, tremor, nervousness, nausea and vomiting and other (specify). Data was entered into SPSS software® (version16). The chi-square test was used to assess associations between variables and a value of $P<0.05$ was taken as statistically significant with a confidence level of 95%.

Permission from the Ethics committee at the University was granted prior to the initiation of this study. This study follows the STROBE guidelines for cross-sectional studies.

Table 1. Characteristics of Study Participants (N = 257)

Characteristic	n (%)
Age	
21	34 (13.2)
22	92 (35.8)
23	85 (33.1)
24	40 (15.6)
25	6 (2.3)
Gender	
Male	78 (30.4)
Female	179 (69.6)
Current year of education (clinical years)*	
4th year students	107 (41.6)
5th year students	72 (28.0)
6th year students	78 (30.4)

Legend: Current year of education in a 6-year program.

Figure 1. Prevalence of Energy Drink Consumption among Medical Students in Clinical Years.

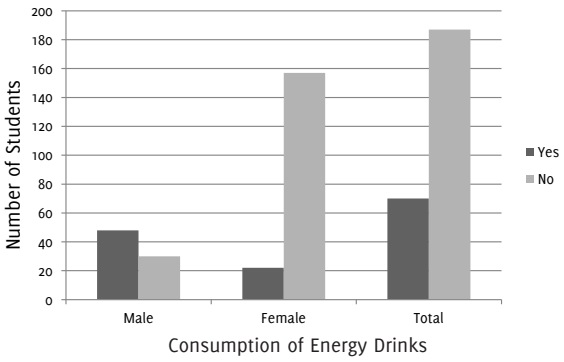
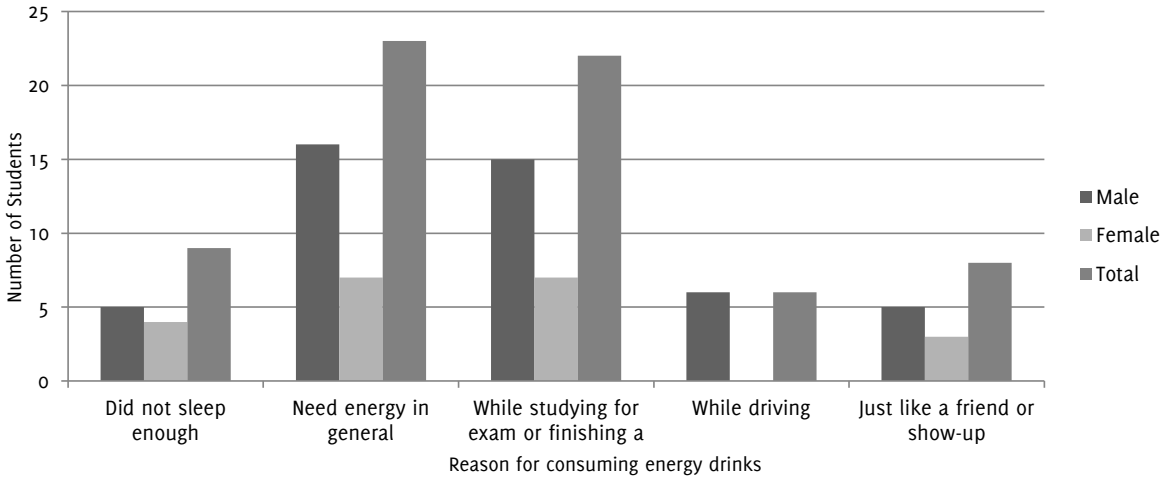


Table 2. Pattern of Consumption among Medical Students (N = 70).

Pattern of Consumption	n (%)
Start of Energy Drink Consumption	
Since joining med school	14 (20.0)
1 year ago	5 (7.1)
2 years ago	10 (14.3)
I don't remember	41 (58.6)
Frequency of Consumption	
Daily	8 (11.4)
Weekly	13 (18.6)
Monthly	5 (7.1)
Occasionally	44 (62.9)
Type of Energy Drink	
Regular	35 (50.0)
Sugar free	5 (7.1)
Did not notice	30 (42.9)

Figure 2. Reasons for Energy Drink Consumption among Medical Students in Clinical Years.



Results

A total of 257 participants (78 male, 179 female), aged 22.58 ± 0.98 years (ranging fromf 21 to 25 years) answered the questionnaire ***(Table 1)***. The total percentage of participants who consumed energy drinks was 27.2% (n=70) of all students ***(Figure 1)***. Regarding the gender of consumers, a significantly higher proportion of male students (61.5% of all male students, n=48) consumed energy drinks when compared to females (12.3% of all female students, n=22, p=0.0001). The pattern of consumption among medical students is presented in ***Table 2***. In the clinical years, the percentage of students that consumed energy drinks was 50.0% among 4th year students (n=35), 27.1% among 5th year students (n=19) and 22.9% among 6th year students (n=16). Among consumers of energy drinks, 71.4% used them once daily, 17.1% used them twice daily, and 1.4% drank more than 3 bottles daily.

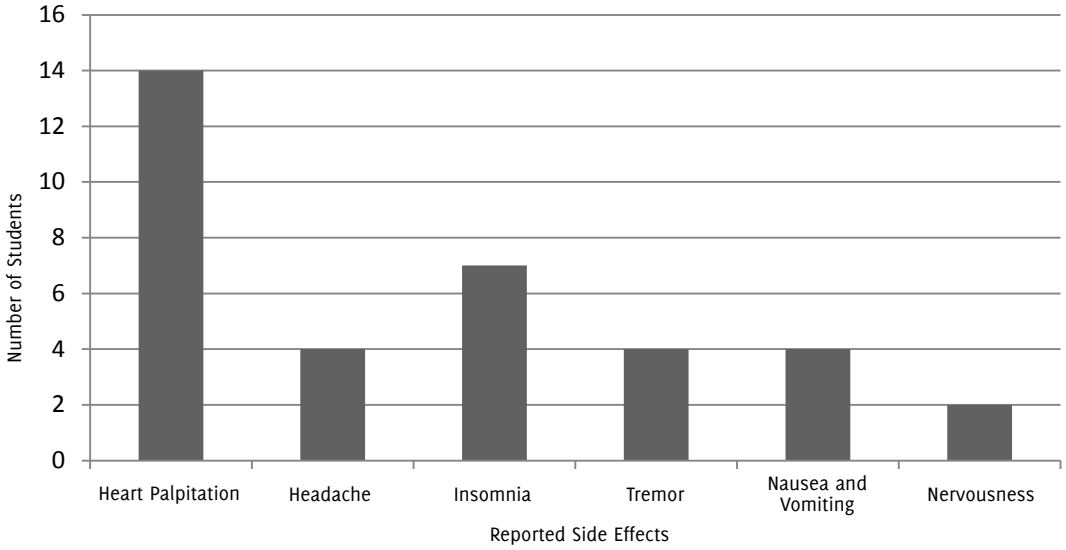
The reasons for consuming energy drinks ***(Figure 2)*** were because they didn't get enough sleep (12.8% of consumers, n=9), because they needed energy in general (32.8% of consumers, n=23), to study for an exam or finishing a project (31.4% of consumers, n=22), to drive a car for a long time (8.5% of consumers, n=6) or to be like friends and show-off (11.4% of consumers, n=8). This study shows that 44.2% of consumers (n=31) feel more alert when they drink, 21.4% of students (n=15) don't feel more alert when they drink, and 34.2% of consumers (n=24) were not sure.

The questionnaire also showed that 27.1% of male (n=13) and 50.0% of female (n=11) consumers of energy drinks manifested some side effect after consumption. Regarding the symptoms experienced ***(Figure 3)***, 20% of consumers (n=14) experienced heart palpitations, 5.7% of consumers (n =4) had headaches, 10% of consumers (n=7) reported having insomnia, 5.7% (n=4) had tremor, 2.8% (n=2) reported nervousness and 4.2% of consumers (n=4) reported nausea and vomiting. Finally, no consumer reported crash episodes as a side effect of energy drink consumption.

Discussion

Over the past ten years expansion of energy drink marketing has been noted over the world in the absence of clear regulations.[13] The present study was aimed at estimating the percentage of students consuming energy drinks among Umm Al-Qura university medical students in clinical years and the difference between male and female consumption patterns. We

Figure 3. Reported Symptoms of Caffeine Intoxication after Energy Drink Consumption among Medical Students in Clinical Years.



found that approximately one-third of this sample consumes energy drinks. In an earlier similar study in another medical school in Turkey, the prevalence reported was 32.6%.[13] On the other hand, similar studies conducted in non-medical college students shows that around 51% and 48.3% of students consume energy drinks.[15,16] Moreover, a study among university student-athletes showed a prevalence of 62.2%.[1] This difference in consumption among college versus medical students may be explained by a more extensive understanding of human physiology and toxicology, or cultural differences among different regions of the world. On the other hand, athletes have the desire to improve performance and experience the energetic effect of these beverages, and consequently student-athletes are more prone to consume energy drinks compared to other students, as suggested by Paddock.[17]

Regarding the gender of consumers, we observed that males consume much more frequently than females. In the Middle Eastern culture, females generally are not interested in products that represent an athletic, modern lifestyle according to the general prevailing opinion, which could explain the higher proportion of male consumers in this particular study. In addition, differences in total sample numbers of males and females in this study (179 females vs 78 males) could have introduced some bias. These findings are similar to those reported for college students in a southern plains university in 2011, where there was a higher mean consumption in males compared to females.[16] However, another study performed on students from an university in the central atlantic region of the United States reported a significantly higher proportion of female consuming energy drinks compared to males (53% vs. 42%).[15] These apparently contradictory results may reflect cultural differences or be the product of other confounders that need to be evaluated in further studies. This will allow further insight into the interesting relationship of gender and energy drink consumption.

The young usually consume energy drinks to benefit from their energetic effects. Nutritionists and health educators should provide education to this population on gaining these effects through healthy diet and exercise. In our study group the majority of students consumed energy drinks for general energy and while studying for an exam or finishing a project. In another context, another study showed similar reasons why students consumed energy drinks: to increase their energy (65%), to study or complete a major course project (50%), and while driving a car for a long period of time (45%).[15] In Saudi Arabia, females are not allowed to drive a car, which explains why none of the female consumed energy drinks for this particular reason. Other major motivations mentioned in the literature are consuming these beverages mixed with alcohol to become inebriated, to reduce the depressive and sedating effects of alcohol compared to alcohol alone, or to add a new flavor to the mixture.[18] A web-based survey in 2006 reported that 24% of the participants mixed alcohol with energy drinks within the last month in the United States.[19] Mixing alcohol with energy drinks may leads to serious events as the mixture is very dehydrating and can reduce the excretion rate for alcohol from the body leading to alcohol intoxication and respiratory depression.[18] Moreover, it will make the consumer drink more alcohol as he cannot recognize if he had enough alcohol or not.[20] In the Saudi culture, alcohol consumption is prohibited, and therefore our study did not investigate the mixing of alcohol with energy drinks.

Caffeine is the main component in energy drinks that gives a stimulating effect for cognitive function. Its amount in energy drinks exceeds the necessary amount to enhance performance, and could reach intoxication levels if consumers drank more than one bottle per serving.[3] We report that the most frequent side effect experienced in our sample was heart palpitations, and to a lesser degree headaches, insomnia, tremor, nervousness, nausea and vomiting, and these side effects were more frequent in females than males. Another side effect of consumption are crush episodes. There were no crush episodes reported in this study. Crush episodes are usually reported in athletes during exercise or a match. Investigators have suggested that the large amount of caffeine and taurine consumption together with strenuous exercise can cause coronary vasospasm with an increase in heart rate and blood pressure. In general, side effects do not prevent students from consuming, and percentages of these side effects in our study are almost similar to those reported in a study among college students published in 2007.[15]

We recommend the promotion of public awareness about the active ingredients of energy drinks and the potential side effects and adverse events from reaching intoxication levels. Further studies are needed to evaluate factors involved in consumption of energy drinks among medical students and to explore the relation of gender and consumption, their understanding of risks involved and possible interventions to promote safe consumption.

There are several limitations in this study. First, response rate was low (34.3%) and this may have introduced some nonresponse or voluntary response bias. This could be reflected in the differing number of female and male participants. The response rate could have been improved by alternate scheduling to conduct the survey with suggestions from direct communication with the participants, allowing more time to respond to the invitation, or offering benefits from participating, among others. Authors limited the number of questions to facilitate that survey would be completed. This study offers important exploratory findings for medical student consumption of energy drinks in Saudi Arabia. Future studies could attempt a different study design to gain more insight into factors contributing to energy drink consumption.

Conclusion

Energy drinks consumption is common practice among medical students. Out of the 257 medical students who participated in this research, 70 students were consuming energy drinks (27.2%), 61.5% (n=48) were males and 12.3% (n=22) were female. Students consumed energy drinks for different reasons, mainly the need for energy in general activities. About one-fifth of the participants manifested some side effect after consumption; heart palpitations were the most frequent side effect reported. We recommend the need to create public awareness about the active ingredients in energy drinks and the potential side effects and adverse events. Further studies are recommended to evaluate factors involved in consumption of energy drinks among medical students, and their understanding of the risks involved as well as possible interventions to promote safe consumption.

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Patient Perception of Physician Attire Before and After Disclosure of the Risks of Microbial Contamination

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Abstract

Background: The white coat is traditionally considered to be the appropriate attire for physicians but it may also be contaminated with microbes and act as a potential source of infection. We aimed to study patients' acceptance of physicians' attire, their underlying reasons, and their reactions to an educational intervention with regards to the risks of contamination. **Methods**: We conducted a voluntary questionnaire survey at a university teaching hospital in Hong Kong from February to July 2012. 262 patient-responses from adult inpatients and outpatients across various specialties were analysed. **Results**: White coats were highly favoured (90.8%) when compared with scrubs (22.1%), smart casual (7.6%) and formal (7.3%) wears. 'Professional image' and 'ease of identification' were the main attributes of the white coat. Most patients (92.2%) would prefer doctors washing their white coats every few days, whilst 80.9% believed that doctors were actually doing so. After patients were informed of the potential risk of microbial contamination, white coats remained as the most favoured attire (66.4%), but with scrubs doubling in popularity (45.8%). Smart casual (9.2%) and formal attire (4.6%) remain the least accepted. **Conclusion**: Despite cross-infections being a significant concern within the healthcare environments, patients' predominant acceptance and perceived attributes towards the white coat were maintained after an educational intervention on the risks of microbial contamination.

Keywords: Clothing, Cross Infection, Patient Preference, Patient Safety (Source: MeSH-NLM)

Introduction

The white coat is commonly regarded as the attire that confers a sense of professionalism and authority within the healthcare industry. The history of white coat attire dates back to the late 19th century, when scientists were in the habit of wearing beige-coloured laboratory coats. Wanting to associate themselves with the scientific community in order to gain trust from the public, doctors began to adopt the laboratory coat as a sign of trustworthiness and the ability to provide empirically supported treatments. The white colour was later chosen as a symbol of purity and dedication to 'do no harm'. The white coat eventually became an important symbol of the synergy between the arts and science of Medicine.[1,2] This practice has since spread to many countries and cultures all over the world, with the white coat being strongly associated with the image of western medical practitioners. The significance of and respect towards this attire is reflected by the "white coat ceremony", a ritual which many western medical schools carry out in the beginning of the school years to emphasize professionalism.[3]

However, there has been intensifying debates as to whether doctors should continue wearing white coats in the hospital setting. The major argument against it being that this formal attire can be subject to microbial contamination, hence a potential source of hospital-acquired infections.[4,5] A recent cross-sectional study of white coats worn by physicians at a large teaching hospital showed that 23% of the coats were contaminated with *Staphylococcus aureus*, where 18% of these were *Methicillin-resistant Staphylococcus Aureus (MRSA)*.[6] In view of the growing concern, white coats have been banned in parts of United Kingdom (U.K.) since 2007 and the "bare below the elbow" policy was adopted in order to reduce the risks of contamination (Available from: http://webarchive.nationalarchives.gov.uk/20130107105354/http://www.dh.gov.uk/prod_consum_dh/groups/dh_digitalassets/documents/digitalasset/dh_078435.pdf, updated 2007, cited 2013 Sep 6).[7-8] The American Medical Association, however, stopped short of banning white coats, opting for the advocation of a dress code that "minimize transmission of nosocomial infections, particularly in critical and intensive care units" (Available from: http://www.ama-assn.org/resources/doc/hod/a-10-bot-reports.pdf, updated 2010, cited 2013 Sep 6). This was presumably partly due to inconclusive evidence that the "bare below the elbow" policy would indeed translate to lesser nosocomial infection rates.[9]

This article aims to add weight to the argument by looking from the patient's point of view. In particular, the study aimed at elucidating the following four pieces of information: 1.) Patients' acceptance of physicians' attires; 2.) Their perceived values of the white coat; 3.) Their preferred and perceived frequencies of white-coat cleansing; and 4.) Changes in patients' acceptance after an educational intervention concerning the potential risk of microbial contamination of doctors' clothing.

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Further understanding from the patient's perspective would allow us to gage the potential impact on patients should an alternative dress code be adopted in the future.

Methods

Study design

A voluntary questionnaire survey was conducted on a convenience sample of 264 patients at Queen Mary Hospital, a teaching hospital in Hong Kong, between February and July 2012. Patients were recruited from both inpatient wards and outpatient clinics of various specialties in the hospital. All but 2 patients who participated met the inclusion criteria of being aged 18 years or above, fully alert, mentally competent, and could read or speak Chinese at the time of the study. The 2 patients who did not meet these criteria were excluded from subsequent analysis. Subjects were briefed and given an information sheet regarding the nature of the study and their rights to refuse to participate, prior to providing verbal consent if granted. Each was given an anonymous non-guided questionnaire survey. Explanations of the survey items were provided upon the subjects' requests. The study was approved by the hospital's Institutional Review Board.

The questionnaire

Subjects were presented with a questionnaire as well as a set of photographs depicting 4 examples of physician attire ***(Figure 1)***. These included casual wear (A), scrubs (B), white coats (C) and formal wear (D). Each example attire was worn by a female and a male model with only slight variations allowed for common gender differences. The models' postures, facial expressions, hairstyles and their backdrops were kept consistent. Subjects were then asked to refer to the photographs to choose their accepted attire, and to rate the four sets of photographs on three aspects: professional image, friendliness, and cleanliness. Subjects were then asked to select their most accepted attire.

Subjects were then asked whether they deemed white coat necessary in different healthcare settings (public hospital, teaching hospital, private hospital and clinic), and why they thought doctors should wear white coats. We also asked the subjects for their preferred and perceived frequencies of white coat cleansing by doctors.

We then provided each subject with a standardized statement on the potential risks of microbial contamination on white coats and long sleeved shirts. The statement, translated from Chinese to English, was as follows: "Studies have shown that doctors, after contact with patients, can be colonized with infective agents on their clothing. In particular, white coats and other long sleeved attire contain the highest colonization rate. A study from a US hospital has shown that 4% of doctors have white coats colonized by antibiotic-resistant MRSA".[6]

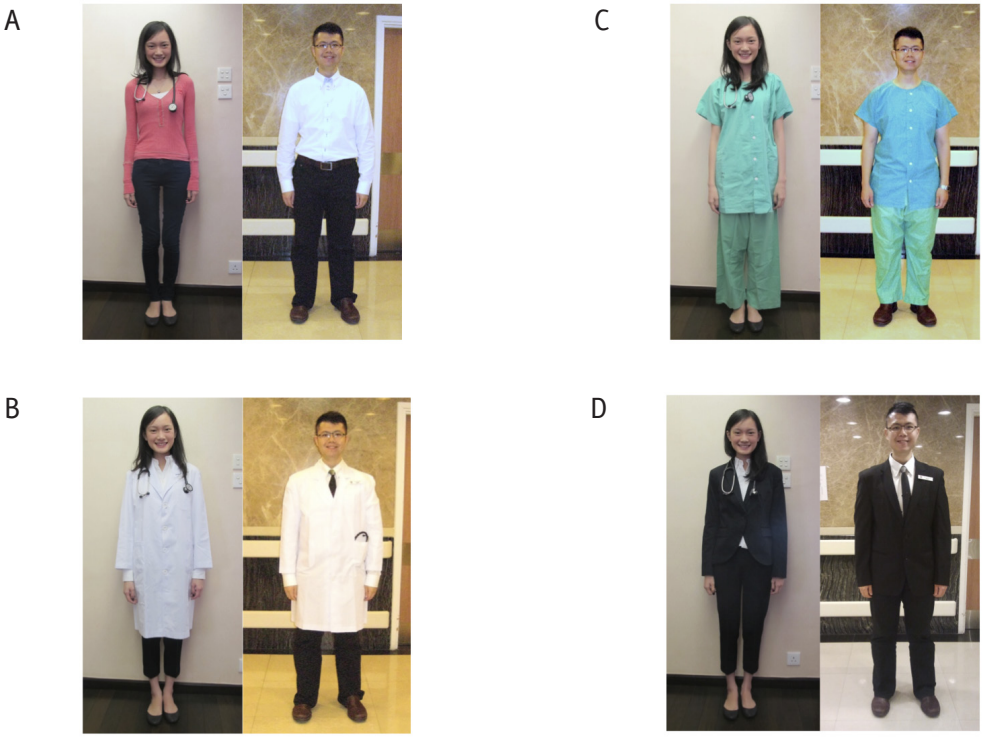
Subjects were then asked to indicate their acceptance of different attires as well as their ratings on professionalism, friendliness and cleanliness again.

The questionnaire was designed and administered by the authors.

Data collection and analysis

Results of the questionnaire were coded into a pre-designed spreadsheet template with validation criteria. The results were analysed using SPSS (IBM version 19). Demographic information, including age, sex, education level, occupation, individual

Figure 1. Female and Male Doctors Dressed in 4 Different Attires (A: Casual, B: Scrubs, C: White Coat and D: Formal)



monthly income and hospital service location, were compared with the results of the surveys using chi-square tests. A statistical significance level of 0.05 was employed throughout the analysis. Patients' preferences pre- and post-disclosure of microbial contamination risks were measured on a Likert scale from 1 to 5, and were compared using paired t-test.

Results

Patients' demographic characteristics are listed in ***Table 1***. Overall, white coats were favoured by the majority of patients (n = 238 or 90.8%), followed by scrubs (n = 58 or 22.1%), smart casual (n = 20 or 7.6%) and formal (n = 19 or 7.3%) attire ***(Figure 2)***. There were no significant differences between patients of different age groups, hospital service location and income levels.

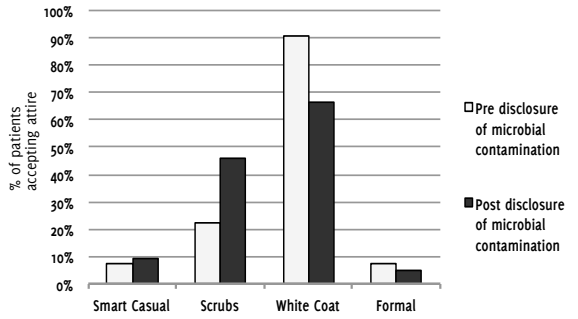
Table 1. Patient Socio-Demographic Characteristics and Hospital Service Location when Surveyed

Characteristics	n (%)
Gender	
Male	111 (42.4)
Female	151 (57.6)
Age Group	
<40	93 (36.5)
40 - 64	135 (52.9)
>64	27 (10.6)
Education Level*	
Non-Tertiary	148 (56.7)
Tertiary or Above	113 (43.3)
Personal Income per month (HKD $)	
<$1,000	59 (23.7)
$1,000 - $9,999	64 (25.7)
$10,000 - $19,999	64 (25.7)
>$20,000	62 (24.9)
Hospital Service Location	
Inpatient	134 (51.1)
Outpatient	128 (48.9)

Note: Percentages from total patient population, N=262.

* Tertiary education: Higher diploma, associate degree, bachelor's degree or postgraduate degree

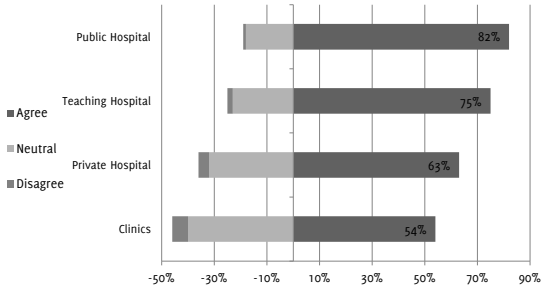
Figure 2. Patients' Acceptance on Physician's Attire Pre- and Post Disclosure of Potential Microbial



Note: Patients may choose to accept more than one attire. Percentages from total patient population, N=262.

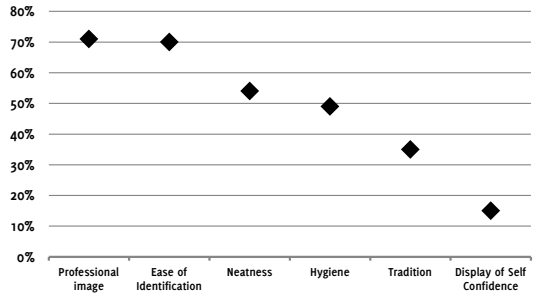
The majority of patients opined that white coats should be worn by doctors in all healthcare setting, especially in public hospitals (n = 213 or 81.6%) and teaching hospitals (n = 196 or 75.1%), followed by private hospitals (n = 165 or 63.5%), and clinics (n = 139 or 53.7%). The differences between the four attires were statistically significant (p <0.001) ***(Figure 3)***. 'Conferring a professional image' (n = 187 or 71.4%) and 'Ease of Identification' (n = 184 or 70.2%) were the two main reasons why patients would prefer doctors wearing white coats. Opinions were relatively more divided on 'Neatness' (n = 141 or 53.8%) and 'Hygiene' (n = 128 or 48.9%). 'Tradition' (n = 93 or 35.5%) and 'Self-confidence' (n = 40 or 15.3) received relatively low ratings ***(Figure 4)***. With regards to white coat cleansing, 92.2% (n = 237) of patients would prefer doctors to wash their white coats every few days, and almost all (97.7% or n = 251) preferred coats to be washed at least once a week. A similar majority (n = 208 or 80.9%) believed that doctors would actually cleanse their white coats every few days ***(Figure 5)***.

Figure 3. Patients' Agreement on whether White Coats should be Worn in Various Clinical Settings



Note: Percentages from total patient population, N=262.

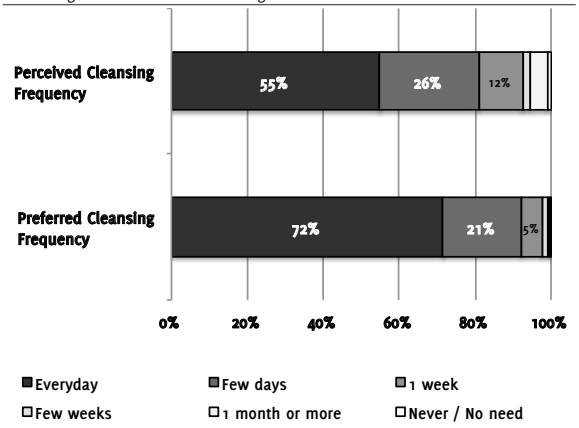
Figure 4. Patients' Perception of Positive Attributes Represented by the White Coat



Note: Percentages from total patient population, N=262.

After receiving the statement on the potential risks of contamination, the majority of subjects still ranked white coat as their most accepted dress code, but the proportion had decreased from 90.8 % (n = 238) to 66.4% (n = 174). On the other hand, the acceptance for scrubs increased from 22.1% (n = 58) to 45.8% (n = 120). Acceptance for smart casual and formal attire remained less than 10% (**Figure 2**). Inpatients became more

Figure 5. Patients' Estimated Frequency and Preference for White Coat Cleansing in the Healthcare Setting



Note: Percentages from total patient population, N=262.

likely than outpatients to accept scrubs post-disclosure (55.2% vs 35.9%, p=0.002). This difference was not observed pre-disclosure.

Following our intervention, the rating for cleanliness decreased for white coat (from 4.56 down to 4.27, p<0.001) and increased for scrubs (from 3.61 up to 3.84, p<0.001) ***(Table 2)***. Interestingly, a similar trend in the attire's 'professional image' rating was also observed for white coat (from 4.73 down to 4.62, p=0.012) and scrubs (from 3.63 up to 3.73, p = 0.001), despite the fact that the statement was not explicitly linked to this attribute. Scrubs were also deemed to be more friendly and acceptable post-disclosure (from 3.24 up to 3.39, p<0.001).

Throughout the whole study, female patients consistently reported a higher preference and acceptance for white coats than their male counterparts, a finding that is not observed in other attires ***(Table 3)***. Prior to intervention, 95.4% of female patients showed acceptance to the white coat attire, as compared to 84.7% of the male patients (p=0.003). The difference between genders were maintained post-intervention where statistically significantly more female patients would still accept physicians wearing white coats as compared to male patients (72.2% vs 58.6%, p=0.021). Moreover, female patients had greater acceptance for white coats in all four clinical settings, with the difference within public hospitals (86.8% vs 74.5%, p=0.020) and teaching hospitals (81.5% vs 66.4%, p=0.011) being statistically significant. No differences were found with regards to other demographic variables (data not shown).

Discussion

It is well known that patient perception of the healthcare professions, doctor-patient relationships and the concept of professionalism varies between societies and patient populations, and can be heavily influenced by social and cultural factors. Our locality is unique in the sense that it consists of predominantly a Chinese population whilst the healthcare system is modeled after the National Health Service (NHS) of the UK. To the best of our knowledge, this is the first study in Hong Kong to be conducted on this topic.

Table 2. Patient's Perception of Professionalism, Friendliness and Cleanliness by Type of Doctor's Attire Before and After the Disclosure of the Potential Risk for Microbial Contamination

	Smart Casual Score (95% CI)	Scrubs Score (95% CI)	White Coat Score (95% CI)	Formal Score (95% CI)
Professionalism§				
Before	2.00	3.63	4.74	2.99
	(1.88-2.12)	(3.49-3.77)	(4.66-4.81)	(2.84-3.14)
After	2.06	3.73	4.62	2.94
	(1.91-2.20)	(3.58-3.88)	(4.51-4.73)	(2.78-3.10)
p-value	0.071	0.001*	0.012*	0.171
Friendliness§				
Before	2.94	3.25	4.03	2.61
	(2.78-3.10)	(3.12-3.38)	(3.91-4.15)	(2.47-2.76)
After	2.98	3.38	4.04	2.59
	(2.81-3.16)	(3.23-3.52)	(3.91-4.18)	(2.43-2.74)
p-value	0.029*	<0.001*	0.681	0.613
Cleanliness§				
Before	2.68	3.61	4.57	3.12
	(2.53-2.82)	(3.47-3.75)	(4.47-4.66)	(2.96-3.27)
After	2.68	3.82	4.27	3.03
	(2.50-2.83)	(3.68-3.97)	(4.12-4.41)	(2.86-3.19)
p-value	0.570	<0.001*	<0.001*	0.015*

Note: Score ratings measured by a 5-point Likert scale where 1 was the worst and 5 the best.

* p<0.05, Chi2 test.

§ Patient's perception of each characteristic before and after disclosure of potential risk of microbial contamination

Abbreviations: 95% CI: 95% confidence intervals

Table 3. Patients' Acceptance on Physician's Attire Pre- and Post-Disclosure and among Various Clinical Settings (for White Coat) by gender

	Total n (%)	Female n (%)	Male n (%)	p-value
Smart casual				
Before disclosure§	20 (7.6)	11 (7.3)	9 (8.1)	0.804
After disclosure§	24 (9.2)	11 (7.3)	13 (11.7)	0.220
Scrubs				
Before disclosure§	58 (22.1)	31 (20.5)	27 (24.3)	0.465
After disclosure§	120 (45.8)	65 (43.0)	55 (49.5)	0.296
White coat				
Before disclosure§	238 (90.8)	144 (95.4)	94 (84.7)	0.003*
After disclosure§	174 (66.4)	109 (72.2)	65 (58.6)	0.021*
*Teaching hospital^*	*196 (75.1)*	*123 (81.5)*	*73 (66.4)*	*0.011**
*Public hospital^*	*213 (81.6)*	*131 (86.8)*	*82 (74.5)*	*0.020**
*Private hospital^*	*165 (63.5)*	*104 (68.9)*	*61 (56.0)*	*0.099*
*Outpatient clinics^*	*139 (53.7)*	*88 (58.3)*	*51 (47.2)*	*0.078*
Formal				
Before disclosure§	19 (7.3)	9 (6.0)	10 (9.0)	0.347
After disclosure§	12 (4.6)	8 (5.3)	4 (3.6)	0.517

Note: Percentages calculated with respect to the total sample N=262, females n= 151, and males n=111.

* p<0.05

§ % of patients accepting physicians' specified attire (as oppose to not accepting)

^ % of patients agreeing to physicians wearing white coat in the specified clinical setting (as oppose to being neutral or disagreeing).

By and large our findings are consistent with those of international studies which showed white coats to be the most preferred, and casual wear the least favoured attires.[10-16] Lill's study in New Zealand where semiformal attire is the most preferred is a notable exception.[17] There are, however, subtle differences in patients' perceptions between countries. For instance, 'hygiene' was found to be the dominant factor in determining attire preference in Japan, as opposed to 'professional image' in our study.[12] Scrubs were also perceived to be more hygienic than white coats in Japan, in contrast to our local findings. When informed of the hygienic risks that "long sleeved white coats might be a vehicle for transmission of pathogens", Japanese patients readily reversed their preferences, and were overwhelmingly in favour of scrubs over white coat (58.4% vs 25.6%). Similar observations of preference reversal were also observed in Shelton's study in the United Kingdom and Huetson's study in the United States.[18,19] The same educational intervention, on the other hand, did not result in the same degree of preference reversal amongst patients in Hong Kong. White coats remained to be the more preferred attire despite post-disclosure. Female patients are also found to have a higher acceptance for white coats than the male counterparts in our study.

We surmised that the persistent preference for white coats amongst the local population may be partly due to the deep-rooted perception of 'professional image' associated with this attire, as indicated by the high score awarded to this item post-disclosure. Another plausible explanation may be that most patients believed doctors were cleaning their white coats at a preferred frequency. Therefore, although patients were aware of the risks of contamination, this could have been compensated for by a perceived practice of frequent cleansing. In this regard, it would be interesting to study whether the white coat cleansing practices amongst local doctors are indeed aligned with the perception. The strong preference for white coats post-disclosure may also be due to the relatively technical and non-specific nature of the statement on contamination risks, thus preventing patients from fully understanding the potential harm in using the coat. The observed phenomenon where female patients prefer white coat attire more than male patients remains to be an interesting area for future studies.

Nevertheless, it can be inferred from our findings that the white coat has its role in establishing a unique form of doctor-patient relationship. This has to be carefully considered and balanced against the potential risks of contamination and cross-infections. There are fine distinctions between the latter two. While white coat contamination has been clearly demonstrated, there has yet to be conclusive evidence linking contamination of white coat to an increased risk of hospital-acquired infections.[4-6,20-21] On the assumption that there is such a causal link and/or that there is an attempt to adopt the U.K. "bare below the elbow" policy here, our findings indicate that there needs to be further enhancement of patient education on the potential risks of nosocomial infection to emphasize the priority of hygiene over other attributes, so as to facilitate patient involvement in improving their own safety.

The study has several limitations. Firstly, the sample size was relatively small and was confined to one institution. A larger sample size would reduce the potential bias due to locality and the institution's nature as a tertiary teaching hospital, making

the results more generalizable to the community. Secondly, while we strived to deliver the education statement in a factual and impartial manner, it may be perceived as too technical for less medically educated patients to comprehend. It would be interesting to test variations of the educational statement with regards to contamination risks, and to study the impacts of different contents. Thirdly, the use of a single statement as an intervention has the downside of being too impersonal and distant as compared to other methods of delivery, for example pictures of cultured bacteria from contaminated attire. Patients may tend to overestimate their perceived tolerance to contaminated attires. Fourthly, disclosure of a single, negative fact may introduce a predictable shift in the participant's response, which makes it difficult to interpret the true risk from this study. Lastly, the questionnaire was developed by the investigators and has not been validated.

Conclusion

The white coat was found to convey a sense of 'professionalism', allow 'ease of identification', and was the patients' attire of choice for physicians. This predominant preference and the perceived attributes were maintained despite an educational intervention concerning the risks of microbial contamination. The majority of patients believed that doctors would clean their coats at a frequency preferred by the former. Cross-infections within healthcare environments are serious concerns. Further studies may focus on the potential risks to patients due to cross contamination, the practices of coat cleansing amongst professional personnel, and effective means of patient education to improve their awareness and safety.

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Bibliometric Studies in CIMEL: A Latin-American Medical Student Journal and the Future of Bibliometric Publications

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Abstract

Background: Bibliometric or scientometric studies are methodological fields focused on the structural analysis of the information contained in scientific publication and generate indicators that help identify challenges and achievements in research. We aimed to characterize the publications that used this method authored by medical students in Latin America. **Methods**: We reviewed articles that performed a bibliometric analysis and were published in a Latin American medical student journal, between 2001 and 2012. We analyzed the characteristics of the articles, authors and references. Linear simple regression and Pearson correlation coefficient (PCC) were developed to identify trends and correlations with 95% confidence. **Results**: There were 12 volumes of the journal available online, with a total of 236 articles. Of these, 13 (5.5%) were bibliometric studies: five original articles, four letters to the editor, two editorials, one short communication, and one review. There was a positive significant relationship between time (years) and number of publications (ß1=0.16, p=0.03, PCC=63%), and citations of each article (not significant, ß1=1.3, p=0.09, PCC=49%). **Conclusion**: There was an increase in the number of bibliometric publications after 2008, possibly influenced by a popularization of these types of studies in Latin America. Findings should motivate new and collaborative studies in this field. Moreover, it will be necessary to clarify publication areas of interest of medical students around the world.

Keywords: Bibliometrics, Medical Students, Latin America (Source: MeSH, NLM)

Introduction

Bibliometric or scientometric studies describe, assess and monitor characteristics of publications in the scientific literature. These studies belong to a methodological field focused on the structural analysis of the information contained in scientific publications that provides different indicators that aid in the analysis of information.[1]

The rationale of these studies is based on the measurement of the scientific activity through established indicators of scientific publications, such as the number of published articles, the countries, institutions, research groups or individual investigators and affiliations, and the number of citations received, among others. This provides objective criteria for the critical evaluation of scientific production. Nevertheless, validity remains as a topic of active discussion due to the possible biases introduced by the same nature of its methodology.[2] Some limitations are, however, inherent to these kind of studies. For instance, they may reflect an unconscious judgment from the investigator and they may not account for aspects of quality as a result of the poor and subjective evaluation of quotation and its influence in science. An additional limitation is the fact that journal indexation is limited to the most important journals, including mainly basic sciences and excluding other sources of data.[3]

Moreover, different areas of science have used bibliometrics, allowing for the assessment of the academic and scientific outlook of research in different regions, centers of education, and for researchers or workers on knowledge areas, among other options.[3-5]

The promotion of research and scientific publication is currently a fundamental aspect of successful medical training. The Latin-American Federation of Medical Students' Scientific Societies (FELSOCEM) and its member associations (Medical Students' Scientific Societies, MSSS) have worked on promoting medical student involvement in research since its foundation in 1986. One of the main strategies to reach this goal was the establishment of their own medical students' journal, the Latin-American Students' Science and Medical Research ("Ciencia e Investigación Médica Estudiantil Latinoamericana" in Spanish, CIMEL).[6]

Bibliometric studies are an alternative for medical students to increase their scientific production given the relatively simple study design and the minimal resources required to plan and execute them.[7] This opportunity has been identified by some members of different Latin American MSSS, as it overcomes some of the difficulties and the lack of incentives that they face when attempting to do research in these countries.[8]

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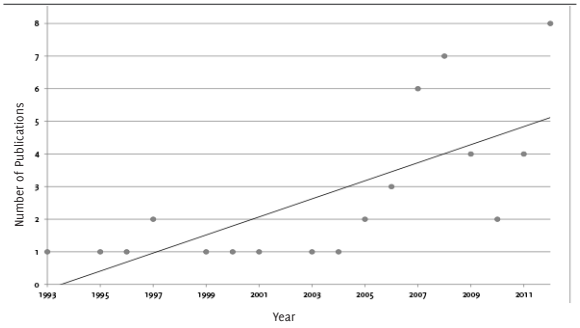
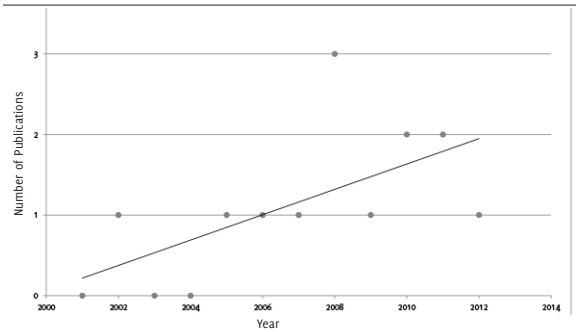
Figure 1. Number of Bibliometric Publications in Latin America, Published in PubMed between 1993 and 2012



Linear fit obtained using simple linear regression (β_1=0.3, p=0.001).
Source: PubMed database. Search strategy: "Bibliometrics"[Mesh] AND "Latin America"[Mesh] (Available from: http://www.ncbi.nlm.nih.gov/pubmed; cited 2013 August 1).

Figure 2. Number of Bibliometric Publications Published in CIMEL between 2001 and 2012



Linear fit obtained using simple linear regression (β_1=0.16, p=0.03).
Source: CIMEL websites. (1) Library System website, Universidad Nacional Mayor de San Marcos [SISBIB-UNMSM] (Available from: http://sisbib.unmsm.edu.pe/bvrevistas/cimel/anteriores.htm, updated date: Not available, cited 2013 Aug 1st), and (2) Official CIMEL website (Available from: http://www.cimel.felsocem.net/index.php/CIMEL/issue/archive, date: Not available, cited 2013 Aug 1).

The initiative to analyze bibliometric studies published in a Latin-American medical students' journal arises from a review publication by Romani et al. where the authors discuss the method as a possible research field for medical students.[7] The objective of this study is to characterize the publications that used bibliometric methods among medical students in Latin America to identify it as a publishing option for medical students and to encourage such publications among them and in the International Journal of Medical Students.

Methods

We conducted a study to identify all published manuscripts where the methodology included a bibliometric analysis of the past 12 volumes in CIMEL from 2001 to 2012. The articles were identified on the official website of the journal (Available from: http://www.cimel.felsocem.net/index.php/CIMEL/issue/archive; cited 2013 Aug 1), and the database of the Library System website of the journal's home institution, the Universidad Nacional Mayor de San Marcos [SISBIB-UNMSM] (Available from: http://sisbib.unmsm.edu.pe/bvrevistas/cimel/anteriores.htm, updated date: Not available; cited 2013 Aug 1).

A data collection instrument was developed using the Google-Drive platform. We performed on a dataset that included variables related to the publication and their authors and then exported the data to Microsoft Excel. Variables relating to the article included the type and year of publication, subject/area, funding, conflict of interest, and number of citations. Variables about the authors were authors' country of affiliation, numbers of authors as medical students and professionals, gender, highest academic degree, participation in a medical student scientific society, and institutional affiliation.

Additionally, a search in PubMed was performed using the Medical Subject Headings (MeSH) "Bibliometrics"[Mesh] AND "Latin America"[Mesh], trying to identify the trend of bibliometric studies in Latin America published in international journals.

The review and consistency of the information, the categorization of the variables, and statistical analysis were all performed in the statistical software Stata 13 (StataCorp, College Station, TX, USA). Quantitative variables are described with measures of central tendency and dispersion, while categorical variables are reported as frequencies and percentages. We used Academic Google search engine (http://scholar.google.es/) to search citations of the articles analyzed. The results were verified for each article included.

Finally, to establish the trend and relationship among the year

Table 1. Description of Published Articles by Article Type and Bibliometric Methodology in a Latin-American Medical Students' Journal between 2001 and 2011.

	Total Publications		Bibliometric Publications		
Type of Article	**n**	**%**	**n**	**% (of total articles published)**	**% (of bibliometric publications)**
Original Articles	92	39%	5	2,1%	38%
Case Reports	52	22%	0	0,0%	0%
Editorials	19	8%	2	0,8%	15%
Letters to the Editor	21	9%	4	1,7%	31%
Special Articles	17	7%	0	0,0%	0%
Short Communications	16	7%	1	0,4%	8%
Reviews	8	3%	1	0,4%	8%
Institutional Publications	11	5%	0	0,0%	0%
Total	**236**	**100%**	**13**	**5,5%**	**100,0%**

of publication and number of bibliometric studies published in PubMed and number of citations of this type of study on CIMEL, a simple linear regression with ß1 coefficient and Pearson Correlation Coefficients (PCC) were calculated, respectively, with a confidence level of 95%.

Results

Twelve volumes of the journal were available online: Vol. 6 to 15 were available in the SISBIB-UNMSM database and Vol. 13 to 17 were available in the official website of the journal, for a total of 236 articles published from 2001 to 2012. Of those articles, 13 (5.5%) corresponded to scientometric studies. The distribution of publications by article type is described in ***Table 1***.

Trends in these publications in Latin America are described in Figure 1. We found 46 articles published in PubMed from 1993 to 2012, with an increase of 0.3 publications per year ($ß_1$=0.3, p=0.001, PCC=70.9%) and, if the trend is analyzed for the period 2005-2008, there is an increase of 1.8 publications per year ($ß_1$=1.8, p=0.02, PCC=97.6%).

In CIMEL, three out of twelve (25%) bibliometric studies were published during the year 2008; one of these articles was an original article and two were editorials. In 2010 and 2011 there were two (17%) studies published per year while there were none published during 2001, 2003 and 2004. There is a significant upward trend of the frequency of scientometric articles (ß1=0.16, p=0.03, PCC=63%, Figure 2). These studies focus mainly on journal analysis (n=3, 25%) and analysis of medical student publications in biomedical journals (n=3, 25%, ***Table 2***).

These studies were performed by a total of 31 authors (median 2, p25=1 and p75=3) and five of them, all from Peru, published twice (26 persons). Authors were medical students in 64.5% (n=20) of all studies and medical professionals in 35.5% (n=11). Three (12%) authors published studies during and after their medical student period. The male to female ratio for authors was 3:1 with nineteen (73%) males and seven (27%) females. The male to female ratio for principal authors was also 3:1 with ten (77%) and three (23%) articles having a male and female principal author, respectively. Most principal authors were Peruvian (n=10, 77%); other nationalities such as Venezuelan, Ecuadorian and Colombian appear in a smaller proportion (n=1, 8% respectively). There were collaboration groups between authors of different countries in two articles: Venezuela - Peru (1, 8%) and Peru - Spain (1, 8%).

Author affiliation to a MSSS was described in ten (77%) articles, four (31%) were published by the Scientific Society of San Fernando – Universidad Nacional Mayor de San Marcos (SCSF-UNMSM) in Peru and two (15%) in the name of the Peruvian Medical Student's Scientific Society (SOCIMEP).

The highest academic degree was not described in nine (69%) of the articles; in those described, five (19%) were medical professionals, one (4%) was a MD and MSc, and one (4%) a MD and PhD. The affiliation of the medical student authors to a research group was reported in 4 articles (31%); for medical professionals it was reported in two of five articles (40%).

The analyzed articles do not state if they had a funding source and only one (4%) out of 26 authors stated the possibility of conflict of interest because he was an editor for the journal at that time. The number of references of the articles varies by the type of publication and editorial policies of the journal, with an average of 10 ± 6 references (range of 4 to 23).

The average citations until 2009 were six with a range from 0 to 27; at least 25% of the articles had one citation while 75% had six citations. We found that three (23%) scientometric studies were cited by other studies in the journal with each having one to three citations. Finally, the current study showed a trend between the year of publication and the number of citations of the article, with a tendency to increase by an average of one citation per year after the publication date (ß1=1.3, p=0.09, PCC=49%).

Discussion

CIMEL is an initiative created by and for medical students in Latin America to increase participation in research and promotion of scientific projects in health during medical training and continuing medical education in the region. This journal is supported by an editorial board that includes medical student members from different South and Central American countries and undergoes peer reviewed evaluation of its manuscripts.

Therefore, this approach generates a space for students to publish their research projects as principal authors, participate in the editorial process as editors, as well as to help train the next generation of medical investigators in the region.[9]

The current study suggests that bibliometric publications could gain more significance among scientists and medical students in Latin America, given the increasing rate of publications especially after 2008 and the correlation between the time in years and the number of publications. Romaní et al. state that these kinds of studies have taken great interest for research development in Latin-American countries such as Peru due the easy access to data and the low cost and the possibility of different methodological approaches.[7] This is reflected by the majority of medical student-authors being from Peru.

Studies in this area are an alternative to analyze scientific literature in different knowledge fields and scenarios.[10] As a relatively simple research methodology, it offers medical students the opportunity to achieve a publication. Results from scientometric studies in Latin America tend to be more cited due to the small number of available articles in the field, leading to a positive impact on the development and consolidation of researchers.[11] Likewise, it opens the possibility for collaborations among authors from different institutions. The combination of physical and intellectual resources is boosting the possibility of scientific publication, reflected by the country partnerships that we found in this study.

The more frequent types of publications in the analyzed journal include original articles of observational studies and case reports. Bibliometric studies were mainly consisting of original articles and letters to the editor. This situation is very similar to the trend of scientific publications, especially in low and middle income countries, where observational studies were the most common study design, reaching its highest number

Table 2. Characteristics of Publications with Bibliometric Methodology in a Latin-American Medical Students' Journal between 2001 and 2012

Author, year	Countries Affiliation	Type of Publication	Topic/Scope	Authors (n)	Medical Student Authors		Professional Authors		Gender First Author	Medical Student's Scientific Society	Citations (n)
					(n)	(%)	(n)	(%)			
Avila, 2002	Ecuador	OA	Characterization of Latin American medical journals	2	0	0	2	100	Male	NA*	3
Galán-Rodas, 2005	Peru	OA	Characterization of medical students' scientific production	6	5	83	1	17	Male	SOCIMEP	27
Pachajoa- Londoño, 2006	Colombia	SC	Medical student publications in a Colombian medical journal	1	1	100	0	0	Male	NAV	9
Corrales- Portales, 2007	Peru	OA	Characteristics and frequency of informed consent in clinical trials	3	2	67	1	33	Female	SOCIMEP, SOCEMUNT	0
Angulo, 2008	Venezuela, Peru	OA	Medical student publications in Venezuelan medical journals	4	3	75	1	25	Male	ACUEM-ULA	5
Arce- Villavicencio, 2008	Peru	Edit	Topics of publication in the journal	2	2	100	0	0	Female	SCSF-UNMSM	6
Angulo-Bazan, 2008	Peru	Edit	Status of medical student journals in Latin America	1	1	100	0	0	Female	SCSF-UNMSM	6
Arroyo-Hernandez, 2009	Peru	LE	Publication of best original papers selected in the International Scientific Congress	1	1	100	0	0	Male	SOCEMI	2
Montenegro-Idrogo, 2010	Peru	OA	Case reports in the journal	2	2	100	0	0	Male	SCSF-UNMSM	1
Montenegro-Idrogo, 2011	Peru	LE	Letters to the Editor in the journal	1	1	100	0	0	Male	SCSF-UNMSM	0
Romaní, 2011	Peru, Spain	R	Bibliometric studies as a research area in biomedical sciences	3	0	0	3	100	Male	NA*	2
Vásquez-Sullca, 2011	Peru	LE	Research manuscripts presented at the National Medical Students Meeting of Peru	3	1	33	2	67	Male	ASOCIEMH UNSAAC	1
Arroyo-Hernandez, 2012	Peru	LE	Anomalies about the author in medical student's publications	2	1	50	1	50	Male	SOCEMI	0

*. All the authors were professionals.

Abbreviations: ACUEM-ULA: Scientific Association of Medical Students of Universidad de los Andes. ASOCIEMH UNSAAC: Medical Students Scientific Society Universidad Nacional de San Antonio Abad del Cusco. Edit: Editorial. LE: Letter to the editor. NA: Not applicable. NAV: Not available. OA: Original article. R: Review. SC: Short communication. SCSF-UNMSM: Scientific Society of San Marcos Universidad Nacional Mayor de San Marcos. SOCEMI: Medical Students Scientific Society of Ica. SOCEMUNT: Medical Students Scientific Society of Universidad Nacional de Trujillo. SOCIMEP: Scientific Society of Medical Students from Peru.

of publications during 2010 with 21.1% of published articles.[5]

The distribution of authors according to gender shows differences, with a high rate of males that exceeds three times the number of female authors. This is a phenomenon that has been identified in multiple areas where the numbers of female medical students and female researchers are less than males, and female research career intentions tend to decrease during medical school.[12] Different movements have been established to decrease this gap, and the number of women as first and senior physician-authors has been increasing significantly but they are still a minority of the authors and members of the editorial boards of journals.[13-15] Therefore, further studies are necessary to inquire about publications according to gender as well as the promotion of incentives that help to find an equitable distribution of female and male authors.[13]

Limitations of the current analysis include the unavailability of all issues of the Journal, as well as the absence of information regarding the institutional affiliation and academic degrees of the authors in the included studies. One of the most challenging limitations of the study is the small number of articles analyzed as the low power limits the significance of statistical tests and the ability to adjust for possible confounders. However, our findings give an idea of the importance that bibliometric studies have been acquiring in the past number of years and their impact as a novel research area with different advantages for medical students. Furthermore, it should be emphasized that these studies have some disadvantages compared to other research methodologies.[10] One of the barriers of this research methodology is the inability to assess the quality of what is being published; this study is not an exception to this limitation.

Despite the reported significant increase of scientometric studies published in the journal, it remains necessary to promote

student publication in this field in order to identify the behavior of the scientific medical student community, orientation and political efforts in research, as well as create networks that promote collaboration and new scientific activities. Thus, these publications encourage and enrich the education of students as they allow a better understanding of new perspectives and innovation in health, providing the opportunity for additional training.[16]

In addition, the understanding and use of bibliometric methods will address some of the difficulties presented in developing countries to do this type of research, such as the absence of experienced professors and researchers in the area and the underestimation of bibliometrics as a research field.[7]

Finally, scientific journals with online publications, open access, and wide dissemination provide an important scenario for publication and international visibility of studies with this approach.[17, 18] Therefore, it is important to increase the visibility and the quality of the articles published in CIMEL, the only regional journal for medical students in Latin-America, in order to be indexed in more visible databases such as PubMed and be able to share their investigations with a widely recognized scientific community. Bibliometric studies are needed in the International Journal of Medical Students to describe the areas of research where medical students around the world are participating in and to discuss their contributions to the scientific community.

Conclusion

Bibliometric studies are a growing area of knowledge in medical sciences and provide an opportunity for medical students to investigate and achieve publication as a result of their methods and advantages. We report that 13 of 236 articles published in 12 volumes of CIMEL were scientometric studies and there was a significant upward trend in the frequency of this type of study since 2008. These articles focused mainly on the analysis of medical student publications, and had an average of six citations with a range of 0 to 27 and a non-significant trend of one citation per year after publication date. Most authors were from Peru and there was a male to female ratio of 3:1. Studies in this area need to be done to gain insight into trends in medical students' research areas and publications and their impact in the scientific community.

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IJMS International Journal of Medical Students

Short Communication

Direction of Umbilical Cord Twist and its Characteristics – a Pilot Study

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Abstract

Background: A right-sided umbilical cord twist is associated with the presence of a single umbilical artery, congenital malformations and placenta praevia. **Methods:** It was an observational study. Data was collected from 137 umbilical cords, all from live births and their patient records. The gestational ages ranged from 28 weeks to 41 weeks. The umbilical cords were categorized into right or left, based on the direction of twist. The independent sample T test and the Chi square test were used to analyze the differences between groups. **Results:** The prevalence of left twist was 84%. Right twist was significantly associated with a larger Hyrtl's anastomosis (p=0.029) and gestational diabetes (p=0.027). **Conclusion:** Two previously unreported associations with right twist of the umbilical cord, gestational diabetes and an increase in the diameter of Hyrtl's anastomosis, were noted in the present study.

Keywords: Diabetes Gestational, Umbilical Cord, Embryonic Structures (Source: MeSH-NLM)

Introduction

The umbilical cord forms the only connection between the placenta and the developing fetus. It is surrounded by the amnion, and contains a pair of umbilical arteries and an umbilical vein supported by loose connective tissue, the Wharton's jelly. The umbilical vessels carry blood to and from the fetus and placenta, and thus, are critical to the survival of the fetus. A fully developed umbilical cord has an average length of 50 cm, and is 1 to 2 cm in diameter. Close to the insertion of the cord on to the placenta the two umbilical arteries are usually connected by a transverse anastomosis called Hyrtl's anastomosis ***(Figure 1)***. The umbilical cord is usually attached near the center of the placenta, from where the umbilical vessels ramify under the amnion and pass into the placenta.[1]

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The umbilical cord is usually twisted on itself, with the number of turns ranging from a few to over 300 ***(Figure 1)***.[1,2] The direction of this twist is usually left sided.[3] Proposed reasons for this twisting include hemodynamic factors and fetal movements.[3] Right sided twist is associated with the presence of a single umbilical artery (SUA), congenital malformations, placenta praevia and stillbirths.[3-6] Previous studies from India have described the helical structure of the umbilical cord and documented the associations between the coiling index and adverse perinatal outcomes. Both hypo and hyper-coiling were noted to be associated with several adverse antenatal perinatal outcomes.[7,8] The aim of the present study was to study the characteristics of umbilical cord twist direction among umbilical cords from South India.

Methods

The study was an observational study. The STROBE guidelines were used to conduct the study. Ethical clearance was obtained from the institutional ethical review board. A total of 137 (131 singleton and 6 twins) umbilical cords were studied, all from live births. The gestational ages ranged from 28 weeks to 41 weeks. The placentae were collected from the labor room, tagged to enable identification and subsequently placed in a container with formalin. They were then transported to the department of anatomy for further analysis. During collection of the placentae, relevant details were noted from the case sheets of the patients.

There were two primary objectives of the present study. The first was to estimate the difference in the following numerical variables between umbilical cords with right and left twist: 1) Age of the mother; 2) Difference in diameters of umbilical artery; 3) Diameter of Hyrtl's anastomosis; 4) Birth weight of the neonate. The second objective was to compare the prevalence of the following categorical variables between umbilical cords with right and left twist: 1) Gender of the neonate; 2) Type of delivery; 3) Gestational diabetes; 4) Pregnancy induced hypertension.

In the anatomy department, the parameters mentioned in the objectives i.e. the twist of the umbilical cord, presence of SUA, presence and diameter of Hyrtl's anastomosis and diameters of the right and left umbilical arteries were noted. The umbilical cord twist was determined as shown in ***Figure 2.***[9] An incision was made on the amnion covering the umbilical cords, close to the site of their insertion onto the placentae. The umbilical arteries were dissected free from the surrounding Wharton's jelly and traced towards the fetal surface of the placenta. The Hyrtl's anastomosis was identified and dissected out from the surrounding connective tissue. No histological study was performed. All diameters were measured using digital Vernier

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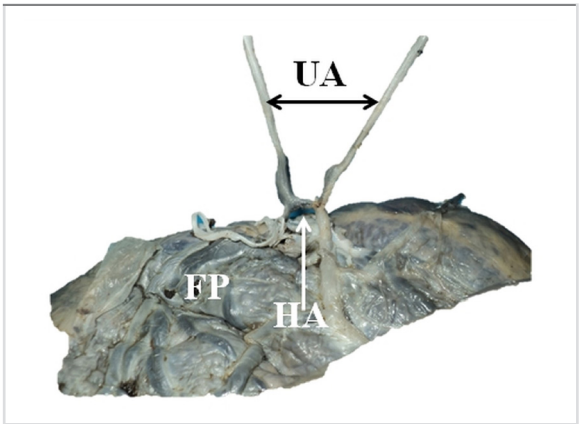
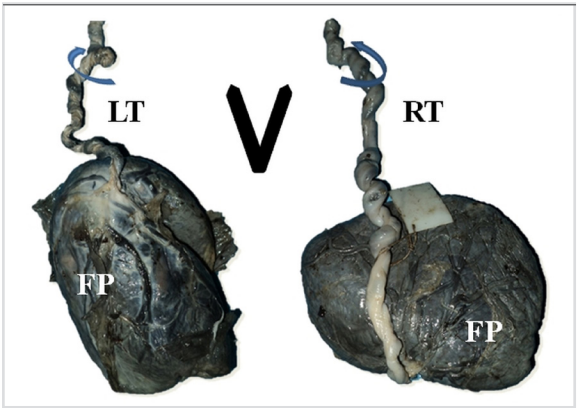
Figure 1. A Dissection to show Hyrtl's Anastomosis between the Two Umbilical Arteries. FP – Fetal Surface of the Placenta; HA – Hyrtl's Anastomosis; UA – Umbilical Arteries.



calipers. The independent sample T test and the Chi square test were used to analyze differences between groups with a significance level (p value) set at 0.05. Statistical analysis was performed using SPSS version 16.

Figure 2. Determination of the Direction of Twist using the Limbs of the Capital Letter V.[6] Umbilical Cords with Left Twist (LT) and Right Twist (RT) have Grooves of Coiling Parallel to the Respective Limbs of the V. FP – Fetal Surface of the Placenta UA – Umbilical Arteries



Results

The prevalence of left twist was 84% (117 of 137). A single Hyrtl's anastomosis was noted in all the placentae. The results regarding the numerical variables are summarized in ***Table 1***. The diameter of Hyrtl's anastomosis was significantly higher in umbilical cords with a right twist (3.4 ± 1.7 mm versus 2.6 ± 1.3 mm, p = 0.029). Among the categorical variables, no significant differences were noted with respect to gender, type of delivery and pregnancy induced hypertension. However, the prevalence of gestational diabetes was noted to be significantly higher in right twist (20%) as compared to left twist (4.3%) with a p value of 0.027 as noted in ***Table 1***.

Discussion

The umbilical cord twist is an important feature of the umbilical cord. Evidence that the helical nature of the cord is not purely of genetic origin comes from the fact that there is an absence of concordance in monozygotic twins.[7] Also in intrauterine fetal deaths and in twins, this twist is less pronounced or absent, suggesting that fetal movements play a role.[3] The absence of a twist should raise the suspicion of the presence of a congenital malformation and adverse foetal prognosis.[3,10] An interesting finding is that a left twist of the cord outnumbers the right twist in a ratio of 7:1,[3] and the prevalence of right twist in the present study is similar. A right twist of the umbilical cord is more commonly associated with a SUA and placenta praevia than a left twist.[3,5] The present study shows a significant difference in the proportion of mothers with gestational diabetes between umbilical cords with a right and left twist, suggesting the possibility of associations between them. Previously diabetes was shown to be associated with hypo or hyper-coiling of the umbilical cord.[8,11] Another study showed that there were definite pathological changes in the umbilical arteries and Wharton's jelly in mothers with gestational diabetes.[12] These effects on the umbilical cord may be a likely cause for the effects on the direction of coiling that were observed.

Hyrtl's anastomosis is the only connection between the two umbilical arteries.[13] It is thought to play the role of either, a safety valve or a pressure stabilizer, between the umbilical arteries at the placental insertion.[14] In a study conducted on 67 full term placentae from adequate for gestational age infants, Hyrtl's anastomosis was found to be absent in only 4 of the placentae.[13] It has been found that the size of the anastomosis is related to the symmetry in the size of the umbilical arteries. Greater symmetry is associated with a smaller size, while asymmetry is associated with a larger size.[13,15] In the present study, though the difference between the diameters of the umbilical arteries was more in right twist, this was not significant.

Table 1. Differences in the Numerical and Categorical Variables between the Groups with Left and Right Umbilical Cord Twist

Variable	Left twist n = 117	Right twist n = 20	p Value
Age of mother (years)	25.9 ± 4.9	27.1 ± 3.6	0.327
Difference in diameters between umbilical arteries (mm)	0.44 ± 0.45	0.57 ± 0.5	0.238
Diameter of Hyrtl's anastomosis (mm)	2.6 ± 1.3	3.4 ± 1.7	0.029
Birth weight (kg)	2.9 ± 0.5	3 ± 0.4	0.603
Gender (% of males)	58 (50%)	10 (50%)	0.971
Type of delivery (% of Caesarean sections)	39 (33%)	11 (55%)	0.067
Pregnancy induced hypertension (% of positive diagnoses)	20 (17%)	4 (20%)	0.765
Gestational diabetes (% of positive diagnoses)	5 (4%)	4 (20%)	0.027

This greater asymmetry in the umbilical arteries with a right twist is a possible reason for the larger Hyrtl's anastomoses seen in these cases. A limitation of the present study was that only a few independent variables were considered. Other variables that could be considered include the following: umbilical cord insertion, distribution of chorionic plate vessels (magistral versus dispersed), evidence of umbilical cord knots and length of the umbilical cord. Future studies with larger sample sizes and more robust study designs such as case-control and cohort studies are required to confirm the findings of the present study.

Conclusion

Two previously unreported associations with right twist of the umbilical cord, gestational diabetes and increase in the diameter of Hyrtl's anastomosis, were noted in the present study. The association of a right-sided umbilical cord twist and gestational diabetes may be due to vascular changes that are produced as a result of the disease. Additionally, the relationship between asymmetry in the size of the umbilical arteries and the direction of twist of the umbilical cord needs to be explored in future studies.

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Fibroblast Growth Factor (FGF) Receptor Mutations: A Pathway to Understanding Multigenic Risk in Disease?

Stuart J. Mires[1]

Abstract

Fibroblast growth factor receptor (FGFR) gain-of-function mutations form the pathogenic basis of multiple congenital pathologies. A pioneering body of work over the past two decades has established that a unique mutation selection process within the testis likely underlies the paternal age effect characteristics of such diseases. This mechanism, analogous to positive selection of mutations promoting proliferation in tumorigenesis, sparked interest in mutation profiling of testicular and other cancers. The resulting discovery of FGFR gain-of-function mutations akin to those of congenital syndromes has enabled a novel hypothesis to be born: that mutations represent a spectrum of activation. As such, FGFR gain-of-function mutations could be pathogenic not solely in defined monogenic syndromes but within myriad disease processes with 'low activation' conferring increased disease risk. Do such mutations contribute to multigenic risk in multiple pathologies? This review evaluates this hypothesis, alluding to the plausible clinical implications that ensue.

Keywords: Fibroblast Growth Factors, Acrocephalosyndactylia, Craniosynostoses, Germ-Line Mutation (Source: MeSH, NLM)

Introduction

A 31-year-old man with dwarfism; an infant with short arms, legs and a clover-leaf skull; premature skull fusion and union of the bones of the digits in a still-born child. Achondroplasia, thanatophoric dysplasia type II and Apert syndrome respectively, appear to represent grossly varying pathologies at the macroscopic scale. However, each illustrates a variant of a common pathological theme: fibroblast growth factor receptor (FGFR) activating mutations. FGFRs are represented in multiple isoforms in the human proteome and they have diverse functions that include cell growth and differentiation and germ cell development. These receptors are predominant in embryological, neonatal, and renewing tissues.[1] The bodies of disease with FGFR gain-of-function (GOF) mutations as a pathogenic agent provide a plethora of opportunity to firmly establish FGFR function.

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This literature review will explore the progression of the field in characterising the disease mechanisms conferred by such mutations. Through analysis of mutation development at the molecular and cellular level it will unravel the complex interactions of function in the testis and fetus, thereby establishing the concept that FGFR GOF represents a spectrum of activation with varying contributions to pathology. Thus, it addresses the question of whether such mutations contribute to multigenic risk in multiple pathologies.

Methodology

A literature review was performed using PubMed, MEDLINE and Embase databases, with the free search terms 'fibroblast growth factor receptor', 'gain of function' and 'Apert syndrome' Additional relevant papers were retrieved from the references. All included articles were in the English language and were relevant to FGFR gain-of-function, identification of relation to a pathological state, or determination of plausible mutation aetiology.

Too Much of a Good Thing?

Apert syndrome, an autosomal dominant inherited congenital malformation syndrome, is characterised by craniosynostosis and syndactyly with a live birth rate of approximately 1 in 70,000.[2] Wilkie et al., 1995 pioneered research into the condition through establishing the molecular basis. By analysing non-recombination (alleles with the same arrangement in affected offspring as parents) across 4 Apert families, the FGF2R locus was implicated as the prime candidate. Amplification of FGF2R complimentary DNA (cDNA) from the patients followed by sequencing revealed two distinct single point transversions at independent loci in the extracellular domain, providing a putative genetic basis for the disease.[3] These mutations were further illustrated to induce GOF through site-directed mutagenesis. Protein was generated from cDNA expressing the identified Apert syndrome mutations and complexed with FGF2 ligand. The resulting complexes were then purified and crystallised. Both receptor mutations appeared to augment ligand-receptor interaction affinity, providing evidence for a clinical GOF model.[4]

A similar body of evidence supports GOF mutations in the FGF3R transcellular domain in achondroplasia and the FGF3R extracellular domain in thanatophoric dysplasia type II patients.[1]

Are Genetic Errors Accumulated or Selected?

A well-documented characteristic of FGFR syndromes is a pa-

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ternal age effect. This stipulates that syndrome incidence increases with the age of the father at the time of conception. Thus, a paternal inheritance was hypothesised. The presence of two polymorphic base substitutions flanking the Apert mutation loci enabled the design of allele-specific primers for polymerase chain reaction (PCR), comparing the haplotype of the affected allele in patients to those of their parents. Original experimentation identified 57/57 families showed mutations linked to the paternal allele and thus paternal inheritance.[5] This exclusivity is apparent in all further published studies to date.

A prevailing hypothesis therefore speculated that the basis of paternal inheritance lay in the accumulation of replication-dependent mutations in spermatogonia over time, leading to an increased frequency of mutations with paternal age and a resulting greater likelihood of mutated spermatozoal fertilisation. This is the copy-error hypothesis.[6,7]

However, a fortunate experimental tool emerged when it was discovered that the Apert mutation loci encompass the restriction site for the enzyme Microtubule organizer protein 1 (Mbo1). Therefore, through the development of PCR primers spanning this site, in non-mutated DNA there would be no amplification following treatment by Mbo1 due to cleavage and prevention of primer annealing whilst in mutated DNA amplification would still occur. As such, mutation prevalence could be estimated. [6] In spermatozoa samples taken from normal men, mutation rate did not appear to vary significantly when assessed over days, weeks or months. This implicated that mutations were not accumulating over time. However, spermatozoa mutation level was positively correlated with age. Further, the mutation was likely pre-meiotic since if it was post-meiotic we would expect a reduction in mutation level with loss of spermatozoa over time.[6] Inaccuracy is present within this experimental protocol as PCR itself introduces mutations; the efficacy of the restriction enzyme is not 100% and any mutation within the restriction site irrespective of whether it is specific to Apert syndrome would show as positive. Despite these limitations, this experimentation still provides strong evidence opposing the copy-error theory.[6]

Further experimentation by the group utilised the same Mbo1 based technique. This illustrated that the serine-tryptophan transversion was approximately 19-fold more common than other mutations, thus being disproportionately high. They reasoned that within a male heterozygous for the adjacent polymorphism to the Apert mutation locus, if the mutation was random and accumulating it would be expected that mutations would be equally divided between each polymorphic variant. However, the group identified that the relative distribution was skewed. Through the use of reverse transcription PCR (RT-PCR) analysis, expression of FGF2R RNA was confirmed in rat spermatogonial stem cells.[7] Thus, this body of evidence argues for the presence of a selection process for the FGFR GOF mutation within the testis. Expression within spermatogonial stem cells is a pre-requisite for selection, suggesting selection at the protein level. As such, a novel hypothesis was born.

Spermatogonia are the basis of the stem cell capacity of the testis. It was originally unclear whether the entire population possessed this capacity, or whether a subset drove spermatogenesis. Through the use of genetic engineering in the mouse testis, spermatogonia can be irreversibly labelled such that their offspring express traceable lineage markers following exposure to tamoxifen. When pulsed with the drug, the majority of labelled spermatozoa were lost by 2 months, due to dissociation from the seminiferous tubule and maturation processes in the epididymis. However, a small fraction of positive cells appeared to persist beyond 3 months, producing an average of 6.1 patches per testis. Utilising a similar genetic labeling system, the group then went on to show that cells isolated from these colonies, when transplanted to recipient testes, could form de novo colonies and resulting spermatozoa, indicating a stem cell capacity.[8] This experimentation presents essential evidence in supporting a selection hypothesis within the testis. It argues for the presence of an original 'actual stem cell' population generating spermatogonia which then go on to differentiate, forming spermatozoa. It implicates that a subset of the generated spermatogonia will become 'potential stem cells', deriving colonies which themselves are able to proliferate and differentiate. Thus, if a spermatogonial stem cell population was to acquire advantageous genetic traits, it could drive selective mechanisms through potential stem cell colony formation.

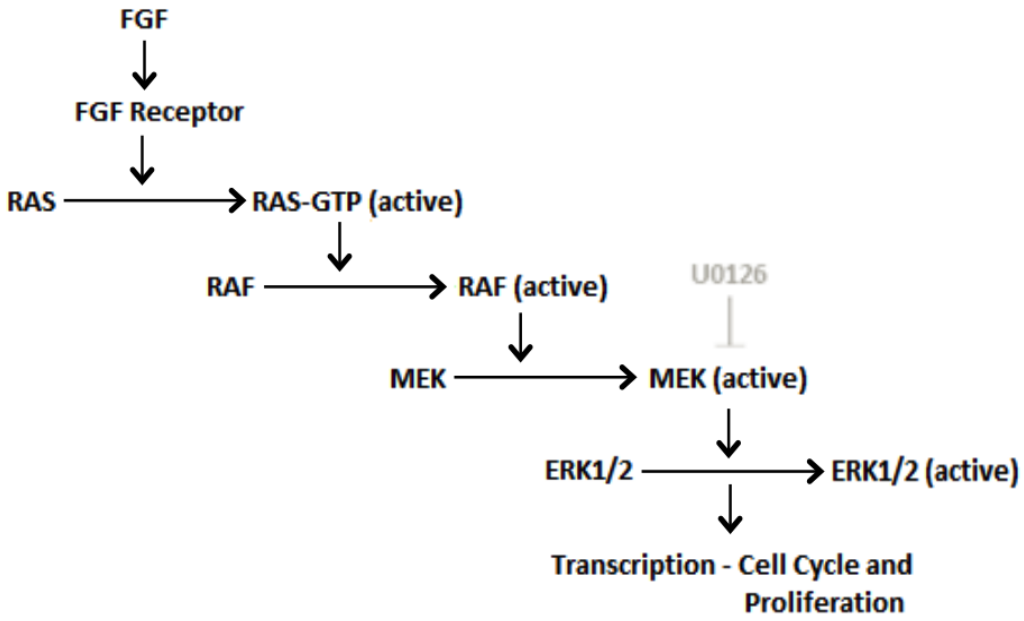
The frequency of the most common Apert mutation is 100-1,000 times higher than would be expected from average background mutation rate. Qin et al., 2007 published pioneering experimentation to examine the spatial distribution of mutated spermatogonia by dividing the testes of two normal men into 200 segments and quantifying the mutation frequency within each segment utilising PCR. This identified foci of mutation frequency 1,000-10,000 fold higher than underlying testis tissue.[9] This experimentation argues for the rejection of a hypothesis that higher mutation rates in older men are associated with Apert syndrome mutation 'hot-spots' (loci prone to mutagenesis). It is highly suggestive of the selection hypothesis with mutation foci analogous to the aforementioned potential stem cell populations.[8]

The 'Selfish Testis' and Beyond

Mouse modelling of Apert syndrome has been achieved utilising CreLox recombination technology to generate a targeted serine-tryptophan mutation within the FGF2R. This animal model has been intrinsic in establishing downstream effector mechanisms mediating pathogenesis. Through the use of RNA interference knockdown of the mutated allele in mice heterozygous for the Apert mutation, Shukla et al., 2007 illustrated that ERK1/2 levels were normalised at the RNA and protein level compared to enhanced expression seen in mutant animals. These members of the mitogen activated protein tyrosine kinase family ***(Figure 1)*** were thus strongly implicated as mediators at the molecular level of GOF FGFR mutations. Treatment of mutant mice with U0126, an inhibitor blocking activation of the extracellular signal-regulated kinase (ERK) pathway, facilitated birth of morphologically normal mice when injected into pregnant mothers, further supporting this pathogenic mechanism.[10-12] Thus, it is apparent that activating FGFR mutations appear to drive mitogenic pathways within affected cells.

FGFR activating mutations have been identified within a range of tumour types. This is particularly apparent in the context of

Figure 1. Fibroblast Growth Factor Receptor Cellular Signalling



Adapted from: Seger R, Krebs EG. The MAPK signaling cascade. FASEB J. 1995;9(9):726-35; Eswarakumar VP, Lax I, Schlessinger J. Cellular signaling by fibroblast growth factor receptors. Cytokine Growth Factor Rev. 2005;16(2 SPEC. ISS.):139-49.

endometrial carcinoma. Through sequencing endometrial cancer cell DNA from cell lines and primary uterine tumours, it has been identified that 30% and 10% of cancers, respectively, expressed varying FGFR activating mutations. These included those identified in congenital syndromes such as Apert syndrome and achondroplasia.[13] Comparable data has been reported in further studies with sequencing and mass spectrometry of endometrial cancers identifying 12.3% with FGF2R mutations, including those mediating Apert syndrome. Similar mutations have been identified within a range of tumour types including myeloproliferative disease, gastric, squamous cell, small cell lung and breast cancers.[14]

The concepts of mutation selection within the spermatogonia of the testis in addition to the probable involvement of mitogenic pathway activation are reminiscent of the apparent involvement of oncogenic mutations in the tumours discussed. Therefore, it was proposed that such mutations could drive tumorigenesis directly within the testis. Classical seminoma germ cell tumours do not show the correct epidemiological characteristics for paternal age effect mutations. However, spermatocytic seminomas, a rarer neoplasm, commonly affect older men. Through sequencing FGFR mutation hot-spots within 30 samples of tumours, two were identified as having GOF FGF3R mutations previously identified in thanatophoric dysplasia II. Similar mitogenic pathway regulators such as Harvey rat sarcoma viral oncogene homolog (HRAS), a factor associated with congenital Costello syndrome characterised by skeletal and visceral morphological defects and mental retardation, were also identified with GOF mutations in spermatocytic seminomas.[15]

This body of evidence proposes that GOF mutations in spermatogonia induce selective advantage and clonal expansion, driving in situ testis tumorigenesis. However, a prominent caveat of this experimentation, in addition to those assessing mutation profiles in varying tumours, is the retrospective nature of the studies with no conclusive evidence that the mutations identified are causative. FGFR GOF as such could represent acquired mutations within the neoplasm, selected for by mitogenic advantage and acquired after the original pathogenic event. Despite this, the work presents a viable theory of a spectrum of pathology with a common FGFR GOF aetiology. Further, a novel, interesting concept in the form of the 'selfish testis' is portrayed.[16] FGFR GOF mutations appear to drive a selective advantage within the testis (spermatogonium) itself but when transmitted to the resulting offspring they induce defects in growth and cellular division due to imbalances in activating signals. Thus, the testis appears 'selfish' in selecting for an intrinsically beneficial mutation that becomes detrimental in the fetus.

A Pathological Spectrum and Multigenic Risk

If we envisage FGFR mutations as a hypothetical spectrum with grades of activation capacity, it is possible to classify the aforementioned pathological outcomes. 'High activating' FGFR GOF mutations would be detrimental when acquired within the testis and other tissues implicated in tumorigenesis. 'Moderately activating' mutations would show the same selection mechanisms within the testis, but have negligible pathogenesis in situ, acting as the pathogenic agent in congenital syndromes within resulting offspring. A prominent question, therefore, becomes 'what of 'low activating' mutations: Do they exist and are they pathogenic?'

Unilateral segmented acne in a mosaic pattern has previously been described as a dermatological hallmark of Apert syndrome.[17] However, this disease has also been identified in patients without the classical Apert syndrome presentation. Within one such patient, sequencing of the FGF2R gene in cells isolated from the naevus demonstrated an identical seri-

ne-tryptophan GOF mutation characteristic of Apert syndrome. Other dermatological stigmata associated with this mutation include hypopigmentation and hypotrichosis (loss or reduction of hair growth).[17] Therefore, this discovery presents two important concepts: Firstly, despite this patient presenting with an acquired FGFR mutation, as opposed to the congenital forms of systemic disease previously described, the resulting findings affirm that GOF underlies the pathological features of Apert syndrome. Secondly, it illustrates that such mutations can alter the equilibrium of tissues constitutively regenerating throughout life, leading to defects in structure and integrity. Thus, it is pertinent to question whether alternative variants of the FGFR, other than those described in congenital syndromes, could contribute to numerous disease aetiologies - particularly in tissues with renewing capacity.

Single nucleotide polymorphisms (SNPs), as DNA sequence variations occurring at a single base, provide an ideal tool to assess the viability of this hypothesis. Breast tissue retains proliferative capacity throughout life, particularly in response to hormonal change. Genome wide sequencing within breast cancer tissue specimens has identified that variation in FGF2R loci, linked to eight SNPs, is associated with a small but significant increased risk of developing breast cancer. Microarray data confirmed by real-time quantitative PCR illustrated that within rare homozygous cells for these SNPs there is amplification of FGF2R expression at the RNA level. Chromatin immunoprecipitation ascertained that two of the SNPs resulted in an increased association of FGF2R DNA with transcription factors such as Oct1 that are known to be associated with proliferative capacity and tumorigenesis. Therefore, this provides a putative mechanism by which sequence variation in the FGF2R can drive increased expression, effectively representing a GOF of the receptor and resulting in tumorigenesis.[18]

The epithelial lining of the mouth and oropharynx also maintain a regenerative capacity. A specific SNP within FGF4R has previously been associated with increased tumour cell motility and progression within breast, head and neck, and sarcoma cancers. Recent experimentation has focussed on the prognostic significance of SNP presence in squamous cell carcinoma of the mouth and oropharynx. Through genotyping DNA from peripheral blood samples of 122 patients and assessing protein expression by immunohistochemistry in tumour cells, SNP presence was associated with lymphatic embolisation and disease-related premature death. Thus, the SNP appears linked with poor prognosis, a phenomenon which has previously been illustrated in a variety of tumours including lung and prostate cancers.[19]

These experiments do, however, exhibit multiple caveats. Neither establishes a direct causative link between the SNPs studied and tumour formation based on their retrospective nature. Further, in assessment of FGF4R prognostic value, the treatment regimens of patients and their responses to therapeutic intervention cannot be adequately controlled between SNP positive and negative groups. In addition, the functional outcome induced by SNP presence has as yet not been characterised, so links to GOF have not been established. Nevertheless, the experimental data presented does illustrate that genetic variation, even at levels as low as a single base, can alter function of the receptor complex and contribute risk to the formation and outcome of varying pathologies. Therefore, it is plausible that these polymorphisms represent a category of 'low activating' mutations, predisposing to increased disease burden within affected populations. It remains to be established whether SNP derivation illustrates the same selection mechanisms within the testis as seen in the GOF mutations discussed, which would be required to justify this assertion. Further, the degree of disease association and the range of implicated pathologies are still to be ascertained. However, this hypothesis signifies an exciting prospect, putatively representing an underlying principle, which will be essential in unravelling the complex issue of multigenic risk factors in disease aetiology over the coming decades.

Conclusion

FGFR GOF mutation is implicated in numerous pathologies. By visualising GOF as a spectrum of activity and studying genetic polymorphism we can speculate that such genetic traits confer alteration in FGFR function and thus contribute to multigenic disease risk.

To prove this hypothesis, however, a number of questions remain to be answered. Although a spectrum of activation provides an attractive model that conceptually relates genotype to the clinical phenotypes produced, a direct comparison of the degree of GOF in each pathology and predisposition is required. This includes assessment of RNA and protein amplification in addition to the strength of ligand-receptor complex formation. Further, selection of SNPs and other mutations related to disease risk need to be confirmed. Finally, although the studies presented centre on tumorigenesis due to the mitogenic activation induced by FGFR GOF mutation, relation to other common morbidities including cardiovascular, endocrine and autoimmune disorders provides an important area of study.

Can this basic science impact on clinical outcomes? Is there a plausible bench-to-bedside application of this evidence? Preimplantation genetic screening for in vitro fertilisation is performed for numerous pathologies including Huntington's disease and cystic fibrosis as well as genetic predispositions such as BRCA1/2 mutation. Were FGFR risk factors to be confirmed, inclusive screening programmes could be developed. Further, as GOF is inherited paternally, offspring are commonly heterozygous. Thus, targeted genetic therapies such as antisense oligonucleotide-mediated knockdown or RNA interference knockdown specifically against the mutated allele are feasible. With the advent of these technologies, our continued understanding of FGFR contribution to multigenic disease could spark progress in reducing clinical disease incidence and burden.

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Case Report

Complete Congenital Heart Block in a Newborn Associated with Maternal Systemic Lupus Erythematosus: A Case Report

Mahmoud A. Kiblawi,[1] Alina Naeem,[1] Elham A. Al Attrash,[1] Subhranshu Kar,[1] B. K. M. Goud[1]

Abstract

Background: Complete Congenital Heart Block (CCHB) is a rare disease of the newborn that carries significant morbidity and mortality. CCHB can be diagnosed early or late in life. In newborns, it is usually associated with maternal autoantibodies or a congenital cardiac structural abnormality. The most common presentation of CCHB is bradycardia that can be diagnosed by an electrocardiogram. **Results**: This is a case report of a male infant born to a mother with an autoimmune disease, Systemic Lupus Erythematosus (SLE), who was found to have third degree heart block at birth. **Conclusion**: Early diagnosis and prompt management of the case is important for a better prognosis and prevention of associated complications. Neonates with CCHB should be managed at a tertiary care center and the only definite treatment is insertion of a pacemaker. Moreover, prenatal diagnosis and specific obstetric counseling of pregnant women with SLE along with careful monitoring with serial ultrasonography and echocardiography are of paramount importance in prevention of the disease in subsequent offspring.

Keywords: Congenital Heart Block, Systemic Lupus Erythematosus, Bradycardia, SS-A Antibodies (Source: MeSH, NLM)

Introduction

Complete Congenital heart block (CCHB) is a rare clinical entity present in about 1 in 20,000 live births and has significant morbidity and mortality.[1] It generally occurs due to the presence of maternal auto-antibodies, anti-Ro/SSA and anti-La/SSB, that are transferred across the placenta to the fetus and affect the fetal heart. More rarely, it may be associated with a congenital structural abnormality of the heart.[2-3] The association between CCHB and maternal autoantibodies has been documented in different case reports.[4-8]

The risk of Neonatal Lupus Erythematosus (NLE) or Congenital Heart Block (CHB) is 1% in infants with positive maternal autoantibodies to SSA/Ro. The risk is much higher if the mother already has had a child with NLE or has hypothyroidism due to thyroid autoantibodies that test positive for anti-Ro/SSA antibodies.[2] The most common clinical manifestations of NLE are related to the cardiac, dermatologic and hepatobiliary systems. Some infants may also have hematologic, central nervous system or splenic abnormalities.[9-10] Infants with NLE have 15-30% risk of developing CHB.[2,11]

In the early part of 19th century, congenital heart block was clinically recognized by slow pulse, syncopal attacks and ECG findings consistent with complete atrio-ventricular block leading to the death of the child early on in infancy.[12-13] Considerable information has also been accumulated since then concerning the clinical profile and circulatory hemodynamics in such cases.[14-15] Mortality is highest in the neonatal period and association with major cardiac malformations is a bad prognostic sign.[16] We present a rare case of Complete Congenital Heart Block (CCHB) in a newborn associated with maternal Systemic Lupus Erythematosus (SLE). A written informed consent was obtained from the parents of the patient for the publication of the available data.

The Case

A 3-days-old full-term male infant, born out of a consanguineous marriage by normal vaginal delivery with a birth weight of 3,330 g, presented with bradycardia (heart rate of 40-65 beats/min) and respiratory distress for which he was admitted to special care baby unit (SCBU). His mother, Gravida 6 and Para 6, had a past medical history significant for Systemic Lupus Erythematosus (SLE) as positive anti-Ro/SS-A antibodies had been discovered 5 years ago. Her antibody titers have been persistently elevated since then. Furthermore, she has had persistent hypothyroidism over the past four years which currently being treated with levothyroxine. Also, two of her previously offspring were found positive when tested for Antinuclear Antibody (ANA) and anti-Ro/SSA antibodies.

The infant was stabilized in the SCBU and kept on two liters of oxygen through nasal cannula for respiratory distress. He was tolerating feeds. His heart rate ranged between 40-65 beats/min despite being given two doses of atropine (0.1 mg/dose). Laboratory examinations showed capillary blood sugar of 72 mg/dl, normal complete blood count and normal electrolyte levels (Na- 137 meq/L, K-3.6 meq/L). At presentation, the arterial blood gas analysis (pH-7.25, pCO_2-58 mmHg, pO_2-40 mmHg, HCO_3- 24 mmHg and base excess of -4) showed respiratory aci-

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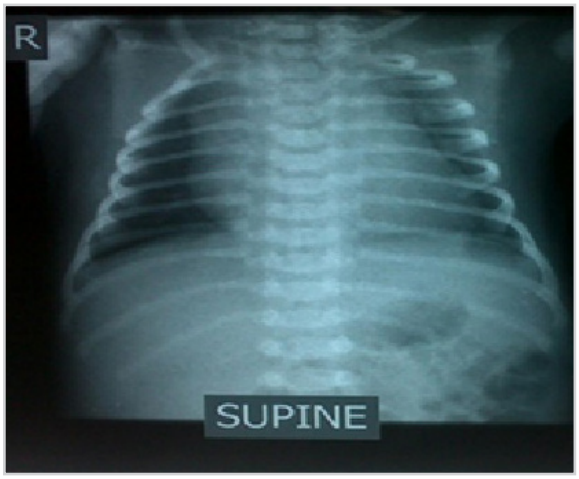
Figure 1. Anteroposterior (AP) Chest Radiograph of the Infant



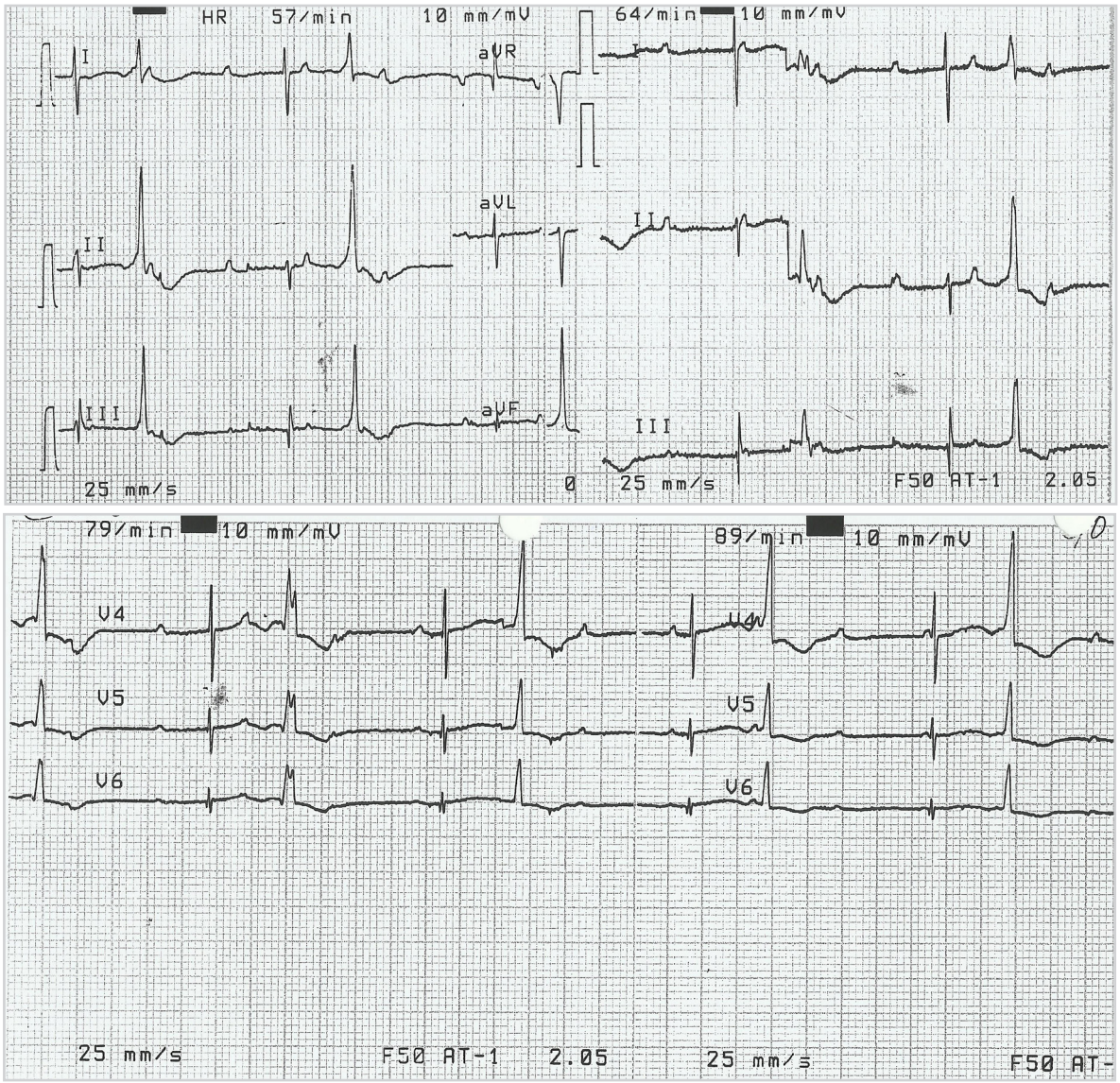
Note: Chest radiograph showed cardiac enlargement.

dosis. Chest X-ray AP view showed cardiac enlargement ***(Figure 1)***. His electrocardiogram (ECG) showed features of complete heart block ***(Figure 2)***. Based on his condition, it was decided to do further evaluation and management (including the possibility of pacemaker insertion) to support the patient in the best possible way. Echocardiography was performed and it revealed no structural abnormality. A permanent pacemaker (St. Jude VVI PM at rate 90 beats/min) implantation was done on the 8th day of the infant's life. Upon further follow up, the patient was stable and his general health status was good. The pacemaker was functioning well at a rate of 90 beats/min. He was thriving well with normal development.

Discussion

SLE is an autoimmune disease characterized by production of large amounts of circulating autoantibodies that can affect any organ of the body and leads to variable clinical manifestations. The ANA is the most sensitive laboratory test for the diagnosis of SLE.[17] The presence of anti-double stranded DNA antibodies

Figure 2. ECG from Infant Demonstrating Complete Congenital Heart Block



Note: ECG of the infant demonstrates no relation between P wave and QRS complex. The P wave has the normal rate and is regular, as it is arising from the sino-atrial node. The QRS complex illustrates the ventricular escape rhythm and hence is very slow.

and anti- Smith antibodies are more specific for the diagnosis of SLE as they have high sensitivity. Other nonspecific subtypes of ANA can be associated with SLE, including antibodies to Ro (SSA) and La (SSB), but these are also seen in patients with Sjogren's syndrome. Studies have shown that congenital heart block is associated with maternal connective tissue diseases such as SLE and in patients with structural heart disease such as L-transposition of the great arteries.[18-19] CCHB can also be observed in patients with neonatal lupus syndrome diagnosed in utero.[20]

Among the conduction defects resulting from maternal SLE, congenital heart block in infants born to mothers with anti-Ro antibodies is the most commonly seen in clinical practice.[21] The anti Ro antibodies have been detected in maternal sera in up to 98% of cases of CCHB.[22] Antibodies to Ro/SSA are detected by enzyme-linked immunosorbent assay (ELISA) and Western blot immunodiffusion tests. The Ro/SSA autoantigen consists of two proteins, Ro52 and Ro60, with the former having close correlation with the development of CCHB.[23] These antibodies induce myocarditis which leads to CCHB by destroying the cardiac conduction system at the atrioventricular node and bundle of His region. Atrioventricular (AV) block occurs due to impairment in the conduction system causing delay or block in transmission of atrial impulse to ventricles. Third-degree heart block, whether its congenital or acquired, is diagnosed when there is no association between P wave and QRS complexes. In less than 10% of cases, congenital AV block may be either 1st or 2nd degree block at birth, of which 50% progress to 3rd-degree block in postnatal life.[15] Congenital heart block can be detected in utero between 18 and 28 weeks of gestation by echocardiography in the presence of fetal bradycardia.[24-25] It may also be associated with other cardiac abnormalities such as endocardial fibroelastosis and dilated cardiomyopathy.[26] As the fetal heart rate is an important indicator for the prognosis during the newborn period, the persistent bradycardia may eventually lead to increased size of both right and left ventricles.[16] In children under three years of age, a heart rate less than 100 beats/min is considered as bradycardia.[1] Our patient had a heart rate of 40-65 beats/min, whereas normal newborns have a heart rate of 120-160 beats/min. In spite of his low heart rate, his birth weight was within normal limits. The ECG showed the most severe type of heart block, third degree heart block, where there is no transmission of atrial impulse to the ventricle. CCHB is the most serious complication associated with maternal SLE and once established it is irreversible.[3]

Occasionally, these cases are symptomatic in the neonatal period, as evident in our case, and they are considered high-risk patients requiring urgent intervention. The mortality is highest during the neonatal period. Glucocorticoid therapy is suggested for management of CCHB in utero and in the perinatal period (if associated with anti-Ro and anti-La antibodies), but the therapy itself carries high risk to both the mother and the fetus.[27] Two third of all congenital heart block patients require pacemaker implantation and it is recommended in symptomatic bradycardia. Pacemaker therapy is recommended in infants with CCHB and heart rates less than 55 beats/min in the absence of structural heart disease or with rates less than 70 beats/min with concomitant congenital heart disease or signs of ventricular dysfunction. Beyond the first year of life, a heart rate less than 50 beats/min or abrupt pauses in ventricular rate merit consideration of pacing therapy. Evidence of cardiomyopathy with ventricular dysfunction, complex ventricular ectopy and wide complex escape rhythm are also indications for pacing.[28] The primary goal of the pacemaker is to prevent sudden cardiac death and to provide symptomatic relief with improvement in quality of life and functional capacity, as was done in our case.[22,29]

Conclusion

In conclusion, anticipation of CCHB in cases of maternal SLE is important. Early detection of CCHB by health care professionals and timely management is the key to the success of the infant's survival. A thorough physical examination and an ECG can be diagnostic in patients presenting with bradycardia. For prevention, it is necessary to implement: 1) Health education and creating awareness among high risk populations, 2) Emphasize good antenatal care and proper screening, especially in underprivileged populations, because frequent assessment of fetal heart rate by echocardiography during pregnancy is beneficial for a patient with positive anti-Ro and anti-La antibodies, and 3) implementing proper obstetric counseling and support to the family.

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IJMS International Journal of Medical Students

From Physics Olympiads to Medical Research: Lessons Learned

Andres Zorrilla-Vaca[1]

The Experience

For the last four years I have been fully dedicated and immersed in the study of Physics. I was part of the National Colombian Team for the Physics Olympiads tournament, organized by the Antonio Nariño University for the past twenty-nine years. This great honor required intensive training sessions in Bogota, Colombia, and rigorous self-study to increase my knowledge and gain experience. With great responsibilities come not only great challenges but also important rewards. In my case, I was lucky to visit fascinating places around the world, such as Tallinn and Tartu, Estonia, and meet interesting people who shared my love and passion for science and the field of physics. In retrospect, now one year after having finished my experience in the Olympiads, I realize the heritage that these learning experiences in physics have imparted on me: the necessary skills to perform medical research in my university.

I assumed the task of applying my investigational skills acquired in the study of physics, to the study of medicine through participation in several medical student research groups derived from the ACEMVAL - Scientific Association of Medical Students' of the Universidad del Valle, in Cali, Colombia.

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My Experience in the Physics Olympiads

Thinking back to the days when I was starting high school, the internal competitions in mathematics and physics were the first step in the path of the Colombian Physics Olympiads. These intra-school competitions were held every year and after progression through different stages, the qualified students were invited to the regional competitions for Southwest Colombia. If successful, they would participate in the National Olympiads. At the National level, everyone would compete for the distinction of medalist, winner and absolute champion of the Colombian Physics Olympiads (CPhO).

I was honored to be among the first places in the ranking for several years in the Regional Mathematics and Physics Olympiads. In 2011 I won the major distinction in the national test and in the same year I represented my country and became the bronze medalist in the 16th Ibero-American Physics Olympiads (IbPhO). Finally, thanks to the effort, dedication and performance in other annual routine tests, in July 2012 I had the honor of representing my country in the 43th International Physics Olympiads (IPhO) organized in Tallinn, Estonia ***(Figure 1,*** available from: http://issuu.com/e-ope.ee/docs/ipho2012/1, updated 16 Sept 2012; cited 2013 Jan 15). At the time, I was completing my final year of high school. Because of my participation in the events of Olympiads, our team got the opportunity to meet and listen to conferences by distinguished scientists. Sir. Harold Kroto, chemistry Nobel Prize, shared with us his

Figure 1. Photograph Taken During my Participation in the International Physics Olympiads, Enjoying the Estonian Capital: Tallinn.

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thoughts on the chemistry of carbon and amusing life-lessons about the dreams he never fulfilled such as becoming a superhero, portraying in this way, to never lose the hope in your own personal goals (Available from: http://issuu.com/e-ope.ee/docs/ipho_uudiskiri_no6_web/1, updated 16 Sept 2012; cited 2013 Jan 15). Another event that had a profound impact on me was the visit to the AHHAA Science Center, where we could have direct contact with amazing technological inventions and biological discoveries that in most of cases have imparted significant impact on the global community. All of these exciting cultural visits allowed me to understand the great impact that research can have in the daily routine of humanity.

Parallels of the Olympiads Skills Set to Medicine

Infancy and adolescence constitute important stages for the dynamic growth of the human being. Scientific literature establishes that some fundamental aspects of these developmental phases are interaction with physical objects and its experimentation to explore new paths or alternatives.[1] In my experience, I grew up in an environment that fostered exploration and consequently, during high school, my principal interest was the competitions in the Physics and Mathematics Olympiads where I was able to explore and experiment with the physical world to propose solutions for problems. These skills developed a suitable platform to succeed in my future endeavor as a medical student-researcher in training.

Focusing on research, an area that was particularly promoted in the Olympiads, I could verify that the tests used in these competitions are based on experimentation. During the competitions, having a strong theoretical knowledge played a very important role, but it was the ability to develop creative solutions with strong justification that was paramount in being able to solve a problem. Furthermore, without a systematic process mistakes would filter in the competitions.

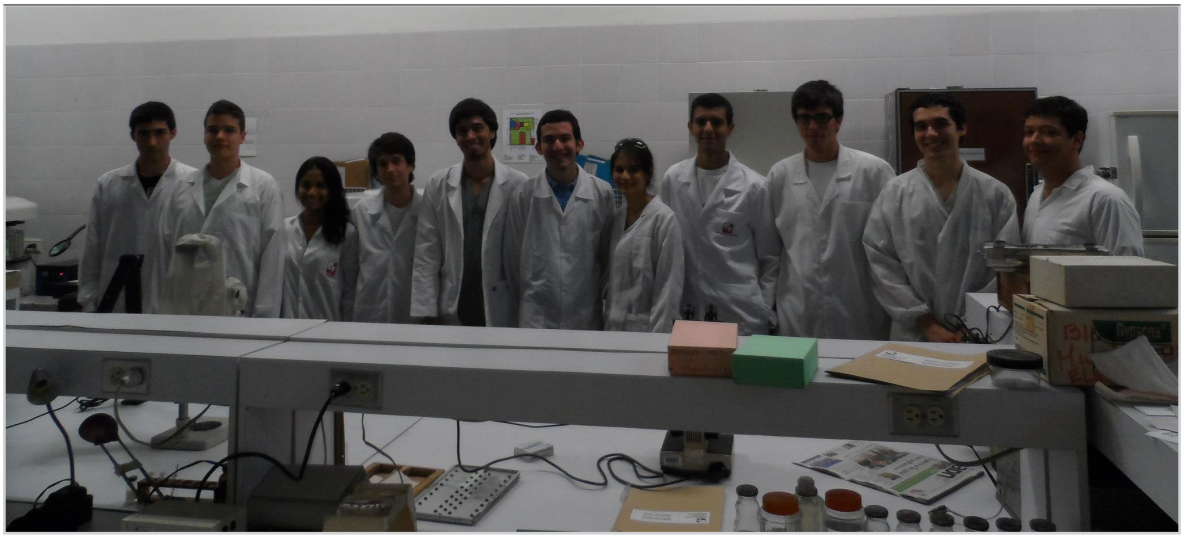
Through understanding the relationship between theoretical knowledge, experimentation, and proposing creative solutions to a problem using a systematic process, I have been able to spend my time as a medical student applying the skills I have learned in the Olympiad competitions to the field in which I wish to progress: Medicine. The experience acquired from the physics exercises prepared me to apply the rigor of the scientific method to the new hypotheses and problems that I want to start addressing in medicine. Furthermore, historically the relation between medicine and physics has been shown and clearly identified as making great contributions to the progress of medicine; for example in fields like radiology, genetics, physiology and many others.[2]

Now that I have started the next phase of my life in medical training, I joined a research group that focuses on Infectious Diseases. I have been able to consider the importance of my early exposure and practice of the scientific method in experimental studies and how this helps to obtain a better understanding of reality. I realized that common themes such as addressing how something works facilitate the development of a skill set applicable to special interests in multiple topics. The scientific method serves as a proper base to develop a special interest around any topic in a systematic approach; therefore you can address questions 'like how does something work?' and know where to start and learn how to think. Also, my participation in the Olympiads encouraged me to develop creativity, passion for competition and dedication to science; all of these factors together provide a fruitful beginning in all areas of Medicine and especially research.

My experience in the Olympiads have allowed me first, a new vision of my interests in medical research, like epidemiology, where quantitative analysis is applied to the study of clinical subjects; second, a major dedication to science as evidenced by my constant participation in several research projects; and third, a great commitment to my duties as a doctor-researcher in early development.

Furthermore, my knowledge of Physics has helped me advance in several research projects. For example, we were conducting a study to evaluate a diagnostic test for Chlamydia trachomatis in urine male specimens, comparing a new PCR technique created previously in the laboratory, to two other inmunoenzimatic (EIA) techniques (data not published yet). Because of my background, I was be able to help in the methodology with

Figure 2. Research Group on Infectious Diseases of the Medical Students' Scientific Association of the Universidad del Valle, in Cali, Colombia, ACEMVAL.



ideas about different statistical models needed to demonstrate possible alterations in the sensitivity and specificity of our PCR due to biologic and socio-demographic factors of the study population. We used ROC curves and other parametric tests to consider the effects of variables such as age, gender, medications (like antibiotics), time elapsed since previous voiding and other urinary tract co-infections, on the diagnostic tests. On another occasion, when our research group was planning a critical article revision on the microbiological effects of local anesthesia, I was able to verify the importance of physical models in the description of bacterial growth and how this growth could be altered by pharmacologic agents.[3] These are but a few examples of scenarios where I have felt how my skills acquired from Olympiad training have helped me, possibly by facilitating the connection of complex physical models to an artistic science as tangible as medicine.

Summarizing my experience in these events and following progression through my university life in medicine, I want to emphasize the concept that many different life-paths can have a positive effect in medicine, especially in countries where medical education is started immediately after finishing high school. In my case, my experience in the Physics Olympiads have facilitated the development of my early interest in medical investigation, further promoted by interacting with other talented medical students of ACEMVAL ***(Figure 2)***. Therefore, it is possible that participation in Olympiads and other competitions are beneficial for the holistic training of medical students.

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Recommendations for Future Articles on Knowledge, Attitudes and Practices in IJMS

To the Editor,

The International Journal of Medical Students (IJMS) was created with the objective of sharing the scientific production and experiences of medical students and recently graduated physicians worldwide. As a scientific dissemination platform, it requires the material published to be of the highest quality.[1]

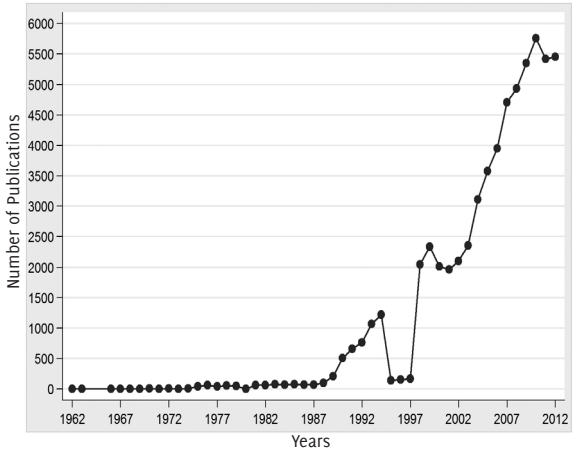
It is striking that the first two issues of the first volume of the journal each had an article with Knowledge, Attitude and Practices (KAP) in health methodology. This fact motivated the authors to write this letter to discuss some methodological issues about KAP studies, to present the evolution of this method as a scientific publication, and to discuss the main limitations of KAP studies recently published in IJMS.

KAP studies are based on a quantitative method that collects both quantitative and qualitative information. These type of articles can reveal characteristics of the knowledge, attitudes and behaviors of health factors relating them to religious, social and traditional factors and can expose some of the personal ideas that each individual has about a given condition.[2]

Furthermore, these types of studies provide a relatively simple study methodology ideal for medical students, in their initial phases of research training, to approach a problem from both a quantitative and qualitative perspective. This methodology offers an initial, wide perspective about a problem, uncovering opportunities for medical students for further research studies that can result in a positive impact on their community, while at the same time aiding in the development of skills as investigators in training.[3,4]

KAP studies have been evolving and their use has demonstrated an average increase of 105 published articles per year (R^2=68%, p <0.00001) in the period between 1961 and 2012 ***(Figure 1)***; however, if the analysis is restricted to encompass articles published from 1990 to 2012, publications have increased by 278 articles per year (R^2=88.9%, p <0.0001).

Figure 1. Number of Publications with Knowledge, Attitude and Practice methodology Published in PubMed® from 1962-2012



Source: PubMed, United States National Library of Medicine, National Institutes of Health. (Available from: http://www.ncbi.nlm.nih.gov/pubmed/, cited 2013 Sept 16) Using the keyword: "Health Knowledge, Attitudes, Practice" and timeline download option (Download Comma Separated Values, CSV).

The growth of KAP articles when compared to Meta-Analysis has shown that they are less frequently used, albeit this difference is non-significant, with a median number of publications in all its history up to 2012 of 99 vs. 795 publications, respectively (Mann-Whitney test, p=0.08, KAP percentile 25 [p25]=41 and percentile 75 [p75]=2,048, and Meta-Analysis p25=371 and p75=2,332 publications). In contrast, KAP articles have a longer history, having their first publication in 1962, close to the year when the first Clinical Trial was published in 1961 and a few years before the first Meta-analysis was published in 1966 ***(Figure 2)***.

To properly design a KAP study, there are four recommendations that should be followed: (1) Development of a survey protocol, which should contain identification of the target population, calculation of sample size, sampling methods, questionnaire, adaptation of the answers, analysis plan, pretest questionnaire, construction of the data entry form, validation of questionnaire and validation of survey protocol; (2) Preparation of the survey, which should be adapted to the target population and should describe the schedule, materials, human resources and logistical needs and a pilot test of the survey; (3) Implementation of the survey including approval and consents, checking questionnaires, general supervision of the survey; and (4) Data analysis and preparation for publication.[5]

Sometimes authors overlook some of the above-mentioned 4 steps in developing a KAP study, or underestimate the importance of the research protocol and the criteria to select a research method and its systematic development while it is written.[4] Therefore if the purpose is to show relevant results from the public health perspective, it is imperative that investigators follow closely the described recommendations.

The IJMS has published two KAP articles in its first volume, the first one by Bonilla-Escobar FJ, with the title "Red Eye: Next Steps for Conducting Research in Knowledge, Attitude and Practice in Ophthalmology" in issue 1, and the second by Eissa AT, with the title "Knowledge, Attitudes and Practices towards Medication use among Health Care Students in King Saud University" in issue 2.[6,7] By following the described recommendations, the authors would like to point out some weaknesses found in these studies:

- Failure to show the calculation of the sample size and selection of the study population: This will tell the reader if the information presented is statistically relevant for a given delta, power and effect size and if the assumptions can be considered true for the study population (internal validity).[8]

- Failure to describe the sampling methods: This information is necessary to understand the generalizability of the study findings (external validity) and comprehend the analysis used.[4]

- Failure to state the objective, conclusions and recommendations of the study: These should be clearly stated, due to the impact that those studies can have in public health and

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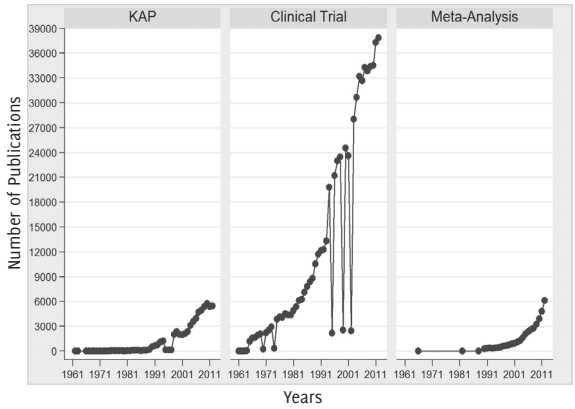
Figure 2. Number of Publications with Knowledge, Attitude and Practice methodology, Clinical Trials and Meta-Analysis Published in PubMed® from 1961-2012



Abbreviations: KAP, Knowledge, Attitude and Practice methodology studies.

Source: PubMed, United States National Library of Medicine, National Institutes of Health. (Available from: http://www.ncbi.nlm.nih.gov/pubmed/, cited 2013 Sept 16) Using the keywords: "Meta-Analysis [Publication Type]", and "Clinical Trial [Publication Type]" and timeline download option (Download Comma Separated Values, CSV).

thus will facilitate the application of the results in their communities.[3]

• Failure to report the survey questionnaire used to collect the data: As this information will be useful for other researchers who may want to replicate the study in other conditions.

•Failure to describe if a pretest survey was performed: A pretest survey helps to identify if the instrument is measuring the construct (idea) that the researcher wants to measure, to recognize problems with the instrument and to adjust the questions to the population.[9]

KAP studies offer a good opportunity for medical students to conduct their first research studies; however, it is important to take into account the specific methodological requirements for these types of studies. Guidelines in qualitative and quantitative methods are needed to improve the systematic design and reporting of KAP studies and facilitate the application of their findings to public health.

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Artist Featured in Volume 1 IJMS: Rebecca Plummer-Rohloff, PhD

Aisha Gharaibeh,[1] Juliana Bonilla-Velez[2]

Rebecca Plummer-Rohloff is an Assistant Professor of Art Education at the Arts and Design Faculty at Salem State University, MA. Among her many professional areas of expertise, she is particularly interested in Expressive Art Therapy and Arts in Medicine. She as expressed that "my studio work is inspired by themes of impermanence, transformation, the imaginary, and biology"[1] making her work very appealing to medical students.

She was an instructor and professor at several high schools and universities in the US, such as the Pennsylvania State University, the University of Illinois at Urbana-Champaign, Unity Junior and Senior High schools, among others. She has also taught English and Art in the JET program in Southern Japan after her graduation. She enjoys spending her summers in Guatemala advocating for Healthcare and Art Education. All of these experiences are reflected in her multiple publications. Furthermore, she has been certified in "Arts & Healing" from the Center on Arts, Healthcare, Research, and Education, (CAHRE), Arts in Medicine Program at Shands Hospital, University of Florida at Gainesville.

For more information:
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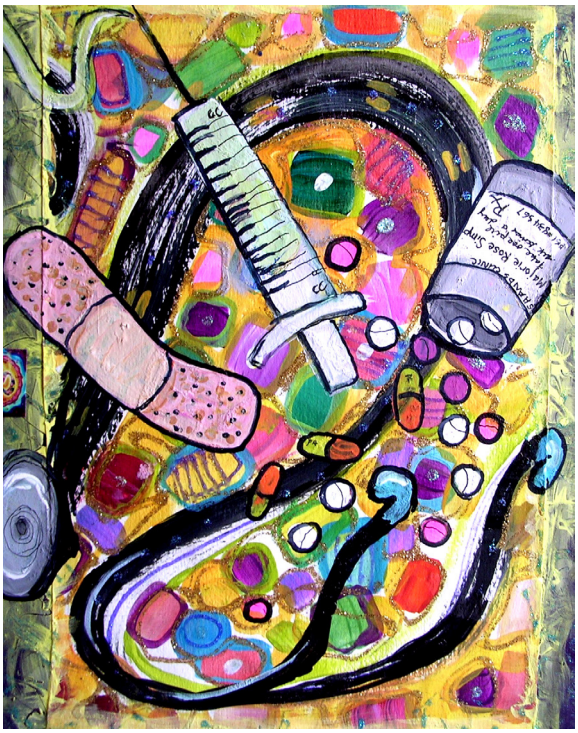
www.salemstate.edu/academics/schools/1039.php?id=4383

At the International Journal of Medical Students (IJMS) we are honoring an artist in each Volume who has been inspired by medicine and made significant contributions to the Arts. Three art pieces are chosen from the artist's repertoire for the cover of each issue. Due to her extensive trajectory and capturing art pieces, our historical first Volume exalted the work of Rebecca Plummer Rohloff, PhD. Thank you Dr. Plummer-Rohloff for your support throughout this year.

1. Available from: http://rprgallery.com/gallery/main.php, cited 2013 Sept 15.



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