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Letter From The Editors

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Case Reports

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JOURNAL of SCIENCE & MEDICINE

Dear Readers,

We present to you the sixth volume of the *Wake Forest Journal of Science & Medicine*. This year has been fraught with challenges that has altered virtually every facet of our personal and professional lives. We are grateful to the clinicians, scientists, and volunteers in our community whose extraordinary efforts have allowed for the *Journal* to publish not only a special issue that focused on the impact of the COVID-19 pandemic, but also this regular issue that includes a broader collection of original science, case report, and perspective manuscripts.

The *Journal* entered its sixth year since the inaugural edition was published. Since its creation, this student-led, peer-reviewed journal has continued to grow and garner more attention and visibility within our community. The *Journal* is now published electronically, as well as in print, with ongoing efforts for journal indexing in the near future. Additionally, a new milestone was achieved this year with the publication of the *Journal's* first special issue. As we have continued to improve the author publishing experience and accessibility of published manuscripts, we have remained dedicated to providing the opportunity to publish without the burden of publication costs to the authors. This would not be possible, however, without the team of volunteers that include student, staff, faculty, and administrators who donated their time and effort to bring this issue of the *Journal* to fruition. It is because of them that the *Journal* can continue its legacy of being a relied upon platform on which up-to-date, accurate and relevant scientific and medical research and ideas can be shared.

For both of us, being involved with WFJSM has been an integral part of our medical school years. From editing manuscripts to managing teams of editors, our work with the *Journal* has allowed us to grow as medical students, leaders, and scientists. It has been a privilege to work alongside our peers and colleagues and to serve our community in this role. Although our departure is bittersweet, we are confident that we are leaving the *Journal* in the most competent of hands to improve and expand this publication to new horizons.

We hope you find novel and compelling knowledge within the pages of this edition of *WFJSM* that inspires you to constantly strive for the best quality of patient care.

Sincerely,

Emilie Lothet and Benjamin Corona
Editors in Chief

Perspectives

Arab Muslim Refugee Women's Health Initiatives: A Pilot Study

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Abstract

There is limited information about the knowledge and beliefs of Arabic speaking refugee women in the United States with respect to women's health. Understanding beliefs and attitudes among a culturally diverse population such as Arab Muslim refugee women can aid in providing comprehensive care including preventative women's health issues. Our objectives are to assess the knowledge and beliefs with regard to reproductive health of the Arabic Muslim refugee women so providers can better understand how to provide gynecologic care and health education. Seventeen adult, Arabic-speaking Muslim refugee women living in North Carolina completed a survey in English or Arabic about their knowledge and beliefs relevant to women's health. The contraception method of choice by the majority was intrauterine device (IUD). Half the women reported that breastfeeding can prevent pregnancy. Only 29% reported that women should start taking folic acid before pregnancy. Fifty percent and 94% of women reported that pap smears and mammograms, respectively, screen for cervical and breast cancer. More than half the women reported they would not or were unsure whether they would have a child vaccinated for human papillomavirus (HPV) at the Center for Disease Control's recommended age. Understanding the knowledge gaps including beliefs and attitudes among a culturally diverse population and associated cultural factors is valuable to implementing strategies to educate Arabic-speaking refugee women on preventive health.

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Introduction

According to the Refugee Processing Center, in 2017, over 53,716 refugees were admitted to the United States (U.S.).[1] Among refugees admitted to the U.S., Arabic was the most common language. The World Health Organization identifies key issues for women's reproductive health including maternal health, cervical and breast cancer, and sexually transmitted infections.[2] Physical and emotional wellness, along with access to healthcare, are foundations for successful resettlement of refugees.[3] Many immigrant women are from societies where they have been historically disadvantaged by discrimination. Understanding their attitudes and beliefs about reproductive health can identify their needs and guide healthcare.[4]

Previous studies demonstrate unmet need for contraceptives among refugee women resettled in Canada, as well as significant differences in cervical screening and mammograms based on immigrant status and cultural background in both Canada and the United States.[5,6] Muslim refugees in the U.S. from 2015 to 2018 totaled 23,511

from Arabic speaking countries in the Middle East and North Africa.[1] Previous research on barriers to cervical and breast cancer screening among Muslims have identified lack of knowledge about preventive care, language barriers, and gender roles as challenges to overcome.[7,8] We seek to assess the knowledge and beliefs of Arabic Muslim refugee women with respect to reproductive health in order to better understand how to provide gynecologic care and health education.

Methods

We invited women to attend a health education session at an Islamic Center in North Carolina serving Arabic refugees to complete a survey in their preferred language (Arabic or English) prior to the session. Participation was restricted to Arab Muslim refugee women 18 to 70 years old. The survey questions addressed their knowledge and beliefs about women's health topics, including closed-ended questions that addressed contraceptive preference, pregnancy preparation, and the purpose of routine types of screenings and human papillomavirus vaccinations (HPV). Participants could mark that pap smears screen for cervical cancer, uterine cancer, ovarian cancer, or fertility. Participants could mark that mammograms screen for lung, uterine, cervical, or breast cancer. Demographic questions were also included. We obtained informed written consent in participants' preferred language. We calculated response frequencies for the full sample by language in which the survey was completed. All procedures were approved by the Wake Forest School of Medicine Institutional Review Board (IRB# 48327).

Results

Three groups of women attended the educational sessions. Seventeen women completed the survey; 13 in Arabic and 4 in English. Some participants did not provide a response to one or more questions. Percentages are based on the number of responses for the specific question. Twelve (70.6%) and 5 (29.4%) were born in Syria and Iraq, respectively. Twelve of 16 respondents (70.6%) had lived in the U.S. fewer than five years. Their mean age was 36 years (S.D. 11.1). Seven (41.2%) participants had completed middle school or less, and 4 (23.5%) and 6 (35.3%) had completed some or all of high school and college, respectively. All 4 of the women who completed the questionnaire in English had a college education. Thirteen (76.5%), 3 (17.6%), and 1 (5.9%) of all participants were married, single, and divorced, respectively. However, only 1 (25.0%) of the women who completed the questionnaire in English was married; the remaining 3 (75%) were single. Three (17.6%), 5 (29.4%), and 9 (52.9%) of all participants had 0, 1 to 3 children, and 4 or more children, respectively. Only 1 (25%) of the women who completed the questionnaire in English had at least one child.

The majority (56.3%) of participants reported an intrauterine device (IUD) was their preferred form of contraception (Table 1). Four (26.7%) indicated that folic acid should be initiated before becoming pregnant. Seven (46.7%) participants affirmed that breastfeeding prevents pregnancy. Although almost half (46.7%) of the participants reported that pap smears screen for cervical cancer, most (93.8%) indicated that mammograms screen for breast cancer. Only 7 (46.7%) reported they would have a child in the recommended age range vaccinated for the HPV. Survey completion language responses were not statistically analyzed due to small sample size. The data suggest that English-writing participants may be less likely than Arabic-writing participants to think that breastfeeding can prevent pregnancy and to vaccinate a child for HPV at the age range.

Discussion

Surveying Arab Muslim refugee women was accepted by the participants. Our survey results indicate that, in the domain of contraception, the majority preferred the use of an IUD compared to other forms of contraception that were surveyed including: contraceptive pills, coitus interruptus, or menstrual tracking. Many reported that breastfeeding could prevent pregnancy. This lends to information for providers to emphasize necessary counseling points. Using lactational amenorrhea as contraception, by women who are amenorrheic, and who are strictly breast feeding their infant for up to 6 months, can have a 98% rate of pregnancy protection. Breastfeeding only, without supplementing her infant for up to 6 months after delivery, have possible 3% and 6% cumulative probabilities of pregnancy by 6 and 12 months, respectively.[9]

Table 1. Muslim Women's Attitudes and Beliefs by Survey Completion Language

	Any Language		Arabic		English	
	N	%[2]	N	%[2]	N	%[2]
Contraception, Pregnancy, and Nursing						
Preferred Contraception[1]						
Intrauterine Device (IUD)	9	56.3	7	53.8	2	66.7
Oral	2	12.5	1	7.7	1	33.3
Coitus interruptus	2	12.5	2	15.4	0	0
Menstrual Tracking	2	12.5	2	15.4	0	0
Etonogestrel implant	1	6.3	1	7.7	0	0
Breastfeeding can prevent pregnancy[1]						
Yes	8	53.3	7	63.6	1	25.0
No or not sure	7	46.7	4	36.4	3	75.0
When folic acid should be initiated[1]						
Before pregnancy	4	26.7	3	27.3	1	25.0
During pregnancy	4	26.7	3	27.3	1	25.0
After delivery	0	0	0	0	0	0
Not sure	7	46.7	5	45.5	2	50.0
Cancer Screening and Prevention						
Pap smear screens for cervical cancer[1]						
Yes	7	46.7	5	45.5	2	50.0
No or not sure	8	53.3	6	54.5	2	50.0
Mammograms screen for breast cancer[1]						
Yes	15	93.8	11	91.7	4	100.0
No	1	6.3	1	8.3	0	0
Would vaccinate child for HPV if child in recommended age range[1]						
Yes	7	46.7	6	54.5	1	25.0
No	2	13.3	1	9.1	1	25.0
Not sure	6	40.0	4	36.4	2	50.0

[1]Responses missing for one or more participants

[2]Percentages are based on number of participant responses for each item; percentages may not equal 100 due to rounding errors

One of the most compelling results from our survey was that almost half of women were not sure if folic acid is needed before (or during) pregnancy. More focused education on preconception care is essential in this population. For cancer screening and prevention, the majority of women did not know that pap smears screen for cervical cancer. The lack of preventive health routinely practiced by Arab Muslim refugee women in their homeland may play a role in how women view this topic. Our survey indicated that the majority knew that mammograms are for breast cancer screening.

Among Syrian refugees, the IUD is the most commonly used method for contraception.[10] Many Arab Muslim refugee women pray at least 5 times per day, and bleeding can interrupt prayer. A report in the Middle East commented that contraception associated with spotting or unscheduled bleeding is not preferred.[11] Half the participants did not understand the role of folic acid and pregnancy, a standard recommendation in preconception and during pregnancy.[12] Consistent with our findings, Ceuleman et al. studied folic acid use during preconception among 17 Arabic-speaking pregnant women (76% Syrian born) with no one using folic acid except one participant who received assisted reproductive therapy.[13]

Most participants were aware that mammograms screen for breast cancer; few correctly understood that pap smears screen for cervical cancer. Research regarding cancer screening in immigrant Muslim women point to limited awareness of cervical cancer screening among participants.[7,14] Women may be reluctant to be seen for gynecologic symptoms, pap smear screen or IUD checks for fear of bleeding following a pelvic examination.[15] Study limitations include a small sample size and that some participants skipped one or more questions. Limited education is often correlated with low health literacy.[16] It is therefore unsurprising that some of our participants, of which 41.2% had a middle school education or less, have gaps in knowledge about women's health.

The data does not enable us to evaluate whether there were differences in attitudes between participants who completed their questionnaires in English or Arabic. Furthermore, those who completed questionnaires in English all had a college education, and only one was married or had at least one child. Any potential differences in attitudes between the groups may therefore reflect difference in education and marital/family status.

Family medicine providers should promote education about pre-pregnancy and pregnancy planning, including the need to take folic acid prenatally, among Arab Muslim refugee women. Providing medical advice about women's sexual health, cervical cancer screening and prevention is necessary. Providers should appreciate the culturally sensitive nature of discussing the HPV vaccine to a population that considers premarital sex unacceptable and may think it is unnecessary. Family physicians should draw upon the cultural knowledge of trusted leaders within the Muslim community to provide culturally and linguistically appropriate education opportunities and next steps for future research.

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Original Science

Launching into Healthcare: Critical Pedagogy to Increase Diversity and Social Awareness in Healthcare Professions Pipeline Programming

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Abstract

This paper outlines an intra-institutional partnership between the Wake Forest School of Medicine and the Wake Forest University College Launch for Leadership (CLL) program, designed to expose high school students to pathways to higher education and careers as healthcare providers. Most of the students enrolled in the CLL program identify as historically underrepresented minorities in higher education (e.g. non-white, low-income or attend a Title I school, undocumented, first-generation college student, etc.). The CLL students participated in an event entitled, LAUNCHing into Healthcare, which was rooted in Paulo Freire's (1970) problem-based pedagogical framework. The event was intended to expose students to careers in healthcare and a need for a more diverse healthcare workforce, while simulating the harsh realities of health disparities in the community. Students reviewed a case study of a fictional patient and then participated in a "simulated hospital" experience. The "simulated hospital" introduced students to different roles on healthcare teams and how these team members work together to deliver care. The students completed pre and post-assessment surveys, which reflected a growing interest in healthcare careers and a statistically significant increase in students' understanding of the need for a more diverse healthcare workforce. Several students in the CLL program later completed Youth Participatory Action Research (YPAR) projects focused on addressing healthcare disparities in the community.

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Introduction

Since the launch of Russia's Sputnik beginning in 1958, federal and state funding rose steadily on projects aimed at training students in the technological sciences. Science, technology, engineering and math (STEM) education has been touted as the "space race" of modern times. With the advent of social media and recent infrastructure cyberattacks on electric, gas, food and water supply systems, the number of qualified students entering STEM industries is an inherent part of any national security agenda.

However, the U.S. is losing ground in STEM education in relation to its peer industrialized nations. Elaine Seymore and Nancy Hewitt posit in their 1997 book, Talking about Leaving: Why Undergraduates Leave the Sciences, that there are complex and multifaceted barriers to students' persistence and success in STEM.[1] One of the barriers was insufficient preparation during high school. Rodriguez (2014) noted that U.S. pupils fail to reach adequate levels of proficiency in STEM disciplines which was attributed to reduced teacher quality and a lack of recent federal government funding.[2]

These academic deficits can be measured along racial, ethnic, and gender lines in relation to the background of students engaging in STEM activities.

The Committee on STEM Education National Science and Technology Council further noted that STEM education prioritization is considered "critical to building a just and inclusive society," as STEM participation and achievement are particularly low in women and minorities.[4]

Contemporary aims of STEM education are to increase exposure of STEM sciences in the formative years of primary and secondary education, termed pipeline enrichment. Ricketts & Gaul (2004) declare that the term pipeline is a metaphor for the process of career preparation, education, and training that starts at birth and continues through some form of "pipeline programing," (p. 382).[5] Drew (2011) in his seminal work Stem the Tide identified "critical junctures" of such programming when exposure enhances the likelihood of engaging in STEM studies.[6] One juncture occurs at the transition between high school and post-secondary schools when a lack of exposure threatens the STEM pipeline.

Recent educational texts echo these sentiments which highlight the need for STEM education for women. Researchers also found that minority students with increased STEM engagement as a result have a better understanding of the importance of STEM in their daily lives and are more interested in pursuing STEM coursework and careers.[8]

Scholars have recognized that lack of diversity in the healthcare workforce significantly impacts healthcare disparities.[24] Despite research and calls for action, lack of diversity in healthcare continues to be an issue impacting the health of our nation. "Effectively addressing these issues," Shaikh et. al (2017) writes, "requires a health care workforce and leaders representing the population they serve and deeply committed to reducing health disparities by promoting equity, diversity, and inclusion," (p. 440).[24] An essential tool for addressing health workforce diversity is pipeline programming.

Literature Review

The rising interest in STEM education is not a recent phenomenon. For generations, policymakers, legislators, and school officials have prioritized the importance of STEM funding, programming, and opportunities in U.S. schools. Although STEM education has advanced since the 1950s and 1960s, there remains glaring disparities in STEM outcomes across race and gender. For this reason, Drew (2011) believes that we must make mathematics and sciences available and attractive to virtually every student in middle and high school. This concern was addressed later by the National Research Council (2011), which saw fit to outline a set of goals aimed at increasing STEM accessibility, equity, and prolonged engagement for students across various backgrounds across race and gender.[7,8]

The first of those goals was to expand the number of students who ultimately pursue advanced degrees and careers in STEM fields and broaden the participation of women and minorities in those fields. If historically underrepresented students in STEM can see the relevance of STEM in their lived experiences, researchers agree that students may develop a more meaningful interest in STEM disciplines.

The next goal of the National Research Council (2011) was to expand the STEM-capable workforce and broaden the participation of women and minorities in that workforce. This goal directly addresses the disparities in STEM education and subsequent outcomes.[7] Keller's (2016) use of the phrase STEM-capable is a slight departure from scholars' consensus that students should be STEM literate.[8] Based on these degrees of STEM engagement, the expansion of a STEM-capable workforce is predicated on the implementation of pedagogies that make STEM concepts accessible to students across various backgrounds, and applicable to their daily lives.

The final aim of the National Research Council (2011) report was to increase STEM literacy for all students, including those who do not pursue STEM-related careers or additional study in the STEM disciplines.[7] Tawfik, Trueman, & Lorz (2014) contend that, even if [non-scientists] are not formally employed in the STEM discipline, they should still contribute responsibly to the ecology for future generations.[10] Tawfik, Trueman, & Lorz (2014) explored the effectiveness of an initiative to improve science pedagogy for non-science students in a general education biology-course at a Midwestern university. The authors determined that the most efficacious intervention for improving student engagement, participation, and outcomes in STEM was including problem-based learning (PBL) and service learning within the course curriculum.

Conceptual Framework

With the growing awareness of STEM-literacy programming, the learning outcomes of Tawfik, Trueman, & Lorz's (2014) study compel STEM educators to reimagine the way STEM curricula is taught. Their concept of PBL[10] was originally developed as an alternative to the didactic, lecture-based forms of learning[11] and has theoretical roots in critical pedagogy. According to Giroux (2011), this concept challenges "the way knowledge is mediated through specific classroom methodologies" (p. 36).[12] Critical pedagogy serves as an overarching conceptual framework for the implementation of PBL teaching strategies, designed to provide students with social and culturally relevant hands-on educational experiences.

This theoretical undertaking was based on the belief that educational outcomes are not merely about issues of work and economics, but as Giroux (2011) states, "[they are] also about questions of justice, social freedom, and the capacity for democratic agency, action, and change, as well as the related issues of power, exclusion, and citizenship," (p. 101).[12] Scholarship on PBL prescribes the following elements for effective learning. [10, 11, 13, 14]

- Student centered learning
- The problem serves as the catalyst for learning
- Self-directed learning
- Collaborative learning in groups
- Group discussions are focused around an ill-structured (complicated) problem to solve
- Instructor serves as the facilitator of student inquiry, rather than the main source of knowledge

It has been shown that scenario-based teaching and learning pedagogies engage students and enhance their understanding of scientific processes.[15,16] Teaching and learning frameworks within critical pedagogy, like PBL, have become more common within medical education. Cavanaugh, Vanstone, & Ritz (2019) contend that reinterpreting Freire's work has much to offer medical educators, learners, and prospective STEM-interested learners, writing:

"[...] medical education has long been charged with tacitly socializing students to stress patients' personal responsibility for poor health, without acknowledging the social contexts that shape their 'lifestyle choices.'" (p. 39)[18]

PBL innovations are direct antecedents from the work of other critical scholars who encourage educators to think about the ways in which their teaching encourage students' awareness of self, the world, and themselves in relation to others.[10, 12, 17, 19] The critical questions that ground PBL include things like: do we show the students that the subject matter is not only relevant, but important for our future? How do we support meaningful learning and retention? How do we go beyond surface level understanding of the material? How do we allow students to understand the connection between the laboratory context and real-world analysis? For this reason, "problem-based pedagogies," according to Cavanaugh, Vanstone, & Ritz (2019), "have been credited with training physicians who are better critical thinkers, more effective working in teams, and more attuned to public health concerns that arise in their clinical practice," (p. 39).[18] Scholars contend that PBL is uniquely capable of promoting the type of higher order learning required in STEM careers – especially healthcare.[10, 13]

Although students enrolled in the CLL program have career interests within and beyond STEM, it has been proven that PBL does increase student interest in the field. LaForce, Noble, & Blackwell (2017) demonstrated PBL can "improve students' engagement and enjoyment of STEM, especially for girls and underrepresented minorities," (p. 4).[20] In their longitudinal study, LaForce, Noble, & Blackwell (2017) concluded that, "PBL showed a direct effect on interest in a future STEM career; when controlling for STEM attitudes, PBL had a reduced but still significant effect on interest in a future STEM career" (p. 15).[20]

Therefore, in designing a STEM-focused learning opportunity for students enrolled in the CLL program, it was important to incorporate PBL in the form of a case study. This endeavor aligned with current trends in medical education that encourage the use of case study libraries to teach problem-solving processes[14] that allow students to apply course content in a meaningful way.[8] According to medical education researchers[21,22] students report that case studies are more engaging than teacher-centered instructional methods, and the inquiry-based activities make course content easier to remember. In utilizing a case study, CLL staff and medical school faculty can demonstrate the nexus between physiological, economic, social, and emotional wellbeing, and

how each influences the ways in which healthcare providers treat patients. Roth (1997) insists that students must not merely mimic experiences from the field, but undertake figuring, working with and refiguring a problem.[23] These case studies, according to Rodriguez (2014), must reflect the complexity of processes and operations that scientists and other practitioners in the field experience.[2] In doing so, "students in the [PBL] classroom," according to Cavanaugh, Vanstone, & Ritz (2019), "would challenge deterministic conceptions of health, coming to see their whole social reality as contingent – a site of activist intervention, in solidarity with the sickest in society," (p. 40).[18]

Given this strong body of evidence, the Wake Forest School of Medicine (SOM) created an innovative partnership with CLL, a multisite college preparatory program for diverse high school juniors, to explore medical careers through a PBL case. The term diverse in this context is used to describe those students who identify as historically underrepresented minorities in higher education, potential first-generation college students, immigrant students or DACA-recipients, low-income, receive free/reduced lunch, and/or attend a Title I high school. The two main sites for the CLL program are Winston-Salem, NC, and Charlotte, NC. Moreover, the use of PBL provides students an opportunity to not only develop a sense of STEM literacy[9] and capability[8], but also to gain exposure to cutting edge problem-based teaching innovations in medical education. This methodology is intended to help future healthcare professionals become better critical thinkers, work more effectively in teams, and be more attuned to public health concerns that arise in clinical practice.[18]

Methods and Materials

In this study, the CLL program partnered with the Wake Forest School of Medicine (SOM) to provide an immersive PBL experience to high school students. The Wake Forest SOM includes approximately 1,000 students in the Doctor of Medicine (MD), Physician Assistant (PA), Certified Registered Nurse Anesthetist (CRNA), and biomedical sciences graduate programs. In 2017, the Student Inclusion and Diversity Office at the SOM identified three strategic goals: (1) pipeline programming, (2) recruitment of students from diverse backgrounds; and (3) student retention.

Aims

CLL program staff members and medical school faculty identified the following overarching goals for a 5-hour, immersive STEM experience in a "simulated" hospital to increase: (1) students' knowledge of careers in STEM/healthcare; (2) interest of historically underrepresented minorities in STEM/healthcare careers; (3) students' awareness of the need for a diverse healthcare workforce; (4) students' awareness of the social determinants of health. These strategic goals laid the framework for the Wake Forest SOM to partner with the CLL program to increase diverse student enrollment through pipeline programming.

A key aspect of this partnership includes involvement of faculty from the SOM to ensure alignment with long-term healthcare workforce needs. These longitudinal aims to diversify the healthcare workforce are designed to encourage a sustained community investment and increase racial diversity in the medical school and the healthcare workforce. Recognizing their common goals, the SOM and CLL program created LAUNCHing into Healthcare, an immersive session exploring healthcare careers with an emphasis on critical pedagogy in identifying health inequities. Students interact with healthcare providers, including MDs, PAs, and social workers, ultimately learning how healthcare providers respond to patient needs in the framework of their community.

In addition, CLL recognizes the academic and social value of providing students with a meaningful community-based research opportunity as a means of preparing for higher education. Thus, CLL students are tasked with working in groups to complete a Youth Participatory Action Research (YPAR) project, exploring a social justice issue of their choice, which is usually something they have observed or experienced firsthand within their community. Together, CLL students gather data, examine existing research, and generate suggested solutions for addressing their particular issue. YPAR work is broken down systematically over the course of nine months, culminating in a research symposium at the end of students' junior year of high school. Although student's individual research interests may vary, CLL tracks the number of completed YPAR projects dedicated to health disparities, to determine how their scholarly and professional interests were informed by their experience at LAUNCHing into Healthcare.

Case Study and Interactive Rotations

Students were presented with a case study (Appendix A) a month prior to the LAUNCHing into Healthcare session. The case study focused on "Mr. Peters", a fictional patient from a rural underserved community whose job and family life were impacted by illness. The case study aimed to present Mr. Peters in a "simulated hospital" with symptoms related to a lower spine injury as well as colon cancer. Students were asked to address the patient's physiological needs and social determinants of health, including medical history, insurance status, mental health, and access to community resources. The case study presented a difficult patient scenario with social and emotional concerns, disability insurance limitations, and potential legal challenges. In order to mirror the interprofessional nature of healthcare, the case study was set in a "simulated hospital", where students assumed the roles of social workers, physician assistants, medical doctors, and nurse anesthetists as part of the patient's care team. Following their review of the case study, students were asked to craft a critical journal response to the patient scenario and to answer two specific questions:

- What can be done on a social or community level to address lack/loss of health resources?
- What factors contributed to lack of screening for colon cancer and did his disability play a role?

The LAUNCHing into Healthcare session utilized both didactic and interactive presentations to engage attendees. The session included a keynote address followed by a review of the case. Students were divided into four groups transitioning between four, thirty-five minute rotations with the MD, PA, CRNA, and Biomedical Sciences Graduate School programs. Each rotation included students and staff from the four educational programs to ensure student participants gained an accurate image of the role each health professional plays while caring for the patient. Rotations included patient simulation mannequins and standardized patient actors who performed certain aspects of the case which allowed students to engage in hands-on learning. In each rotation, students and healthcare providers facilitated several guided activities (see Table 1).

In addition to the interprofessional rotations, CLL students engaged with health professions students on a myriad of topics, including high school class selection, college majors, interesting clinical experiences, and plans to pursue social justice in their future roles as providers (Appendix B). The LAUNCHing into Healthcare session concluded with a discussion led by a clinical social worker who focused on social determinants of health in the community.

Data Collection

To capture the student perspective, LAUNCHing into Healthcare employed a mixed-methods descriptive cohort pre- and post-survey design, allowing collection and analysis of quantitative and qualitative data. Literature argues for the use of varied research strategies in collecting, analyzing, and integrating information sources in a single study4. Students were asked to rate their level of understanding of various healthcare professions, including PA, MD, and CRNA, on the pre- and post-surveys (0 = Did Not Attend, 1 = Very Low, 5 = Very High).

Additionally, they rated the need for underrepresented minorities in healthcare fields to address health disparities. Statistical analyses included descriptive statistics of the sample (percentages, means, and standard deviations), descriptive differences in means/proportions of the sample (paired t-tests), and any associations noted (correlations, regression analyses). IRB approval was determined to be unnecessary.

Results

Quantitative Analysis

Cohort 1 Participants

Of the 94 CLL participants in the 2018 cohort (Table 2), 62 (66%) attended the LAUNCHing into Healthcare session. Most of the 2018 CLL participants self-identified as black or African American (69%), followed by Hispanic/Latino (19%), Asian (5%), white (3%), or biracial/multiracial (1%) with two participants declining to report. Most of the participants arose from Charlotte area high schools (56%) versus Winston-Salem (44%). Regarding gender, 53% self-identified as female, 46% as male, and one was not reported. The participants had an average age of almost 17 years (16.8 +/- 0.6), with an age range of 14 to 18 years. Forty-three percent of the participants reported having received free or reduced lunch at school.

Table 1. Groups and activities

Rotation	Activity
PA Room	Students delivered post-operative care, wound care, colon cancer diagnosis, patient colostomy bag care, and surgery.
CRNA Room	Students conducted a pre-anesthesia assessment of a patient actor using an anesthesia machine. The assessment included the use of a general anesthesia drug cart and hands-on task training for intubation skills.
MD Room	Students performed ultrasounds of the chest area, and they were trained on how to find and label abnormalities in lungs and in the abdomen based on the patient's history.
Graduate Studies Room	Students explored the intricacies of a research study and how to obtain informed consent from a patient to participate in a clinical trial. Students also witnessed the set-up of a clinical trial and explored the interdisciplinary nature of research between science and medicine.

Cohort 2 Participants

Of the 96 CLL participants in the 2019 cohort (Table 2), 55 (57%) attended the LAUNCHing into Healthcare session. Most of the 2019 CLL participants self-identified as black or African American (64%), followed by Hispanic/Latino (15%), Asian (10%), white (7%), or biracial/multiracial (3%) with one participant declining to report. The CLL participants were evenly split between Charlotte (49%) and Winston-Salem (51%) area high schools. Regarding gender, 64% self-identified as female, and 36% as male. The participants had an average age of almost 17 years (16.6 ± 0.7 years) with an age range of 14 to 18 years. Forty-eight percent of the participants reported having received free or reduced lunch at school.

Survey Results

Of the 190 total CLL participants, 108 participants [53 (2018); 55 (2019)] who attended the LAUNCHing into Healthcare session completed both the pre and post surveys and were included in the analyses. On average, the participants in 2018 prior to the event reported low levels of understanding related to healthcare roles and responsibilities (range of 2.27 to 2.87; Table 3). However, exposure to the conference improved this understanding significantly for every medical specialty with reported "High" levels for all categories (range of 3.9-4.09; Table 3). It should be noted that this survey item was not re-administered to the 2019 cohort.

In relation to the how the participants perceived the need for underrepresented minorities in the healthcare field to address health disparities, there was a statistically significant increase in this perceived need between pre and post surveys (Figure 1).

Qualitative data analysis includes student feedback captured in a post-survey along with reflective papers. Many (58.2% in 2018; 42.6% in 2019) of the post-surveys revealed that the respondent's career goals had changed. The comments indicated that most would explore additional health-related professions including those highlighted in the LAUNCHing into Healthcare session (PA, CRNA, MD, and graduate biomedical sciences). When offered a list of health-related

Table 2. Demographics of College LAUNCH participants 2017-2019

	2017-2018 Cohort		2018-2019 Cohort	
Variable	Frequency/ Mean	%/SD (n= 94)	Frequency/ Mean	%/SD (n= 96)
Age (yrs)	16.8	SD 0.6	16.6	SD 0.7
Gender				
Female	50	53%	63	64%
Male	43	46%	35	36%
Not reported	1	1%	0	0%
Race/Ethnicity				
Black or African American	65	69%	61	64%
Hispanic/Latino	18	19%	14	15%
Asian	5	6 %	10	10%
White	3	3%	7	7%
Biracial/Multiracial	1	1%	3	3%
Not reported	2	2%	1	1%
Location				
Large urban students	53	56.4%	47	49%
Moderate-sized city students	41	43.6%	49	51%
Attended Pre-Health session				
Yes	62	66%	54	56%
No	32	34%	42	44%
Barriers to Attending			*Survey item removed 2019*	
Not reported	21	23%		
School-related function	8	9%		
Family commitment	1	1%		
Employment	1	1%		

Table 3. Cohort 1 survey responses: What is your level of understanding related to the following healthcare roles?

	Very Low %	Low %	Moderate %	High %	Very High %	Mean	Mean change	P value
MD								
Pre	12.7	21.8	36.4	21.8	7.3	2.87	1.13	<0.01
Post	0	1.9	22.2	40.7	33.3	4.0		
PA								
Pre	14.5	27.3	41.8	12.7	3.6	2.63	1.46	<0.01
Post	0	0	18.2	45.5	34.5	4.09		
CRNA								
Pre	29.6	31.5	27.8	5.6	5.6	2.27	1.64	<0.01
Post	1.9	5.6	16.7	42.6	31.5	3.9		
Various Specialties								
Pre	13.2	26.4	39.6	11.3	9.4	2.77	1.43	<0.01
Post	0	0	25.5	38.2	34.5	4.02		

Paired samples T-tests, Likert scale: Very Low = 1; Low = 2; Moderate = 3; High = 4; Very High = 5

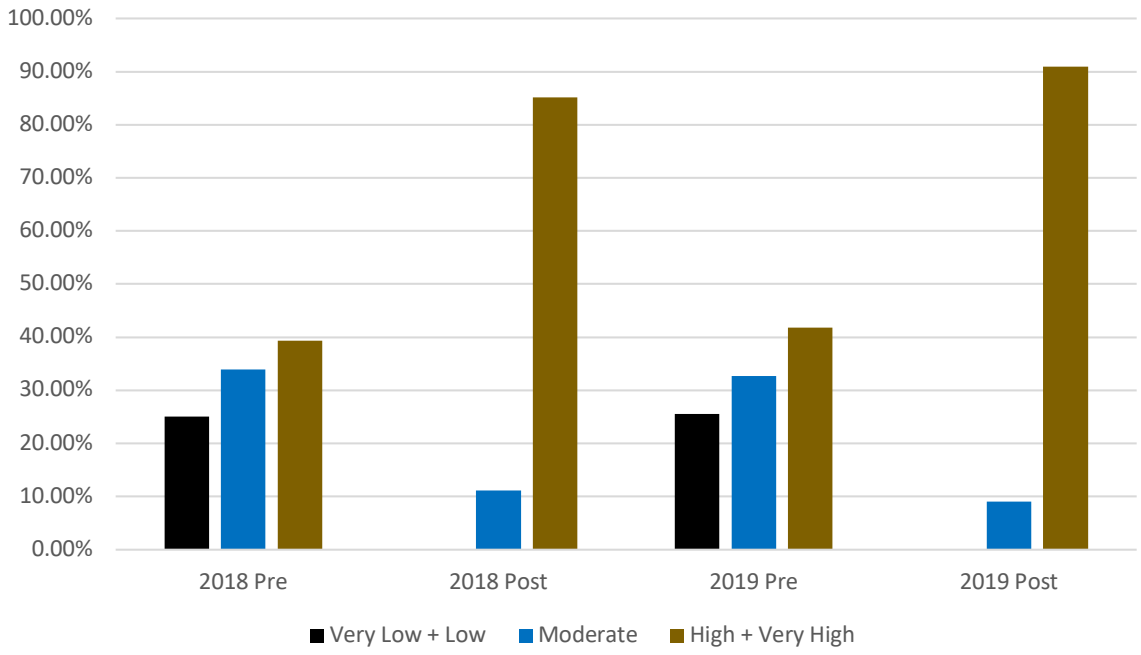

Figure 1. Percent of CLL participant pre- and post-survey responses rating the need for diverse professionals in the healthcare field to address health disparities.

Table 4. Interest in health-related professions following College LAUNCH

Career Selected	2017-2018 Cohort	2018-2019 Cohort
Other health -related	21	11
Physician	11	23
Physical Therapy	13	6
Registered Nurse/CRNA	11	13
Mental Health	9	10
Physician Assistant	7	9
Non-health related	7	12
Public Health	5	7
Dentist	4	3
Healthcare Administrator	4	1

professions, the attendees had a variety of career interests and were prompted to select as many as they were interested in (Table 4). Attendees could select multiple options and an aggregate of these selections by cohort are presented. In 2018, "Other health-related" was the most frequently chosen category and written-in options included Pediatrician (n=3), Athletic Trainer (n=2), Neonatal Specialist (n=2), and Surgeon (n=2) as well as others. In 2019, the "Physician" category was the most selected (n=23), followed by "Registered Nurse/CRNA" (n=13), or "Non-health-related" careers (n=12).

Youth Participatory Action Research (YPAR) Projects

Cohort 1

In 2018, a total of 78 YPAR projects were completed by the 94 participants. This resulted in an 86.7% completion rate. The YPAR projects varied in scope and topic. Examples included "Misrepresentation of Refugees," "Marginalization of Black Women," and "Equity versus Equality." When categorized by topic, social justice (33%) and education reform (22%) comprised most topics followed by race and racism (20%), health disparities (15%), and immigration and human rights (10%).

Cohort 2

In 2019, there was a decline in YPAR completion rates resulting in a total of 66 projects from the 96 participants (69% completion rate). Examples of projects included "Islamophobia," "Inequitable Distribution of Scholarship Funding," and "Minority Women and Maternal Mortality." When categorized by topic, social justice (42%) and health disparities (37%) comprised most topics followed by education reform (14%), race and racism (14%), and immigration and human rights (6%). There was an increase in the number of YPAR projects dedicated to health disparities between cohorts 1 and 2. The overall decline in completed projects however, could be attributed several factors, including but not limited to: inaccessibility of transportation, inconsistent participation, student attrition in lieu of mounting Advanced Placement coursework, standardized testing, and extracurricular activities.

Impact

The feedback regarding the impact of the CLL program was overwhelmingly positive. One participant remarked, "It has changed my views on the issues present in my community and what I can do to impact my community. I was already a leader in my community, but with a deeper knowledge of social justice, I can be an even better leader." A different participant wrote "Fun - learned a lot, learned how to be a leader, talk to people, and serve the community."

When asked to identify action steps following the conclusion of the CLL program, the participants were able to articulate their plans for undergraduate education as well as being more aware of social justice issues that can hinder their progress. Some of the written comments are presented in Figure 2.

The CLL participants also indicated future places of study. These included, in no particular order, various North Carolina colleges as well as others: Wake Forest University and School of Medicine, University of North Carolina at Chapel Hill, North Carolina A & T, Winston-Salem State

University, Appalachian State University, Duke University, Johns Hopkins, University of California in Los Angeles, University of North Carolina at Charlotte, Elon University, Johnson & Wales University, University of North Carolina at Asheville, and the University of South Carolina. This illustrates a continued interest in pursuing higher education, and the preliminary steps students have taken to achieve that goal at the conclusion of the CLL program.

Discussion

The unique intra-institutional partnership between the Wake Forest SOM and the CLL program provides a social justice framework for high school students to explore healthcare careers and identify healthcare inequities. Although LAUNCHing into Healthcare was considered successful, there were a few barriers influencing implementation of the program. Some students were either unable to attend or left early because of conflicting school-related or personal commitments (e.g. prom, sports, part-time jobs, etc.). Perhaps our greatest impediment was students' level of engagement during the sessions that relied solely on discussion-based teaching methods. Conversely, rotations featuring patient simulation mannequins and standardized patient actors garnered higher praise from survey respondents. These limitations provide faculty and staff possible pathways to improving future iterations of the LAUNCHing into Healthcare session.

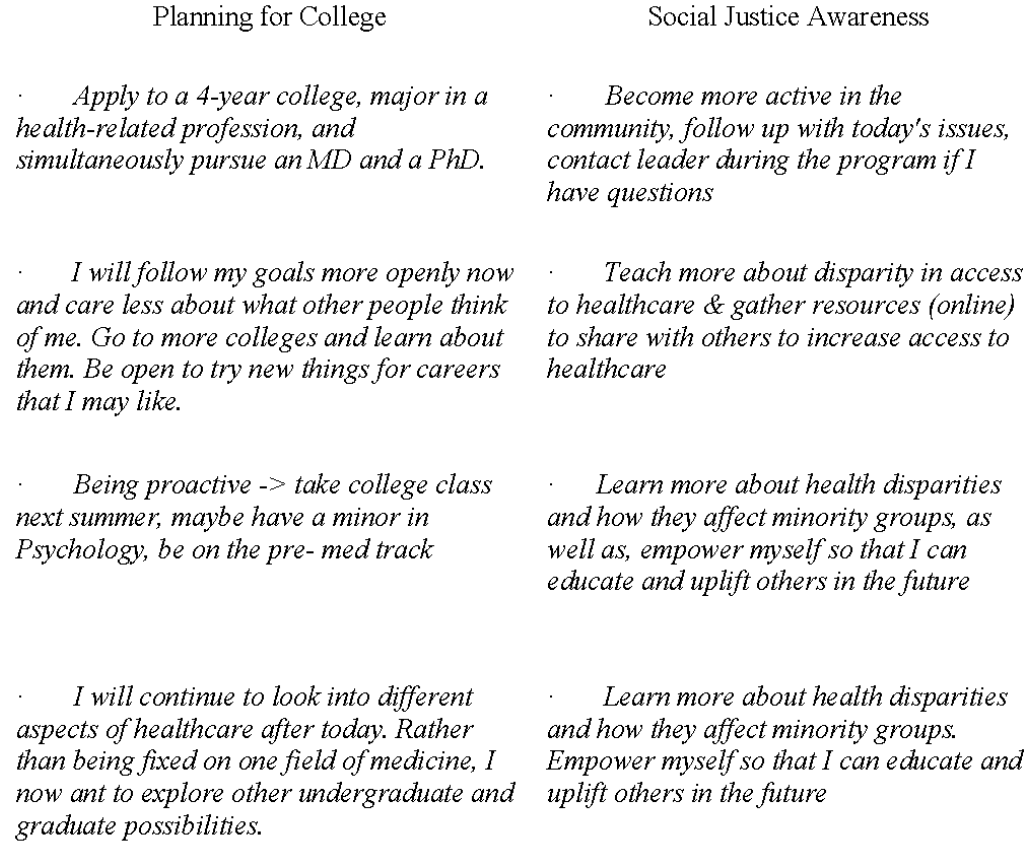

Figure 2. Written Comments from Survey.

It is the goal of the CLL program to prepare students for college and to become lifelong learners, critical thinkers, and civically engaged citizens, poised to make an impact on the world through their passion for social justice. PBL provided an innovative framework for high school students to explore healthcare careers and identify healthcare inequities in their community. Through completion of YPAR projects, students demonstrated interest and increased awareness of social justice issues across various themes. Authors, Scott, Pyne, & Means (2015) unpacked the relationship between YPAR and college-access stating, "YPAR created a space in which students could articulate connections between their personal realities and those of the world beyond their immediate experience in more subtle and critical ways," (p. 154).[25] By incorporating social justice through career exploration, students were able to engage with leaders of those professions in a more relatable fashion. Although about a quarter of the participants across Cohorts 1 and 2 completed YPAR projects related to health disparities (15% in Cohort 1 and 37% in Cohort 2; n=190), post-survey data revealed that students had an increased understanding of the need for diverse professionals in the healthcare field to address health disparities. These finding indicate that PBL instructional strategies, in conjunction with social justice-oriented research opportunities, are effective when facilitating pipeline programming for prospective students in the healthcare professions.

Other academic medical institutions can replicate this program and pedagogical approach within existing or planned pipeline programs. Collaborating with existing college-access organizations in this way creates opportunities for sustained engagement between academic medical institutions and local youth. These institutions may also consider connecting with the Minority Association of Pre-Medical Students (MAPS) and other pre-health student organizations at surrounding undergraduate institutions as a means of enhancing communication and interaction with underrepresented student populations interested in healthcare. Additionally, intentional partnerships with Historically Black Colleges and Universities (HBCUs) will assist with diversifying the pipeline of college students entering the healthcare professions.

There is a sense of urgency to increase enrollment of underrepresented minorities in medicine. Interacting with these students at a formative time in their lives helps to spark an early interest in healthcare professions and provides a platform for sustained engagement. This outcome is demonstrated by students' feedback indicating aspirations to "become more active in the community, follow up with today's issues" and look "into [their] future, planning, and budgeting for life ahead."

Tracking pipeline students and connecting with student organizations allows maintenance of relationships with student participants, which helps them connect with resources around the state and nation to ensure their success and/or increase the likelihood they will become a healthcare professional. The COVID-19 pandemic has exposed the systemic nature of health and economic disparities among our nation's most vulnerable populations. To that end, it is important that medical institutions continue to provide educational opportunities for students from these populations to not only understand the landscape of healthcare inequalities but also to introduce diverse students to the healthcare workforce.

Disclosures

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Appendix A: Case Study Provided to Students

2019 College Launch Interdisciplinary Case study
School of Medicine

Read the following case study. As you read, think critically about the social/emotional, economic, and physiological problems this patient encounters on their road to recovery. Highlight any of the patient's social/emotional concerns in yellow; highlight their economic concerns in green; highlight their physiological (or health-related) concerns in red. Respond to the short critical journal prompt at the end.

Eric Peters is a 49-year old widowed father of 10-year old twin daughters and Head Groundskeeper at a large high school in rural Swain County, North Carolina. Mr. Peters has worked at the high school for 7 years, he moved to the area to be closer to his family. He describes himself as a handy man, outdoorsman and a family man. When asked about his family and background, most of the time he simply says, "We have all different colors in my family, and that's one of the things that makes it great".

Mr. Peters is recovering from a recent injury to his lower spine sustained by a fall while putting up decorations for a breast cancer awareness event. This injury has resulted in pain that will not go away as well as left leg and left foot weakness and numbness. At the time of the accident, he was taken the local hospital and then transferred to a larger hospital, where he remained for one week. A **Social Worker** was asked to address aspects of his care after leaving the hospital (physical therapy, occupational therapy, financial concerns) and potential childcare challenges. He was discharged to the care of his primary care **Physician Assistant (PA).**

As a result of his back injury, Mr. Peters is no longer able to perform the functions of his job and his employer must let him go. Mr. Peters decides that once his disability payment benefits are exhausted, he will pay for his own insurance if he is able while he begins the process of applying for disability. Unfortunately, he has not been able to attend church regularly because of his pain and disability and feels isolated; he wonders if the church has forgotten him.

Appendix A *continued*

Medical History:
Mr. Peters considers himself to be generally healthy, aside from the occasional cold/flu or other virus and the medication he takes for his high blood pressure (hypertension). Prior to the injury to his spine, Mr. Peters had not been hospitalized. He has received an annual physical every year from his **PA**. Due to the fact he has gained some weight in recent years and given his hypertension, his **PA** has recommended Mr. Peters lose 10-15 pounds to achieve a healthier weight and make sure to eat a healthy diet.

Physical Examination:
During a physical exam approximately 2 weeks after his injury, Mr. Peters' **PA** notes he has pain in the low back and some tenderness over lower spine. He also has pain shooting down his left leg and some numbness over the leg and his foot. Aside from these significant factors related to the injury, Mr. Peters appears to have no other health issues and has no other complaints.

Admission to the hospital, 1 year later:
Mr. Peters is admitted to VIRTUAL HOSPITAL. Mr. Peters arrives at the emergency department complaining of stomach pain for the past three days. He reports a 15-pound weight loss within the last 2-3 months and a new complaint of bloody stools. To determine the source of the blood in the stool, a colonoscopy was done, and he was found to have colon cancer.
After his colon cancer diagnosis, his in-laws talk with Mr. Peters about his ability to care for his children (now 11 years old). Following the conversation, the in-laws decide they want to seek custody of the children.

Critical Journal Response
After reviewing the case of Mr. Peters, write a response to ONE of the following prompts. There are no right or wrong answers.

1. In your opinion, what can be done on a social or community level to address the lack of access to/loss of health resources?
2. In your opinion, what factors contributed to Mr. Peters *not* being screened for colon cancer sooner?

Appendix B: Questions for Panel Discussion

Questions for Panelists: College LAUNCH for Leadership

Panelists' responses should not exceed 2 minutes.

1. Share your name, hometown, year in program, and something you wish you would've known about your program when you were in high school.
2. What was your undergraduate major, and how did that major prepare you for your current program? (Note: the aim of this question is to get students thinking outside of the box; debunking myths about undergraduate majors/course requirements)
    a. What course(s) in high school most prepared you for your current academic program?
3. What has your experience in your academic program taught you about your specific role on healthcare team/healthcare provider?
4. What do you do to find balance in your daily lives?
5. Describe your craziest clinical experience as a student.
6. How do you plan to pursue social justice – especially health equity – in your future roles as healthcare providers?

Original Science

The Influence of Recipient Age on Outcomes Following Simultaneous Pancreas-Kidney Transplantation: A High Volume Single Center Experiencs

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Abstract

The influence of recipient age on outcomes following simultaneous pancreas-kidney transplantation (SPKT) in the modern era is uncertain. We retrospectively studied 255 patients undergoing SPKT at our center from 11/01 to 8/20. Recipients were stratified according to age group: age <30 years (n=16); age 30-39 years (n=91); age 40-49 years (n=86), and age ≥ 50 years (n=62 [24.3%], including 9 patients ≥60 years of age). Three-month and one-year outcomes were comparable. The eight-year patient survival rate was lowest in the oldest age group (47.6% versus 78% in the 3 younger groups combined, p<0.001). However, eight-year kidney and pancreas graft survival rates were comparable in the youngest and oldest age groups combined (36.5% and 32.7%, respectively), but inferior to those in the middle 2 groups combined (62% and 50%, respectively, both p<0.05). Death-censored kidney and pancreas graft survival rates increased from youngest to oldest recipient age category because of a higher incidence of death with functioning grafts (22.6% in oldest age group compared to 8.3% in the 3 younger groups combined, p=0.005). Recipient age does not appear to significantly influence early outcomes following SPKT. Late outcomes are similar in younger and older recipients, but inferior to the middle 2 age groups.Intro

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Introduction

Vascularized pancreas transplantation was originally developed as a therapeutic modality to re-establish endogenous insulin secretion responsive to normal feedback control and represents a method of complete β-cell replacement that frees the patient with diabetes mellitus (DM) from the need to monitor serum glucose and from dependence on exogenous insulin administration.[1] In return for these potential benefits, however, pancreas transplant recipients under major surgery and require long-term immunosuppression. Consequently, despite the high likelihood of rendering patients ex-diabetic, pancreas transplantation is considered a treatment for DM rather than a cure. For these reasons, pancreas transplantation is frequently reserved for those patients with insulin-requiring DM that will already be committed to chronic immunosuppression for another reason, most commonly a kidney transplant for end stage diabetic nephropathy.[2-4] In the previous century, pancreas transplantation was performed predominantly in young to middle-aged adults with type 1 diabetes mellitus

(T1DM), usually as a simultaneous pancreas-kidney transplant (SPKT) in patients with end stage renal disease (ESRD).[5] However, steadily improving outcomes in the new millennium have occurred secondary to better donor and recipient selection and management, advances in organ preservation and immunosuppression, refinements in surgical techniques, and improved medical care of these patients in parallel with better understanding of the pathophysiology of DM.[2-4] Consequently, recipient selection for SPKT has expanded to include patients with a type 2 diabetes mellitus (T2DM) phenotype (that disproportionately affects minorities, the elderly, and obese patients).[2,6,7] Concurrently, improvements in diabetes management, education and awareness, better insulin analogues and glucose sensors, sophisticated and more patient-friendly insulin pumps, and the promise of the artificial or bionic pancreas have potentially reduced the number of younger patients with diabetes developing ESRD. As a result, an aging of the DM population being referred for transplant evaluation has occurred.[8]

There has been a growing body of literature evaluating outcomes of SPKT in elderly patients.[9-19] Whereas "elderly" following kidney transplantation alone usually refers to patients in the age range of 65-70 years and older[20-22], the definition of "elderly" following SPKT is much younger (age range of 45-50 years and older). Although many transplant centers apply age limits of 45-50 years or less for SPKT consideration, there is currently no consensus on a strict chronological age cut-off for candidacy. Recipient age is an important variable that influences patient and graft survival outcomes, with some data suggesting that SPKT is most beneficial for recipients <40-45 years of age compared to those >45-50 years of age.[23-26]

Most patients <45 years of age are considered to be acceptable candidates for SPKT until proven otherwise, provided that they are not obese and do not have significant coronary or peripheral vascular disease. Patients with DM older than 55 years of age are not considered candidates for SPKT at many transplant centers and this barrier to access is further compounded by the fact that many kidney transplant centers do not perform pancreas transplants.[2-4,9-19] The majority of literature has focused on assessing transplant outcomes in elderly compared to younger SPKT recipients. The purpose of this study was to retrospectively analyze our single center experience in 255 SPKT recipients in the modern era and determine the effects, if any, that age has on short and long-term outcomes.

Materials and Methods

Study Design

We retrospectively reviewed 255 SPKTs performed at Wake Forest Baptist Health between 11/14/01 – 8/12/20 (minimum 4 month follow-up) and identified 62 recipients age 50 years and older (24.3%) including 9 patients age 60 years and older. The oldest SPKT recipient in this study (age 64 years) was actually #13 in our overall experience, dating back to 10/8/02. The youngest recipient (age 16 years) was a highly sensitized teenager with a previously failed living donor kidney transplant. All patients received similar immunosuppression and perioperative management strategies.[27-31]

Recipient Selection

General indications for SPKT were insulin-requiring diabetes with complications and the predicted ability to tolerate the operative procedure, manage the requisite immunosuppression, and deal with the need for close follow-up post-SPKT irrespective of chronologic age or C-peptide production.[27-31] Specific indications for SPKT included stage 4/5 chronic kidney disease or ESRD and the absence of any contraindications. An extensive cardiovascular and peripheral vascular evaluation is an important part of the pretransplant evaluation in patients with DM.[26,32-35] Contraindications at our center included age >65 years; insufficient cardiovascular reserve; current substance abuse; active infection or recent malignancy; major ongoing psychiatric illness, recent noncompliance or lack of adequate social support; significant obesity (body mass index [BMI] >32 kg/m2); severe vascular disease; or inability to either understand or commit to the more intense follow-up associated with SPKT compared to kidney transplantation alone.[27-31] Selection criteria for SPKT in T2DM included patients <65 years of age, insulin-requiring for a minimum of 3 years with a total daily insulin requirement <1 u/kg/day, a fasting C-peptide level <12 ng/ml, absence of severe vascular disease or tobacco abuse, adequate cardiac function, and presence of "complicated" or hyperlabile diabetes.[27-31] For purposes of this study, T2DM was defined as having a pretransplant C-peptide level ≥2.0 ng/ml (n=50).

Technical Aspects

All patients were blood type ABO compatible and T- and B-cell negative by flow cytometry crossmatch. Nearly all SPKTs were initially approached as intent-to-treat with portal-enteric (P-E drainage, n=216) using an anterior approach to the superior mesenteric vein (pancreas positioned above the small bowel mesentery) and enteric exocrine drainage to the proximal ileum in the recipient (side-to-side duodeno-enterostomy without a diverting Roux limb).[36] Arterial inflow was based on the recipient's right common iliac artery after the pancreas dual artery blood supply was reconstructed with a donor common iliac bifurcation "Y" graft.[37] In patients with unsuitable anatomy for P-E drainage, systemic-enteric (S-E) drainage (n=39) was performed with the pancreas positioned below the mesentery with vascular anastomoses to the right common iliac artery and vein.[38] Of the first 121 SPKTs (from 11/01 – 8/10), all but two were performed by transplanting the kidney to the left iliac vessels and the pancreas to the right common or external iliac artery through a midline intraperitoneal approach. However, since 8/10, most SPKTs were performed with ipsilateral placement of the kidney and pancreas to the right iliac vessels in order to reduce operating time and to preserve the left iliac vessels for future transplantation.

Anti-coagulation

In selected SPKT recipients, 2000-3000 units of intravenous heparin (30-50 u/kg) was administered as a single dose during surgery prior to implantation of the pancreas and a heparin infusion was continued post-transplant (continuous infusion of 300 units/hour for 24 hours, then 400 units/hour for 24 hours, and then 500 units/hour until post-operative day 5) in the absence of bleeding.[39] Indications for intravenous heparin included preemptive SPKT, history of thrombophilia or clotting disorder in the recipient, small or diseased donor or recipient vessels, prolonged pancreas cold ischemia (>16 hours), extended donor criteria, or history of prior pancreas graft thrombosis. Oral aspirin (81 mg/day) was administered to all patients.

Immunosuppression and Post-Transplant Management

Patients received depleting antibody induction with either single dose alemtuzumab or multi-dose alternate day rabbit anti-thymocyte globulin (RATG, 1.5 mg/kg/dose, total 3-5 doses) in combination with tacrolimus, mycophenolate mofetil or mycophenolic acid, and tapered steroids or early steroid withdrawal.[31-35] RATG was the primary induction agent from 2001-2004. From 2005 through 2008, 46 SPKT patients were prospectively randomized to receive either alemtuzumab or RATG induction therapy.[28,29] Since 2009, alemtuzumab has been the primary induction agent. The majority of SPKT recipients (n=191) received single dose alemtuzumab induction (30 mg intravenous administered intra-operatively) in combination with tacrolimus (target 12 hour trough levels 8-10 ng/ml), full dose mycophenolate (720 mg bid), and either early steroid elimination or rapid prednisone taper (dose reduction to 5 mg/day by 1 month following SPKT).[28,29] The remaining 64 patients received RATG induction with triple maintenance immunosuppression ± early steroid withdrawal. All patients received anti-infective prophylaxis with peri-operative cefazolin for surgical site prophylaxis, fluconazole for one month, valganciclovir for 3-6 months (6 months in patients for primary cytomegalovirus [CMV] exposure, 3 months for all other patients), and trimethoprim-sulfamethoxazole long-term.[27-31] Most patients were discharged from the hospital after placement of a tunneled central venous catheter and received intravenous fluid and electrolyte supplementation as an outpatient for a variable period. Treatment of hypertension, hyperlipidemia, anemia, and other medical conditions was initiated as indicated, aiming to maintain the blood pressure <140/90 mm Hg, fasting serum cholesterol <200 mg/dl, and hemoglobin >7-8 gm/dl.

Statistical Analysis

Data were compiled from both prospective and retrospective databases, with confirmation by medical record review in accordance with local Institutional Review Board approval. We examined relationships between recipient characteristics (age, gender, race, weight, BMI, dialysis history, waiting time, surgical technique, induction therapy) and donor characteristics (kidney and pancreas cold ischemia time, immunocompatibility, CMV status, Kidney Donor Profile Index) with outcomes classified into early (up to 1 year) and late (>1 year) time periods. Early outcomes included hospital length of stay, re-laparotomy in the first 3 months, and one year kidney and pancreas graft survival rates as well as patient survival. Late outcomes included long term kidney and pancreas graft survival rates and patient survival. For

categorical variables, the chi-square test and Fisher's exact test were utilized when appropriate. Categorical data were summarized as proportions and percentages and continuous data were summarized as means and standard deviations. Renal allograft loss was defined as death with a functioning graft (DWFG), transplant nephrectomy, return to dialysis, kidney retransplantation, or a return to the pretransplant serum creatinine level in a preemptively transplanted patient. Pancreas graft loss was defined as DWFG, allograft pancreatectomy, pancreas retransplantation, or resumption of daily exogenous insulin therapy for >1 month. Actuarial survival rates were determined by Kaplan-Meier analysis. A two-tailed p-value of <0.05 was considered significant.

Results

From 11/14/01 – 8/12/20, we performed 255 SPKTs at our center with a minimum 4 month follow-up through December 2020. A total of 4 recipient age groups were stratified: age <30 years (n=16); age 30-39 years (n=91); age 40-49 years (n=86), and age ≥50 years (n=62 [24.3%], including 9 patients ≥60 years of age). Mean follow-up ranged from 86 to 105 months in the 4 groups (187 patients [73.3%] had at least 5-year follow-up and 160 patients [62.7%] had at least 8-year follow-up). The 4 groups were similar for many donor, preservation, and immunologic characteristics (Table 1). However, the youngest age group had proportionately fewer male donors (44% vs 68%, p=0.056, Table 1) and more African American recipients (56% vs. 24%, p=0.02, Table 2) compared to the 3 older age groups combined. Other recipient characteristics did vary by age group (Table 2). The oldest age group had fewer male recipients (42% vs 61%, p=0.012) compared to the 3 younger age groups combined. Increasing recipient weight (p=0.03) and BMI (p=0.007) were noted with each older age group. The two older age groups combined also had proportionately slightly more patients with an elevated (≥2.0 ng/ml) pretransplant C-peptide level (23%) compared to the 2 younger groups combined (15%, p=0.15). Duration of pretransplant DM increased with each older recipient category (p<0.001). Differences in these latter variables suggested that a T2DM phenotype was more prevalent in the older age groups.

Table 1. Donor, Preservation, and Immunologic Characteristics

	Age <30 years (n=16)	Age 30-39 years (n=91)	Age 40-49 years (n=86)	Age ≥50 years (n=62)	p-value
Donor age (years)	27 ± 8.8	23 ± 8.8	26.5 ± 10.3	28.5 ± 11.2	NS
Donor gender: Male	7 (43.75%)	64 (70.3%)	56 (65.1%)	43 (69.4%)	0.056
Donor Race: Caucasian	12 (75%)	61 (67%)	57 (66.3%)	46 (74.2%)	NS
African American	2 (12.5%)	20 (22%)	21 (24.4%)	11 (17.7%)	
Other	2 (12.5%)	10 (11%)	8 (9.3%)	5 (8.1%)	
Donor weight (kg)	68.7 ± 16.5	71.9 ± 18.5	72.1 ± 15.6	68.6 ± 14.4	NS
Donor BMI (kg/m^2)	23.4 ± 4.0	24.8 ± 6.3	23.8 ± 4.0	23.3 ± 3.6	NS
Kidney cold ischemia (hours)	15.6 ± 4.4	16.5 ± 4.3	16.0 ± 4.0	15.1 ± 4.2	NS
Pancreas cold ischemia (hours)	14.9 ± 4.3	15.4 ± 4.4	15.0 ± 4.1	14.8 ± 3.8	NS
5-6 HLA-mismatch	10 (62.5%)	43 (47.3%)	51 (59.3%)	34 (54.8%)	NS
HLA-mismatch	4.8 ± 0.9	4.4 ± 1.3	4.6 ± 1.4	4.4 ± 1.3	NS
PRA ≥20%	2 (12.5%)	10 (11%)	9 (10.5%)	8 (12.9%)	NS
CMV D+/R-	4 (25%)	28 (30.8%)	23 (26.7%)	17 (27.4%)	NS
Organ import	2 (12.5%)	14 (15.4%)	17 (19.8%)	15 (24.2%)	NS
Kidney Donor Profile Index (%)	16 ± 14.6	19 ± 16	18.5 ± 15	24 ± 19	NS

D (Donor), R (Recipient); Values are Mean ± SD or Number of subjects (% of age sample size).

Table 2. Recipient Characteristics

	Age <30 years (n=16)	Age 30-39 years (n=91)	Age 40-49 years (n=86)	Age ≥50 years (n=62)	p-value
Recipient age	25.9 ± 3.5	35.0 ± 3.0	44.3 ± 2.6	55.5 ± 4.0	<0.0001
Recipient gender: Male	9 (56.25%)	49 (53.8%)	59 (68.6%)	26 (41.9%)	0.012
Recipient African American	9 (56.25%)	24 (26.4%)	21 (24.4%)	12 (19.4%)	0.02
Recipient weight	65.5 ± 13.6	69.3 ± 13	74.2 ± 13.7	71.4 ± 13.5	0.03
Recipient BMI (kg/m^2)	24.1 ± 4.1	23.5 ± 3.2	25.3 ± 2.8	25.1 ± 3.6	0.007
Dialysis history: Hemodialysis	9 (56.25%)	50 (55%)	44 (51.2%)	27 (43.6%)	NS
Peritoneal Dialysis	4 (25%)	26 (28.6%)	24 (27.9%)	16 (25.8%)	
None (preemptive)	3 (18.75%)	15 (16.4%)	18 (20.9%)	19 (30.6%)	
Duration of dialysis (months)	18.1 ± 11.5	27.1 ± 24.5	22.9 ± 21.4	24.2 ± 18.2	NS
Duration of diabetes (years)	17.9 ± 4.3	23.5 ± 6.1	27.8 ± 9.0	28.8 ± 12.8	NS
Pretransplant C-peptide ≥2.0 ng/ml	3 (18.8%)	13 (14.3%)	18 (20.9%)	16 (25.8%)	<0.001
Systemic-enteric technique	3 (18.8%)	10 (11%)	13 (15.1%)	13 (21%)	NS
Retransplant	1 (6.25%)	1 (1.1%)	5 (5.8%)	1 (1.6%)	NS
Time on waiting list (months)	9.0 ± 7.3	9.8 ± 7.9	8.9 ± 7.5	8.5 ± 8.5	NS
Alemtuzumab induction	12 (75%)	73 (80.2%)	60 (69.8%)	46 (74.2%)	NS

Values are Mean ± SD or Number of subjects (% of age sample size).

Early outcomes

One-year patient and kidney graft survival rates were comparable across age groups (95-98% for the 3 older groups and 93% for the youngest group, Table 3). One-year pancreas graft survival rates were 92% in the 2 older groups compared to 86% in the 2 younger groups (p=NS). The rates of graft loss secondary to pancreas thrombosis ranged from 3.5% to 6.6% whereas early (≤3 months) technical pancreas graft failure rates ranged from 4.8% to 8.8% but recipient age was not a significant factor. Hospital length of stay was observed to be one day longer for patients age 40 and older but this was not statistically significant. The rate of early (≤3 months) relaparotomy was highest in the youngest group (50%) compared to 31.4% (p=NS) in the other 3 age groups combined. Overall, recipient age did not appear to significantly influence early outcomes following SPKT.

Late outcomes

Patient survival was slightly higher in the 2 middle groups (80.2% combined) compared to the youngest and oldest groups combined (66.7%, p=0.06, Table 3). Kidney graft survival rates (68.4% combined for 2 middle groups versus 55.1% for youngest and oldest groups combined, p=0.048) were significantly higher whereas pancreas graft survival rates (61.6% combined for 2 middle groups versus 51.3% for youngest and oldest groups combined, p=0.13) were slightly but not significantly higher in the 2 middle groups. Actuarial patient, kidney, and pancreas graft survival rates (uncensored) according to recipient age category are shown in Figures 1-3, respectively. Patient survival in the oldest age group was inferior to the other age groups (particularly beyond 6 years follow-up) whereas kidney graft survival was highest in the age 40-49 year group and lowest in the age <30 year group (both p<0.05). In contrast, pancreas graft survival was comparable across age groups. For patients with at least 8-year follow-up, the 8-year patient survival rate was significantly lower in the oldest age group (47.6% versus 78% in the 3 younger groups combined, p=0.0004). However, 8-year kidney graft survival rates were comparable in the youngest and oldest age groups (36.5% combined), but inferior to those in the middle 2 groups (62% combined, p=.0038). Similarly, 8-year pancreas graft survival rates were comparable in the youngest and oldest age groups (32.7% combined), but inferior to those in the middle 2 groups (50% combined, p=.043). Actuarial death-censored kidney and pancreas graft survival rates are shown in Figures 4 and 5. Death-censored kidney

Table 3. Outcomes According to Recipient Age

	Age <30 years (n=16)	Age 30-39 years (n=91)	Age 40-49 years (n=86)	Age ≥50 years (n=62)	p-value
Overall outcomes					
Patient survival	12 (75%)	72 (79.1%)	70 (81.4%)	40 (64.5%)	0.06
Death with functioning grafts	1 (6.25%)	8 (8.8%)	7 (8.1%)	14 (22.6%)	0.002
Kidney graft survival	9 (56.25%)	59 (64.8%)	62 (72.1%)	34 (54.8%)	0.11
Death-censored kidney survival	9/15 (60%)	59/83 (71.1%)	62/79 (78.5%)	34/45 (75.6%)	NS
Pancreas graft survival	8 (50%)	54 (59.3%)	55 (64%)	32 (51.6%)	NS
Death-censored pancreas survival	8/14 (57.1%)	54/83 (65.1%)	55/79 (69.6%)	32/44 (72.7%)	NS
Follow-up (months)	98 ± 69	98 ± 64	105 ± 66	86 ± 58	NS
Early outcomes					
One year patient survival	14/15 (93.3%)	84/86 (97.7%)	82/83 (98.8%)	55/57 (96.5%)	NS
One year kidney graft survival	14/15 (93.3%)	82/86 (95.3%)	81/83 (97.6%)	55/57 (96.5%)	NS
One year pancreas graft survival	13/15 (86.7%)	74/86 (86.0%)	77/83 (92.8%)	52/57 (91.2%)	NS
Early pancreas thrombosis (<1 month)	1 (6.25%)	6 (6.6%)	3 (3.5%)	3 (4.8%)	NS
Early technical pancreas graft loss (≤3 months)	1 (6.25%)	8 (8.8%)	5 (5.8%)	3 (4.8%)	NS
Early relaparotomy (≤3 months)	8 (50%)	27 (29.7%)	29 (33.7%)	19 (30.6%)	NS
Days of initial hospital stay	9.5 ± 3.5	9.8 ± 5.1	10.9 ± 7.3	10.6 ± 7.3	NS
Late outcomes					
8-year patient survival	7/10 (70%)	38/53 (71.7%)	47/55 (85.5%)	20/42 (47.6%)	<.001
8-year kidney survival	4/10 (40%)	26/53 (49.1%)	41/55 (74.5%)	15/42 (35.7%)	<.001
8-year pancreas survival	3/10 (30%)	23/53 (43.4%)	31/55 (56.4%)	14/42 (33.3%)	NS
Death-censored dual graft loss (excluding thrombosis)	5 (31.25%)	10 (11.0%)	7 (8.1%)	2 (3.2%)	0.007
Cause of death: Cardiac	2 (12.5%)	4 (4.4%)	6 (7%)	5 (8.1%)	
Malignancy	0	1 (1.1%)	2 (2.3%)	5 (8.1%)	
Infection	1 (6.25%)	4 (4.4%)	3 (3.5%)	5 (8.1%)	
Stroke	0	2 (2.2%)	2 (2.3%)	2 (3.2%)	
Respiratory failure	0	2 2.2%)	1 (1.1%)	1 (1.6%)	
Other/Unknown	1 (6.25%)	6 (6.6%)	2 (2.3%)	4 (6.5%)	
Late deaths (>8 years)	2/4 (50%)	8/19 (42.1%)	8/16 (50%)	10/22 (45.5%)	
Kidney graft loss from death	1/7 (14.3%)	11/32 (34.4%)	9/24 (37.5%)	17/28 (60.7%)	0.02
Pancreas graft loss from death	2/8 (25%)	10/37 (27.0%)	11/31 (35.5%)	18/30 (60%)	0.007

Values are Mean ± SD or Number of subjects (% of age sample size).

and pancreas graft survival rates increased from youngest to oldest recipient age category because of a higher incidence of DWFGs (22.6% in oldest age group compared to 8.3% in the 3 younger groups combined, p=0.002, Table 3). There was a trend toward lower death-censored kidney graft survival in the youngest age group whereas death-censored pancreas graft survival was comparable across age groups. Each of the actuarial graft survival curves was notable for a decrease in in both kidney and pancreas graft survival occurring at 3 years follow-up in the youngest age group.

Mortality and graft loss

In the 9 patients ≥60 years of age, patient, kidney, and pancreas graft survival rates were 44.4% with a mean follow-up of 78 months. Three of the five deaths occurred >8 years following SPKT. Four patients experienced DWFGs (2 secondary to infection, one cancer, one cardiovascular cause) and the remaining patient developed ESRD at 19 months and refused to return to dialysis treatment (she died with a functioning pancreas graft). In all 4 groups combined, of the 61 deaths, 28 (46%) occurred >8 years post-SPKT. In the 3 older age

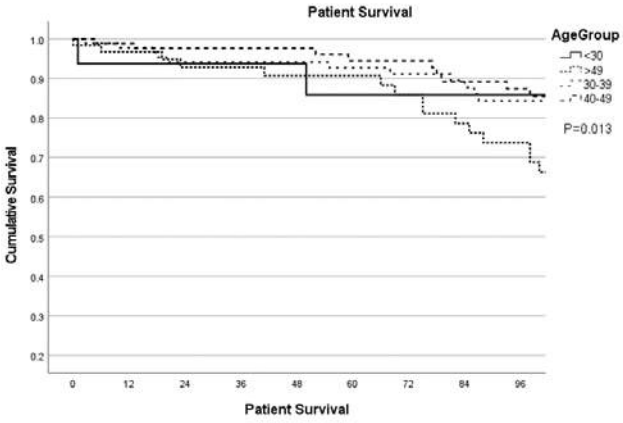

Figure 1. Actuarial patient survival (uncensored) following SPKT according to recipient age category.

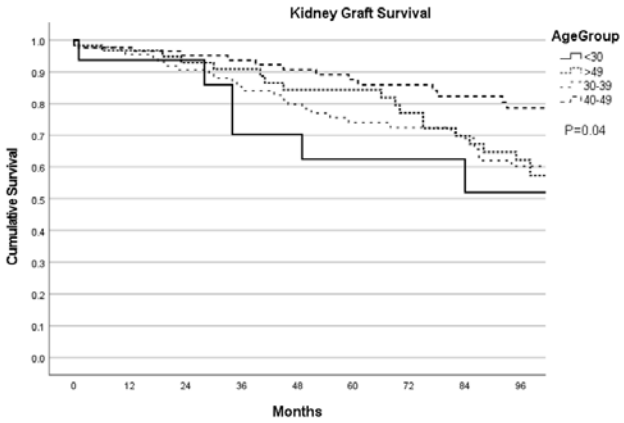

Figure 2. Actuarial kidney graft survival (uncensored) following SPKT according to recipient age category.

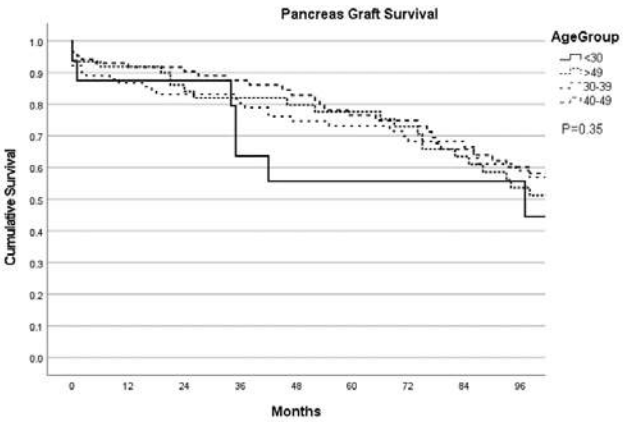

Figure 3. Actuarial pancreas graft survival (uncensored) following SPKT according to recipient age category.

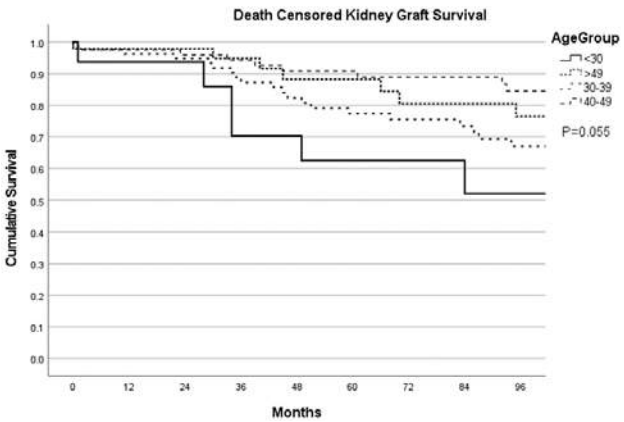

Figure 4. Actuarial death-censored kidney graft survival following SPKT according to recipient age category.

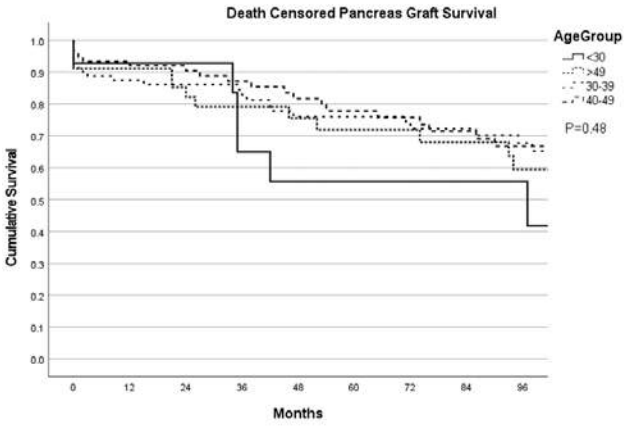

Figure 5. Actuarial death-censored pancreas graft survival following SPKT according to recipient age category.

groups, major causes of death were cardiac, malignancy, infection, stroke, and respiratory failure, whereas in the youngest group the causes of death were primarily cardiac or infection. Death as a cause of kidney graft loss increased from 14% to 61% (p=0.02, Table 3), whereas death as a cause of pancreas graft loss increased from 25% to 60% (p=0.007) from youngest to oldest recipient age category. The rate of death-censored dual graft loss (excluding early graft losses), which were usually secondary to acute or chronic rejection in both organs, was highest in the youngest age group (31.25%) and progressively decreased in each successive recipient age category such that it only accounted for 7.9% of graft losses in the 3 oldest age groups combined (p=0.007).

Discussion

Diabetes and kidney disease remain among the top ten causes of death in the United States (US). A functioning pancreas transplant mitigates glycemic variability and achieves endogenous glucose homeostasis while eliminating the daily stigma and burden of diabetes in exchange for the administration of and side effects associated with chronic immunosuppression. Moreover, a functioning SPKT treats not only DM but kidney failure, resulting in improvements in quality of life and life expectancy compared to other renal replacement options. According to the International Pancreas Transplant Registry (IPTR), as of 2020, >34,000 pancreas transplants have been performed in the US in the past 50+ years including >80% in the SPKT category.[2-4] At present, approximately 1000 pancreas transplants are performed annually in the US including >800 SPKTs in patients with diabetes and advanced kidney disease or kidney failure.[2-4]

Success rates for SPKT have progressively improved secondary to refinements in diagnostic and therapeutic technologies and surgical techniques, advancements in immunosuppression and anti-infective prophylaxes, new and effective techniques in organ retrieval and preservation technology, and increased experience in the selection of donors and recipients.[2-4] In evaluating trends, the proportion of patients age 50–64 years listed for pancreas transplantation doubled from 1998 to 2010 [17], but remained relatively stable at 20% of all waitlist additions for SPKT from 2015-2019.[2-4] Patients age 50-64 years currently represent 2.3% of all pancreas transplants performed annually, including 2.1% of SPKTs.[3] In patients age 65 years or older, waitlist additions likewise remained stable at a mean of 1.0% of all waitlist additions and 0.3-0.7% of SPKT waitlist additions in the past 5 years. The proportion of pancreas transplants performed in patients >65 years of age was also relatively stable (mean 0.5% of all pancreas transplants and 1.2% of SPKTs) from 2015-2019.[2-4,40] In the past two decades, education and management of DM, including advanced insulin delivery and glucose monitoring technologies, have improved dramatically, resulting in delayed progression to chronic kidney disease and ESRD in patients with DM.[8,41] As a result, there is an increasing population of patients with DM being referred for transplantation at older ages, underscoring the need to better understand criteria for candidacy (other than chronological age alone) based on an acceptable risk-benefit balance and ethical considerations for both the patient and the transplant waitlist.[2-4,8,17,18,40,41]

An important consideration in evaluating transplant outcomes is understanding the interaction between donor and recipient factors and their effect on early technical failure. Finger, et al., retrospectively reviewed all pancreas transplants (n=1115) at a single institution over a 13-year period and developed a composite risk model to predict early technical failure in pancreas transplantation. They demonstrated that while donor age (>50 years) played a predictive role for technical graft failure, recipient age did not.[42] Another concern is the growing disparity between pancreas and kidney donor availability and demand, thus warranting

careful examination of expansion of the candidate pool, specifically older individuals who presumably have shorter life expectancies. Salvalaggio, et al., analyzed the implications of SPKT from older donors on recipient survival and graft longevity and determined that utilization of a graft from an older donor is superior to waiting longer, even for younger recipients.[43] These data suggest that perhaps age matching is a potential strategy for increasing both the donor and recipient pools. Kayler, et al., examined age matching utilizing data from the Scientific Registry of Transplant Recipients (SRTR) to analyze all waitlisted candidates for SPKT over a 15-year period.[44] Transplantation of older donor organs (>40 years) into either old or young recipients was inferior as compared to transplantation of young donor organs (<40 years). However, there was a clear survival benefit for older patients undergoing SPKT compared to not receiving a transplant. In general, most studies support the contention that SPKT is feasible in older recipients, and that recipient age alone is not a primary risk factor for patient mortality or graft failure. However, careful selection of donor organs and recipients is important to optimize outcomes.

Shah et al., in a retrospective single institution analysis, examined the effect of recipient age on posttransplant outcome in all pancreas transplants (n=405) over an 8-year period.[13] A total of 64% of pancreas transplants occurred in patients older than 40 years of age, and 25% in patients older than 50 years. Analysis of outcomes stratified according to recipient age by decade (<30, 30-39, 40-49, 50-59, >60 years) demonstrated similar short-term (7 and 90 day) pancreas graft survival and equivalent one-year patient, kidney, and pancreas graft survival rates. Regression analysis demonstrated a trend towards worse five-year patient survival with increasing recipient age, although survival was still excellent in the oldest groups (84%). Interestingly, in this study, the youngest recipient age group (<30 years) actually had the lowest pancreas graft survival rate while all other age groups had equivalent pancreas graft survival rates. However, the causes of graft loss varied significantly by recipient age. For example, younger patients were more likely to lose grafts to acute or chronic rejection whereas older patients were more likely to lose functioning grafts to death. This finding of lower pancreas graft survival in the younger age groups is also borne out by IPTR data.[2-4,17,25]

In another single center retrospective study from 1996–2010, Afaneh, et al., reported on 136 consecutive pancreas transplants, 17 of which were in patients age 50 years or older.[12] The two groups studied had comparable major and minor surgical complication rates and the incidence of non-surgical infections and overall patient and graft survival rates were similar in younger and older recipients. Scalea, et al., reported a single center retrospective analysis of SPKT and solitary pancreas transplants in recipients ≥55 years of age transplanted from 1999-2012.[16] Of the 740 patients studied, only 28 (3.8%) were ≥ age 55 years. Patient and graft survival outcomes were comparable for younger and older recipients, although cardiovascular events were more frequent in patients >45 years of age. In 2020, Mittal, et al., reported a single center retrospective analysis comparing patients age 23–54 years (n=444) to those age 55–67 years (n=83, 15.7%) receiving pancreas transplants between 2002 and 2016.[19] While there were no differences in death-censored pancreas or kidney graft survival rates between groups, the authors concluded that mortality was higher in older patients and strongly associated with pancreas and kidney graft failure.

Larger database studies include a retrospective SRTR analysis of all adult solitary pancreas transplant and SPKTs between 1996 and 2012.[14] Of the 20,854 pancreas transplants included in the analysis reported by Siskind, et al., 3440 (16.7%) of the recipients were 50 years of age or older. For older patients, long-term graft survival (10-15 years) was diminished compared to younger recipients and as age increased, survival decreased. The authors also demonstrated inferior uncensored patient and graft survival rates in the older group and recommended taking this data into consideration when making candidacy decisions rather than using it as exclusion criteria. Similarly, Gruessner, et al., analyzed outcomes and risk factors for patients ≥60 years of age.[45] Using SRTR and IPTR data between 2000-2017, 358 deceased donor pancreas transplants (327 SPKTs) were reported in patients age 60 years or older (the oldest recipient was age 73 years). Approximately 25% of these patients were identified as having T2DM. Wait-list mortality for elderly patients with diabetes was 50% at 5 years but mean waiting time for pancreas transplantation was <1 year. The most common cause of graft loss in this group was DWFG and the most common causes of death were cardiovascular, infection, and malignancy. In the SPKT

category, the death-censored pancreas graft survival rate was >90% at 5 years follow-up. The authors concluded that SPKT in elderly patients with labile diabetes can be successfully performed with careful patient selection and using young donors with short cold ischemia times.

Independent of recipient age, recent studies have focused on the impact of sarcopenia and functional status on outcomes following SPKT.[46-48] DM is believed to contribute directly to the pathophysiology of frailty by increasing the risk of sarcopenia. Patients with T1DM in particular are at greater risk for sarcopenia secondary to the catabolic effect of insulin deficiency and excess accumulation of intramyocellular lipids and advanced glycation end products. Consequently, the distribution of impaired functional status in the SPKT candidate population is fairly equal across age groupings. Similar to data in other solid organ transplant recipients, the presence of frailty and reduced functional status are important predictors of patient survival in SPKT candidates and recipients irrespective of age.

In our series ranging from November 2001 to August 2020, we report a large single center retrospective experience with SPKT in 255 patients, including 62 (24.3%) ≥ age 50 and 9 ≥ age 60 years. All patients received depleting antibody induction (75% with single dose alemtuzumab) in combination with tacrolimus/mycophenolate ± steroid maintenance immunosuppressive therapy and 85% underwent pancreas transplantation with P-E drainage. A total of 66 patients (26%) were African American and 20% overall had a T2DM phenotype. Similar to most previous studies, we found that recipient age did not influence 3-month and one-year outcomes following SPKT. However, we corroborated an "age effect" on late outcomes characterized by more dual immunologic graft losses in younger patients and more DWFGs in older patients. The net effect of these findings was that kidney and pancreas graft survival rates were comparable at the extremes of age but inferior to those achieved in the middle 2 age groups. In all 4 groups combined, DWFG accounted for 39% of both kidney and pancreas graft losses and was the single most common cause of graft loss. Additionally, of the 61 deaths, 28 (46%) occurred >8 years post-SPKT. It is important to note that the 5-year survival rate in this patient group in the absence of transplantation is <50%. Moreover, the ultimate goal of transplantation is for the allograft to "outlive" the patient, so DWFG is actually a desirable outcome provided that death was neither premature nor directly related to the transplant or chronic immunosuppression. Not surprisingly, the major causes of death were cardiovascular, infectious, and malignancy (particularly in the older recipient group). Death-censored graft survival rates progressively improved from youngest to oldest recipient age category, which mirrors outcomes with kidney alone transplantation in elderly recipient groups.[20-22]

This study has the typical limitations of an observational study from a single center including the retrospective design. In addition, the number of patients in each group, particularly the youngest age cohort, are relatively small, which could bias the statistical analysis. The age group designations may seem arbitrary but reflect previous studies pursuant to this topic and are of clinical relevance because many centers apply age limitations in recipient selection. Potential strengths of the study are the standardization of management protocols and granularity of data collection during the period of study. Unique aspects of this experience include the long duration and completeness of follow-up in all 4 age groups, the administration of depleting antibody induction (primarily alemtuzumab), use of the portal-enteric drainage technique, the relatively large number of elderly recipients as well as African American recipients, differentiation of the T2DM phenotype, and presentation of both early and late outcomes.

As SPKT outcomes have improved in the past two decades, long-established contraindications for populations that were generally excluded due to concerns of excessive risk with uncertain benefit, including elderly patients, are now being challenged.[18,43-45] Similar data exists amongst deceased donor kidney transplant recipients where the oldest recipients have the worst overall survival but death-censored graft survival rates improve with older recipient age[20-22], suggesting perhaps a benefit of immunosenescence, the presence of more aggressive disease in younger patients, or reflective of more stringent patient selection with older age.[49] Additionally, age-related differences in compliance may likewise account for the equivalence in death-censored graft survival rates when comparing younger and older recipient populations.

In summary, improvement in SPKT outcomes likely reflects adjustments in both candidate and donor selection. The transplant community has continued to pursue serving the DM population with ESRD in an environment of improved diabetes management, resulting in candidate evaluation and transplantation at ages that were once considered exclusions. As a result, there has been an increase in SPKT in elderly patients that has appeared to have leveled off in the past five years. While outcomes in this population are mixed[9-19,43-45], SPKT is generally supported when disease severity, comorbidity, and likely benefit is considered, rather than age alone. Limitations in the current data include the small number of patients represented in single center retrospective analyses and the lack of granular information in registry data. However, analogous to kidney transplantation alone, SPKT may provide both a survival and quality of life benefit to all appropriately selected candidates regardless of age. [25,50-54]

Disclosures

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Original Science

National Trends in Inpatient Diagnosis of Acute Kidney Injury and Associated Outcomes between 2000 and 2014

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Abstract

The prevalence of factors predisposing to acute kidney injury (AKI) — older age, diabetes, obesity and atherovascular disease — has increased exponentially. This study analyzed the national trend in AKI incidence along with related health care costs and mortality. Using the National Inpatient Sample database, we analyzed individuals age 18 years and older who were hospitalized from January 2000 to December 2014 and had AKI (ICD-9: 584.9) as the principal discharge diagnosis. Longitudinal differences in the total number of hospital discharges, mean length of stay (LOS), rate of in-hospital mortality, and inflation-adjusted cost related to AKI versus the calendar year were assessed using general linear model (GLM) for testing trend of linear regression. To account for single year viability, the generalized linear model (GENMOD) was used to estimate the linear trend for five consecutive year groups, each of which contained three consecutive years. The total number of discharges with the principal diagnosis of AKI increased by 27,811 cases per year and the mean LOS per hospitalization decreased by 0.2 days per year ($p<0.0001$, GLM and GENMOD). The AKI-related in-hospital mortality rate decreased by 62% per year ($p<0.0001$, GLM and GENMOD). The mean charges per AKI hospitalization increased by $915 per year and the mean aggregate charges (the "national bill") associated with all AKI hospitalizations increased by $1,000,000,000 per year ($p<0.0001$, GLM and GENMOD, adjusted for inflation). In spite of declining hospital LOS and mortality in patients with AKI, the per patient hospitalization charge increased.

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Introduction

The diagnosis of acute kidney injury (AKI), regardless of etiology, is associated with serious immediate complications (e.g., fluid overload, electrolyte and acid-base abnormalities, coagulopathy, and death)[1] and long-term sequelae (e.g., proteinuria, de-novo chronic kidney disease [CKD], de-novo end-stage kidney disease [ESKD]).[2-4] The prevalence of factors predisposing to AKI — older age, diabetes, obesity and atherovascular disease — has increased exponentially over the past decades.[5-7] In parallel with these trends, the incidence and prevalence of AKI is expected to change.[8]

Acute kidney injury epidemiology has been studied in several cross-sectional and longitudinal studies[9-12], many not spanning the United States territory[10] and focused on AKI incidence in patients admitted with specific diagnoses[13] or in patients admitted to the intensive care unit (ICU).[9,11,14,15] Epidemiological data for AKI incidence and its relative effects on mortality, hospital length-of-stay (LOS) and charges spanning

contemporary medical care are scarce. This study analyzed all national inpatient data between 2000 and 2014 from the Healthcare Cost and Utilization Project's (HCUP) National Inpatient Sample (NIS) to identify cases of AKI as a principal discharge diagnosis, using International Classification of Diseases, Ninth Revision (ICD-9) codes. Temporal trend in the rate of inpatient diagnosis of dialysis- and non-dialysis requiring AKI was analyzed as 1) at-risk AKI rate (i.e., number of AKI cases of the total discharges), and 2) population-based AKI rate (number of AKI cases per million person-years). The relative effects of AKI on mortality, LOS and charges over the same time span were also evaluated.

Materials and Methods

Study population Yearly datasets were extracted from the Nationwide Inpatient Sample (NIS), a United States nationally representative administrative database of hospitalizations.[16] The NIS is the largest all-payer, publicly available national hospital database. Hospitals are sampled according to geographic region, location, teaching status, ownership, and bed size; all discharges from the sampled hospitals are included in the database. Each data entry represents an individual hospitalization and includes demographic variables, discharge diagnoses, procedures, hospital charges, and length of stay. Cases with an AKI diagnosis were identified using validated International Classification of Diseases, Ninth Revision, Clinical Modification codes.[17] Cases with the following diagnosis code in any position were included: 584.9 (acute kidney failure, unspecified). Cases with a diagnosis of end-stage renal disease (ESRD) requiring dialysis (585.6) were excluded. This study used de-identified data and was exempt from IRB approval.

Statistical analysis Continuous variables were described in terms of their means (standard deviation) and compared using t-tests when appropriate. Categorical variables were described as proportions and compared using the χ^2 test. We log-transformed mean age at hospitalization to accommodate data that were expectedly right-skewed and used Mallow's C_p to assess model fit. To quantify the change in risk of AKI among hospitalized patients per year, we fit a univariate logistic regression model with calendar year as the primary predictor and AKI as the primary outcome. We calculated population incidence rates for AKI in the US from 2000 to 2014 by dividing the number of discharges with AKI by the US population in each year.[18] Incidence estimates were stratified by sex and age for subgroup investigation. We used linear regression analysis to evaluate the associations of AKI with hospital length of stay (LOS) and healthcare charges. With data from 2000 as a reference, we used multiple logistic regression models to determine the odds of AKI and corresponding in-hospital mortality for each year included in the study. All data was analyzed using Stata 11.2 (StataCorp, College Station, TX).

Results

Between 2000 and 2014, a total of 554,266,249 hospital discharges were recorded. Of these, 4,578,674 hospitalizations had a diagnosis of dialysis- or non-dialysis-requiring AKI on discharge (Table 1). The overall number of hospital discharges grew as follows: 35,300,425 in 2000; 37,843,039 in 2005; 37,352,013 in 2010; and 35,358,818 in 2014. This corresponds to an average rise in all-cause hospitalizations of 1.0% per year. However, normalized by total U.S. population per corresponding year, the average change in all-cause hospitalizations was 0.1% per year (Table 2, Figure 1).

Table 1. Total count of Acute Kidney Injury (AKI) discharges, patient age, length of stay (LOS), in-hospital mortality, and healthcare cost per year

Year	Total number of discharges* (N)	Age, years (mean)	LOS, days (mean [SE])	In-hospital deaths (N [%])	Per patient-hospitalization charge (U.S.D.)# (mean [SE])	National bill (U.S.D.)#
2000	106091	69	7.6 (0.105)	11746 (11.07 %)	27,994 (1035)	(mean [SE])
2001	123104	70	7.4 (0.074)	12746 (10.35 %)	30,181 (1076)	3.09 Billion (154,703,125)
2002	132819	69	7.3 (0.088)	12816 (9.65 %)	32,257 (1278)	3.71 Billion (171,243,108)
2003	184575	70	7.1 (0.077)	16041 (8.69 %)	33,574 (1028)	4.27 Billion (225,397,054)

Table 1. Continued

Year	Total number of discharges* (N)	Age, years (mean)	LOS, days (mean [SE])	In-hospital deaths (N [%])	Per patient-hospitalization charge (U.S.D.)# (mean [SE])	National bill (U.S.D.)#
2004	224950	70	6.9 (0.070)	16109 (7.16 %)	32,778 (886)	6.19 Billion (245,998,302)
2005	257289	70	6.7 (0.073)	17007 (6.61 %)	33,297 (968)	7.37 Billion (279,619,989)
2006	302298	70	6.4 (0.062)	16881 (5.58 %)	33,367 (816)	8.56 Billion (363,479,218)
2007	357116	70	6.1 (0.064)	17432 (4.88 %)	33,681 (872)	10.08 Billion (406,753,850)
2008	379144	70	5.9 (0.056)	17860 (4.71 %)	33,533 (895)	12.02 Billion (406,411,460)
2009	337226	69	5.8 (0.053)	14924 (4.43 %)	35,241 (1034)	12.68 Billion (485,537,987)
2010	356785	69	5.6 (0.050)	14513 (4.07 %)	35,704 (869)	11.88 Billion (480,407,346)
2011	442697	70	5.2 (0.046)	14086 (3.18 %)	34,244 (844)	12.72 Billion (420,649,262)
2012	446885	69	5.1 (0.024)	13340 (2.99 %)	33,375 (413)	15.14 Billion (560,882,781)
2013	460480	69	5 (0.022)	13525 (2.94 %)	34,139 (404)	14.91 Billion (241,760,873)
2014	467215	69	5 (0.028)	12580 (2.69 %)	34,390 (390)	15.72 Billion (239,994,804)

***Discharges with AKI as one of the principal discharge diagnoses. #Adjusted for inflation. AKI, acute kidney injury; LOS, length-of-stay; N, number; SE, standard error.**

Table 2. Total count of AKI discharges normalized by total U.S. population per corresponding year

Year	Total population	Total number of discharges* (N)	Incidence (%)
2000	282171957	106091.07	0.038
2001	285081556	123103.93	0.043
2002	287803914	132819.26	0.046
2003	290326418	184575.09	0.064
2004	293045739	224949.69	0.077
2005	295753151	257288.67	0.087
2006	298593212	302298.02	0.101
2007	301579895	357116.32	0.118
2008	304374846	379144.38	0.125
2009	307006550	337225.80	0.110
2010	309134118	356785.21	0.115
2011	311432712	442696.82	0.142
2012	313790434	446885.14	0.142
2013	316041156	460479.77	0.146
2014	318420556	467215.20	0.147

***Discharges with AKI as the principal discharge diagnosis. AKI, acute kidney injury; N, number.**

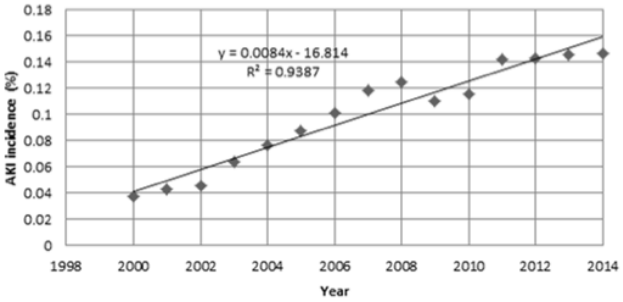

Figure 1. Annual AKI incidence normalized by total U.S. population per corresponding year

The annual number of discharges with a diagnosis of AKI increased significantly over the study period: from 106,091 in 2000, to 257,289 in 2005, 356,785 in 2010, and 467,215 in 2014 (P<0.0001) (Figure 2). The proportion of discharges with an AKI diagnosis of the total hospital discharges changed from 0.3% in 2000, to 0.68% in 2005, 0.95% in 2010, and 1.32% in 2014. The mean ages of patients diagnosed with AKI were around 69 and 70 years of age.

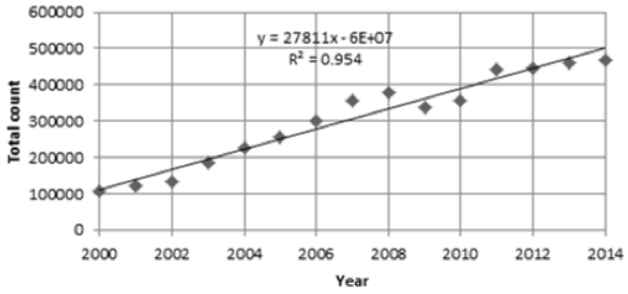

Figure 2. Total number of discharges with AKI

The hospitalization LOS and in-patient mortality associated with a diagnosis of AKI declined significantly from a mean (SE) hospital LOS of 7.6 (0.105) days in 2000, to 6.7 (0.073) days in 2005, 5.6 (0.050) days in 2010 and 5 (0.028) days in 2014 (P<0.0001) (Figure 3). In-hospital mortality related to a diagnosis of AKI, calculated as percentage of AKI-associated deaths of all discharges with a diagnosis of AKI, changed from 11.07% in 2000, to 6.61% in 2005, 4.07% in 2010, and 2.69% in 2014 (P<0.0001) (Figure 4).

Healthcare charges associated with AKI hospitalization, adjusted for inflation, increased from 27,994 (1035) U.S.D. in 2000, to 33,297 (968) U.S.D. in 2005, 35,704 (869) U.S.D. in 2010, and 34,390 (390) U.S.D. in 2014 (P<0.0001) (Figure 5). The national bill, representing the aggregate healthcare charges per all AKI hospitalizations, increased from 3.09 billion (154,703,125) U.S.D. in 2000, to 8.56 billion (363,479,218) U.S.D. in 2005, 12.72 billion (420,649,262) U.S.D. in 2010, and 16.06 billion (248,270,936) U.S.D. in 2014 (P<0.0001), adjusted for inflation (Figure 6).

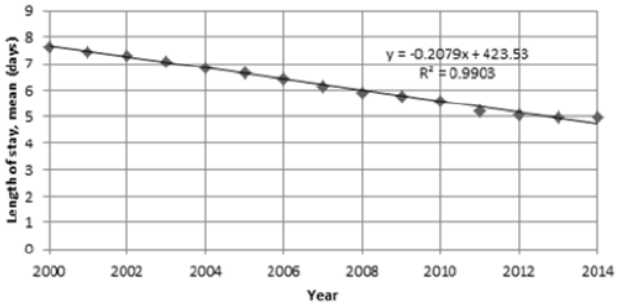

Figure 3. Trends in hospitalization length of stay associated with AKI

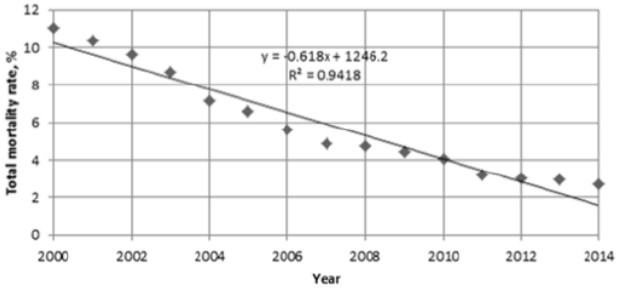

Figure 4. Trends in in-hospital mortality associated with AKI

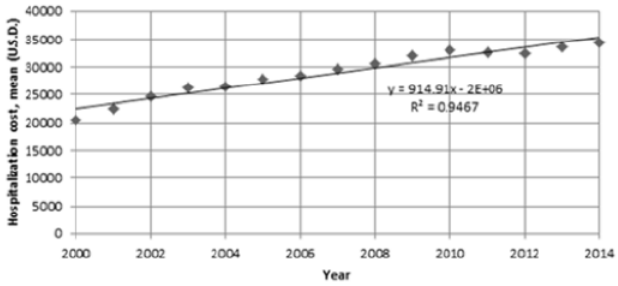

Figure 5. Trends in healthcare charges per patient hospitalization associated with AKI

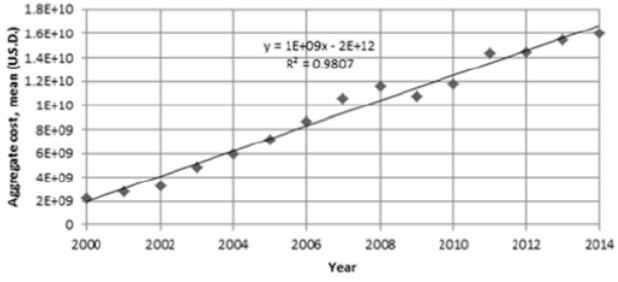

Figure 6. The "national bill" for all AKI hospitalizations

Discussion

This study analyzed contemporary trends of dialysis- and non-dialysis-requiring AKI epidemiology from a large national inpatient database. Our results show that the total count of hospital discharges with a diagnosis of AKI has increased significantly over the years, and that these differences remained significant even when adjusted by total U.S. population. Several prior studies examined longitudinal trends in AKI epidemiology between as early as 1988 and as recently as 2014, with a range in longitudinal analysis of 2-11 years.[12,19-23] Waikar et. al. reported a rising incidence in dialysis- and non-dialysis-requiring AKI per 100,000 population in hospitalized patients between 1988 and 2002 on a population level in the United States from 1988 to 2002.[20] Similar results were later reported in a study cohort limited to Northern California between 1996 and 2003.[21] Hsu et. al. showed that the population–level incidence rates of dialysis-requiring AKI between 2000 to 2009 increased by an average of 10% per year, with a more than doubling in the number of deaths associated with dialysis-requiring AKI.22 On the other hand, Amin et. al. observed an opposite trend in crude AKI incidence among patients hospitalized with acute myocardial infarction from 26.6% in 2000 to 19.7% in 2008, corresponding to an overall adjusted decline of 4.4% per year.[13] These discrepant trends suggest that AKI may be occurring more frequently overall but less commonly in certain subgroups of patients (e.g., those with acute myocardial infarction). Notably, none of the aforementioned studies that reported population-based trends of AKI incidence had adjustment for U.S. population.

Possible explanations for the rise in AKI incidence throughout the years may stem from changes in AKI awareness, recognition, monitoring, or changes in coding practice. Separated by the date of release of consensus definitions for AKI including the Risk, Injury, Failure, Loss of kidney function, and End-stage kidney disease (RIFLE) criteria in 2004, Acute Kidney Injury Network (AKIN) criteria in 2007, and Kidney Disease Improving Global Outcomes (KDIGO) criteria in 2012, there seems to have been a spike in AKI incidence following the inclusion of AKI definition criteria, driven largely in part by less severe AKI.[24] In addition, the sensitivity of administrative codes for AKI has increased over time with implementation of AKI criteria.[25]

Similar to our analyses, one study evaluated AKI incidence rate normalized by total regional population. Kashani et. al. used electronic data from Mayo Clinic Hospital to study the temporal trends in the population incidence rate of AKI between 2006 and 2014 in Olmsted County, Minnesota; AKI incident cases were normalized by all adult Olmsted County residents. In contrast to our report and previous studies[20-22], the authors found a relatively stable incidence of AKI, from 473 cases per 100,000 person-years in 2006 to 497 cases per 100,000 person-years in 2014. An important difference between our study and the study by Kashani et. al. is that the current report analyzed national AKI incidence over a 15-year period while Kashani and colleagues analyzed AKI incidence in restricted region and over a 9-year period.

This study notes that despite a declining hospital LOS and mortality among patients diagnosed with AKI, healthcare costs associated with AKI continually rose and the results did not differ statistically when adjusted by total U.S. population. Many of the previous studies also showed a concurrent decline in AKI related mortality, although this finding has been inconsistent across studies. We speculate that increased recognition and reporting of milder AKI, earlier and more liberal use of acute renal replacement therapy, increased recording of renal replacement therapy use, and financial incentives associated with renal replacement therapy use could contribute to the decline in AKI-related mortality over time.[24] Factors responsible for the rise in healthcare costs other than renal replacement therapy include higher use of interventional procedures, presence of a higher number of concomitant morbidities addressed in hospitalized patients, as well as differences in disease reporting and billing over the years. For example, the decision to enter a discharge code is influenced by multiple factors including whether the event is deemed clinically significant or as part of health-care reimbursement. Therefore, this study cannot secure that rising healthcare costs associated with hospital AKI diagnosis are due to the AKI event per se.

Our study has some limitations. Although the NIS is a large dataset, it lacks laboratory measurements, differentiation between dialysis vs non-dialysis AKI and readmission information. Because AKI begets AKI[26], a prior episode of AKI (even with recovery of renal function) increases the risk of additional admissions with AKI; thus, the number of AKI

hospitalizations or discharges could be inflated without an actual increase in the number of individual patients with AKI per year.

Conclusion

In conclusion, our study shows that at a national scale there has been a significant increase in the total count of hospital discharges with the diagnosis of AKI over the years. There has also been an increase in the reported healthcare costs associated with AKI. Simultaneously we see decrease in the hospital length of stay and mortality associated with the diagnosis of AKI.

Disclosures

No financial support given. The authors report no conflicts of interest.

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Original Science

Prognostic Factors in Oral Squamous Cell Carcinoma Treated with Primary Bone Resection

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Abstract

This study aims to determine prognostic factors for survival and recurrence in cases of oral squamous cell carcinoma (SCC) undergoing surgery including bone resection by examining patient characteristics, pathological findings, and treatment variables including the type of bone resection. This analysis is a retrospective chart review of 84 adult patients with oral SCC treated with rim or segmental mandibulectomy or maxillectomy. Patient characteristics, pathologic findings, and treatments were collected by chart review and analyzed for correlation with outcome measures of overall survival, disease-specific survival, and local, regional, and distant recurrences. Review of pathologic slides was performed for the presence and extent of bone invasion. Median follow-up was 28 months with a median overall survival of 10 months. Medullary bone invasion was detected in 41 patients (49%) and cortical bone invasion in 2 patients (2%). Predictors of overall survival (OS) in univariate analysis were tumor grade (p=0.03), tumor size (p=0.003), tumor thickness (p=0.002), lymphovascular invasion (LVI) (p=0.0006), perineural invasion (PNI) (p=0.04), N stage (p<0.0001), and type of bone resection (p=0.01). T stage (p=0.058) and medullary bone invasion (p=0.070) neared significance. Only N stage remained significant on multivariate analysis (p=0.009). N stage predicted regional (p=0.003) and distant (p=0.006) recurrence. Tumor grade (p=0.007), tumor thickness (p=0.012), and LVI (p=0.0003) also predicted for distant recurrence. Nodal stage is a stronger clinical prognosticator for survival and recurrence in oral SCC than patient or tumor factors includingtumor stage, bone invasion, and type of bone resection. Patients with known nodal metastases may benefit from more extensive neck dissection, intensified adjuvant therapy, and more rigorous surveillance imaging schedules.

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Introduction

Bone invasion is a frequently observed event in the pathogenesis of oral squamous cell carcinoma (SCC). Subsites with increased proximity to the mandible such as the alveolar ridge, retromolar trigone (RMT), and floor of mouth (FOM) have an increased risk of bone invasion1. Bone invasion through the cortical bone of the mandible or maxilla contributes to staging and is classified as T4a in the American Joint Committee on Cancer (AJCC) v7 staging system.[2-3] Staging is a significant factor in determining management of oral cavity cancer, which typically includes primary surgery with or without bone resection and adjuvant radiation therapy (RT) or concurrent chemoradiotherapy (CRT) as indicated by pathology results.[4]

Conflicting literature leaves the prognostic value of bone invasion in oral SCC in question. Some studies argue that bone invasion is not a prognostic factor[4-6] while some suggest otherwise.[7-10] Reasons for these disparate findings may include failure to control for the depth or pattern of invasion, differences in type of surgery, and presence of other factors such as cervical lymph node metastases. Determining prognostic factors in cases of oral SCC with potential bone invasion is important to providing patients with a more informed prognosis and guiding adjuvant therapy recommendations.

Our primary aim is to examine the potential prognostic factors in oral SCC treated with primary surgery including bone resection and determine whether patient characteristics, pathologic findings, or treatment variables have a significant impact on survival and recurrence.

Methods

This study is a retrospective chart review of adult patients diagnosed with oral cavity SCC and treated with surgery that included a form of bone resection between January 2011 and September 2017 at the Wake Forest Baptist Medical Center. This study was approved by the hospital's Institutional Review Board. Diagnoses were confirmed through histological examination of tumor tissue slides. Patient characteristics, operative variables, pathologic variables, and outcome measures were collected by chart review. Exclusion criteria included histology other than SCC, carcinoma in-situ, and incomplete documentation. Outcome measures collected from chart review included overall survival (OS), disease-specific survival (DSS), time to recurrence, and type of recurrence (local, regional, or distant). Local disease recurrence was defined as within the ipsilateral side of the oral cavity, regional disease recurrence was defined as within the head and neck, and distant disease recurrence was defined as below the head and neck.

Tumors that extended into multiple contiguous subsites due to size were classified as the central site of the tumor. Staging and determination of margins was performed in accordance with the AJCC v7 TNM staging guidelines.[3] Extent of bone invasion was identified through review of original histology slides of bone tissue. Two pathologists determined the extent of bone invasion with independent examination and were blinded to clinical outcomes. Patients lost to follow-up at this institution were queried in the Wake Forest Baptist Health Cancer Registry for last known follow-up, recurrences, treatments, and deaths.

Statistical Analysis

Descriptive statistics, including means and standard deviations for continuous measures and frequencies and proportions for categorical data, were calculated for all study measures. Subjects who were alive at their last known follow-up were censored as of that date for survival and censored for recurrence if recurrence-free at that point; OS was calculated as the interval between the date of surgery and date of death or last date known to be alive. DSS was censored at the time of death of those patients known to have died of non-disease causes. Time to recurrence (local, regional, distance) was calculated from surgery date to known recurrence date or last date known to be disease-free. The Kaplan-Meier method was used to estimate survival (overall survival and time-to-recurrence) data. Cox proportional hazards models were used to assess the association between survival endpoints and independent measures; hazard ratios and 95% confidence intervals were created for predictors. Univariate models were analyzed initially; variables with p-values <0.10 were included in an initial multivariate model. A best-fit model was created by dropping non-significant variables from the model in a singular fashion until only significant effects remained. P-values less than 0.05 were considered to be statistically significant. SAS (version 9.4, Cary, NC, USA) was used for all analyses.

Results

Eighty-four patients met criteria for inclusion. Patient and tumor characteristics are included in Table 1. Fifteen patients had a prior history of head and neck cancer (18%) including 10 patients with a remote history of radiation for a previous primary tumor (12%). Adjuvant therapy was not recommended in 38 patients (45%), recommended and received in 28 patients (33%), and recommended but not received in 15 patients (17.9%).

Table 1. Patient and Tumor Characteristics

Patient Characteristics	No.	%	Tumor Characteristics	No.	%
Age at Surgery			Histologic Grade		
Mean, Range	68	33-96	Grade 1	24	28.6%
Gender			Grade 2	48	57.1%
Male	51	60.7%	Grade 3	9	10.7%
Female	33	39.3%	Positive Margins	24	28.6%
Alcohol Use			LVI	19	22.6%
Heavy	21	25.0%	PNI	31	36.9%
Social/Occasional	18	21.4%	ENE	15	17.9%
None	45	53.6%	Tumor Location Subsite		
Pack-Years			RMT, Buccal Mucosa, Lip	24	28.6%
0	23	27.4%	Mandibular Alveolar Ridge	24	28.6%
0.5-20	22	26.2%	Maxillary Alveolar Ridge	7	8.3%
20.5-40	17	20.2%	Floor of Mouth	29	34.5%
>40	22	26.2%	T Stage		
Oral Tobacco Use	27	32.1%	T1	11	13.1%
Prior History of Head and Neck Cancer	15	17.9%	T2	25	29.8%
			T3	10	11.9%
			T4	36	42.9%
Treatments Received	No.	%	N Stage		
Remote History of RT for Prior Head and Neck Cancer	10	11.9%	N0	50	59.5%
Neoadjuvant RT or CRT	8	9.5%	N1	11	13.1%
Type of Surgery			N2	19	22.6%
Rim Mandibulectomy	41	48.8%	Bone Invasion		
Segmental Mandibulectomy	34	40.5%	No Bone Specimen	5	6.0%
Maxillectomy	9	10.7%	None	36	42.9%
Postoperative RT	13	15.5%	Cortical	2	2.4%
Postoperative CRT	16	19.0%	Medullary	41	48.8%

LVI: Lymphovascular Invasion, PNI: Perineural Invasion, ENE: Extranodal Extension, RMT: Retromolar Trigone, RT: Radiotherapy, CRT: Chemotherapy and Radiation Therapy.

Pathological Findings

Tumor size ranged from 0.4-10 cm with a median of 4 cm. Tumor thickness ranged from 0.2-4.8 cm with a median of 1 cm.

Clinical Outcomes

Postoperative follow-up ranged from 1-95 months with a median of 28 months. In patients still living at the time of this analysis, the median follow-up was 35 months. Indications for recommending adjuvant radiotherapy included bone invasion, lymphovascular invasion (LVI), perineural invasion (PNI), N2 or N3 stage; addition of chemotherapy was recommended for positive margins or extranodal extension (ENE). Sixty-three patients met criteria for adjuvant therapy; of these, 10 received RT and 16 received CRT. OS ranged from 0-74 months with a median of 10 months. Within 2 months of surgery, 5 patients died due to complications of disease and 1 due to unrelated causes. Time to recurrence ranged from 1-71 months with a median of 10 months. Including patients with multiple types of recurrences, 21 patients (25%) developed local recurrence, 16 (19%) developed regional recurrence, 12 (14%) developed distant recurrence, and 52 patients (62%) did not recur. 5 patients (6%) developed a second primary Head and Neck SCC.

Risk Factors for OS

Table 2 demonstrates analysis of risk factors for survival. In univariate analysis, significant predictors of OS were

Table 2. Analysis of Overall and Disease-Specific Survival

	Overall Survival						Disease-Specific Survival					
	Univariate Analysis		Multivariate Analysis		Best Fit Analysis		Univariate Analysis		Multivariate Analysis		Best Fit Analysis	
Variable	**HR (95% CI)**	***P***	**HR (95% CI)**	***P***	**HR (95% CI)**	***P***	**HR (95% CI)**	***P***	**HR (95% CI)**	***P***	**HR (95% CI)**	***P***
Age, per 5 years	1.1 (0.9-1.2)	0.36					1.0 (0.9-1.2)	0.78				
Sex, Female vs Male	0.9 (0.4-1.7)	0.66					0.9 (0.5-1.9)	0.83				
Head and Neck Cancer History	0.7 (0.3-1.7)	0.42					0.6 (0.2-1.7)	0.34				
Alcohol Use		0.2						0.13				
Oral Tobacco Use	1.5 (0.7-2.9)	0.29					1.4 (0.6-2.9)	0.43				
Smoking History	1.2 (0.6-2.5)	0.66					1.2 (0.5-2.7)	0.68				
Histological Grade		0.033		0.26				0.016		0.52		
Grade 2 vs 1	0.9 (0.4-2.0)		0.7 (0.3-2.0)				1.04 (0.5-2.5)		0.8 (0.2-2.3)			
Grade 3 vs 1	2.9 (1.1-7.9)		1.7 (0.5-6.0)				3.6 (1.3-10.3)		1.4 (0.4-5.3)			
Grade 3 vs 2	3.2 (1.3-7.7)		2.5 (0.8-7.3)				3.5 (1.4-8.6)		1.9 (0.6-5.5)			
Margins	1.4 (0.7-2.8)	0.38					1.6 (0.8-3.4)	0.19				
Tumor Size, per 1 cm	1.3 (1.1-1.5)	0.0031	1.1 (0.9-1.4)	0.41			1.3 (1.1-1.5)	0.0078	1.1 (0.8-1.3)	0.62		
Tumor Thickness, per 1 cm	1.8 (1.2-2.6)	0.0024					1.6 (1.1-2.5)	0.016				
LVI	3.3 (1.7-6.6)	0.0006	2.0 (0.7-5.6)	0.19	2.2 (1.01-4.6)	0.048	4.2 (2.0-8.5)	<0.0001	1.9 (0.7-5.2)	0.10	2.2 (1.03-4.7)	0.043
PNI	2.0 (1.02-3.9)	0.043	1.0 (0.4-2.8)	0.97			2.6 (1.3-5.3)	0.0084	1.4 (0.5-4.0)	0.63		
ECS/ENE	0.9 (0.4-2.1)	0.82					1.1 (0.5-2.7)	0.82				
Medullary vs No Bone Invasion	1.9 (0.9-3.9)	0.070	1.6 (0.6-4.0)	0.34	2.5 (1.2-5.4)	0.017	2.1 (0.98-4.7)	0.051	2.1 (0.8-5.6)	0.15	2.5 (1.2-5.3)	0.02
Tumor Subsites		0.71						0.52				
T Stage		0.058		0.35				0.14				
N Stage		<0.0001		0.0094		0.0011		0.0001		0.0039		0.0008
Rim vs Segmental vs Maxillectomy		0.01		0.89				0.029		0.83		
Postop RT	0.8 (0.3-2.1)	0.63					0.7 (0.2-2.1)	0.53				
Postoperative CRT	1.5 (0.7-3.2)	0.3					1.8 (0.8-3.8)	0.16				

Statistically significant results (p<0.05) are in bold. HR: Hazard Ratio, CI: Confidence Interval, LVI: Lymphovascular Invasion, PNI: Perineural Invasion, ENE: Extranodal Extension, RT: Radiotherapy, CRT: Chemotherapy and Radiation Therapy. Details of Multivariate and Best-Fit Analysis are discussed in the statistical analysis section.

histological grade (p=0.033), tumor size (p=0.0031), tumor thickness (p=0.0024), LVI (p=0.0006), PNI (p=0.043), N stage (p<0.0001), and surgery type (p=0.010). On multivariate analysis in which histological grade, tumor size, LVI, PNI, ENE, medullary versus no bone invasion, T stage, N stage, and type of bone resection met criteria for inclusion, N stage (p=0.0094) remained a significant predictor. LVI (p=0.048), N stage (p=0.0011), and medullary versus no bone invasion (p=0.017) were significant predictors in the best-fit analysis. Age, sex, margins, ENE, T stage (p=0.058), smoking history, tumor subsite, and postoperative RT/CRT were not significant predictors of OS or DSS. See Figures 1-3.

Risk Factors for DSS

Histologic grade (p=0.016), tumor size (p=0.0078), tumor thickness (p=0.016), LVI (p<0.0001), PNI (p=0.0084), N stage (p=0.0001), and surgery type (p=0.029) were significant predictors of DSS in univariate analysis. Medullary versus no bone invasion neared significance (p=0.051) in univariate analysis. N stage (p=0.0039) remained significant in

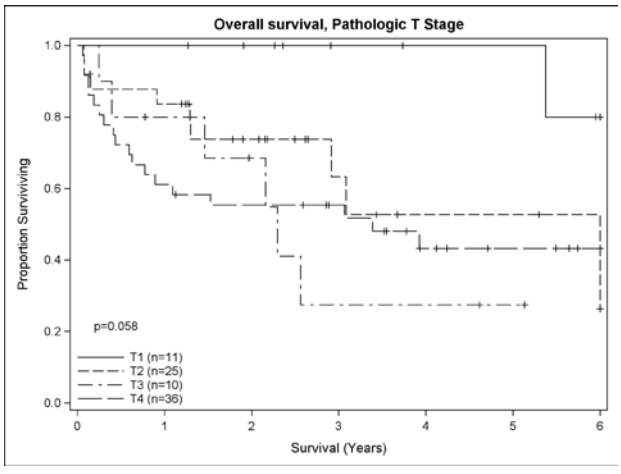


Figure 1. T Stage and Overall Survival

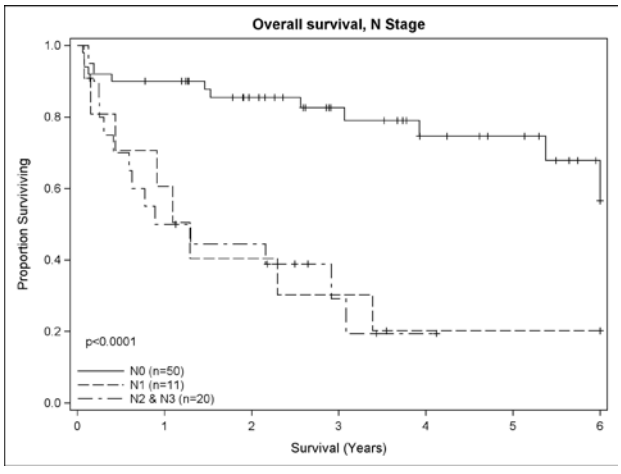


Figure 2. N Stage and Overall Survival

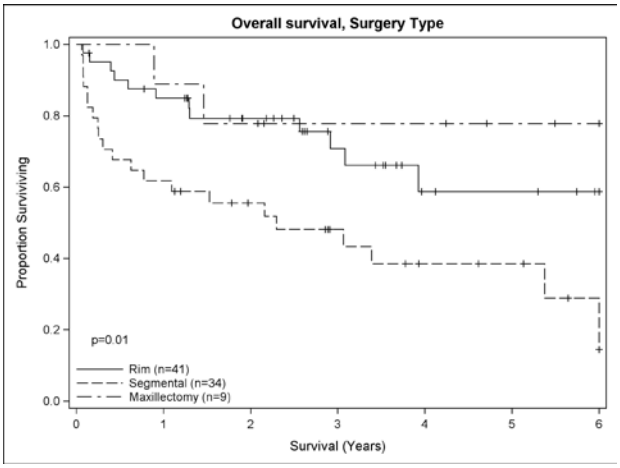


Figure 3. Surgery Type and Overall Survival

Rim: Rim Mandibulectomy, Segmental: Segmental Mandibulectomy

multivariate analysis in which histological grade, tumor size, LVI, PNI, ENE, T stage, N stage, and type of bone resection were included. Predictors in the best-fit analysis were LVI (p=0.043), N stage (p=0.0008), and medullary versus no bone invasion (0.020).

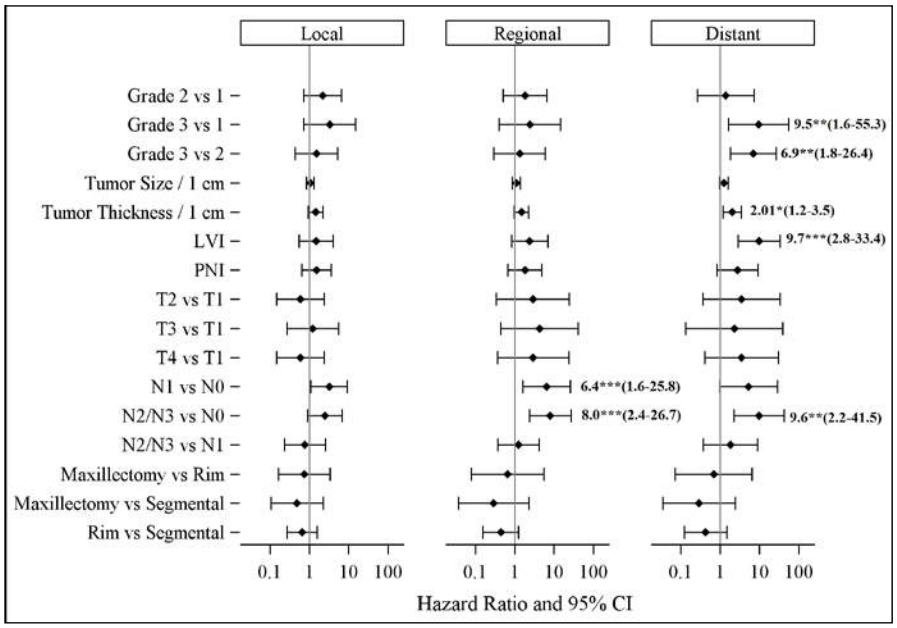


Figure 4. Risk Factors for Local, Regional, and Distant Recurrence

Forest plots of univariate analysis of risk factors for local, regional, and distant recurrence. Rim: Rim Mandibulectomy, Segmental: Segmental Mandibulectomy, LVI: Lymphovascular Invasion, PNI: Perineural Invasion. Statistically significant data are presented as Hazard Ratio (95% Confidence Interval) with *p<0.05, **p<0.01, and ***p<0.005.

Risk Factors for Local, Regional, and Distant Recurrence

Risk factors for recurrence were analyzed and are shown in Figure 4. No risk factors were significant for local recurrence, but N stage (p=0.057) trended toward significance. Regional recurrence was predicted by N stage (p=0.0025). Significant predictors identified for distant recurrence included histological grade (p=0.0073), tumor thickness (p=0.012), LVI (p=0.0003), N stage (0.0064), and postoperative CRT (p=0.035). Margins, tumor size, ECS/ENE, T stage, tumor subsite, smoking history, alcohol use, and surgery type were not significant predictors of recurrence.

Discussion

This study is a single-institution retrospective review with the aim of evaluating prognosticators in oral SCC treated with bone resection. Controversy remains concerning the impact of primary tumor factors, staging, bone invasion, and type of bone resection. Further analysis is needed to inform prognosis and treatment and address these conflicting results.

Our analysis finds that the strongest predictor of outcomes following these surgeries is nodal stage. This was true for both overall and disease-specific survival. Nodal stage is well established in literature as a reliable prognosticator of survival in oral SCC1.[3,4,8,9,11,12] We found that soft tissue factors such as tumor size, tumor thickness, LVI, and PNI were prognosticators in univariate analysis, but nodal status was the only remaining significant predictor in multivariate survival analysis. While N+ status fared worse than N0 patients, we did not see significantly poorer outcomes in advanced nodal status (N2/N3) compared to N1 patients. Also notable was the lack of significance of ENE on prognosis, although this analysis could be influenced by the small number of cases with ENE (n=15).

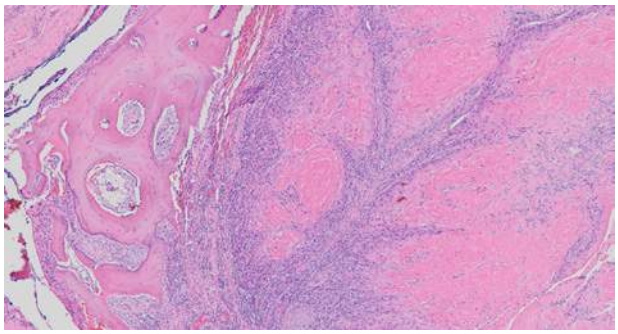
We also found that nodal stage neared significance for prediction of local recurrence and became a significant predictor of regional and distant recurrence. The predictive value of nodal status for recurrence has been demonstrated in literature.[11,13] Our finding of its influence specifically on distant recurrence is similar to the results of an analysis of 498 oral SCC patients by Ebrahimi et al[3]. In our study, the two strongest predictors of distant recurrence were LVI and nodal stage, supporting the established risk of lymphatic involvement for distant recurrence.

Interestingly, margin status was not a significant predictor in any of our analyses, which is consistent with a recent study of 96 patients with oral SCC by Fives et al1 but distinct from most literature.[3,8-12] Potential reasons for this discrepancy in the significance of margins include difference in surgeon preference or institutional practice for the procurement of margins or lack of an adequate number of patients with positive margins (n=11 in this series, 8 of which had other risk factors as well). We also noted several cases where positive margins were seen in the "main" pathology specimens but additional margins obtained from the surgical defect were negative; we classified these as positive margins in our analysis and would seem to have a lower risk of recurrence than "true" positive margins than cannot be cleared. With the preponderance of evidence in the Head and Neck Oncology literature demonstrating high risk of recurrence with positive margins, we do not advise de-intensifying adjuvant therapy in patients with positive margins based on this portion of our analysis.

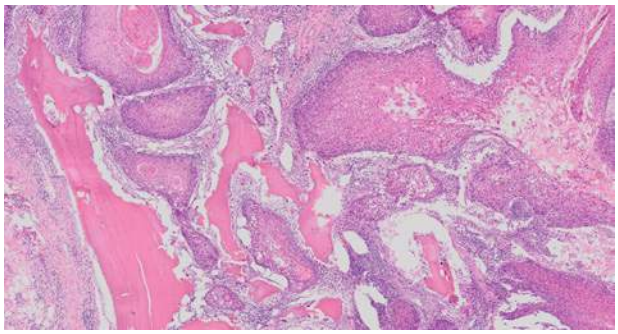
Analysis of T stage neared significance in our analysis but did not achieve it, which is similar to the findings of Fives et al[1] but inconsistent with more literature to date.[4,8,9] Over half of the patients in this study had advanced pathologic T staging (T3 or T4), with 11.9% and 42.9% of patients staged as T3 and T4, respectively (Table 1). In this study, we found 8 patients with T4 stage treated with surgery alone (they had no other risk factors and each declined recommended adjuvant therapy). Only one patient recurred locally, at 11 months. It is worth studying whether an adequate aggressive resection may be sufficient therapy for this particular group of patients with no other high-risk features.

Type of mandibulectomy was significant in univariate but not multivariate analysis of survival, which is supported by findings of Mucke et al in a study of 982 patients with oral SCC4. Lack of prognostic value is also demonstrated in other literature[6,8,13] and argues against the importance of the extent and method of bone resection in determining prognosis. The preoperative judgement of the surgeons in these series using physical exam and imaging findings to decide on a rim vs. a segmental mandibulectomy appears to be adequate to determine the likelihood of complete tumor resection. Factors that influence this decision include signs of mandible erosion, size and location of tumor, and available remaining mandibular height below the resection.[6]

Though bone invasion has a significant impact on staging, controversy remains over the prognostic impact of the presence and depth of bone invasion. We aimed to examine this issue, but of 43 patients with bone invasion, invasion was medullary in 41 cases and cortical in only 2 (Supplemental Figures 1 & 2). This finding was confirmed by each pathologist independently and upon additional review. It differs with a number of studies which found a higher instance of cortical



Supplemental Figure 1: Example of Cortical Bone Invasion



Supplemental Figure 2: Example of Medullary Bone Invasion

bone invasion[3,8,12,13] but is similar to the findings in a recent study by Fives et al.[1] The underrepresentation of cortical bone invasion may be due to the use of drills or burs for marginal mandibulectomy in several instances, resulting in a lack of bone specimen in cases of potential cortical invasion. This may have also resulted in a few false positive margins, where the tumor and periosteum were "peeled" off the mandible, with a positive deep margin that was subsequently cleared by the surgeon's drilling of the adjacent mandibular margin.

Our analysis is therefore unable to examine the influence of cortical bone invasion but may serve to examine the effect of medullary bone invasion. In that context, medullary bone invasion neared significance in univariate and multivariate analyses of survival but achieved significance in the best-fit analysis. Prognostic significance of medullary invasion is supported in findings of several other studies.[1,3,6,11,12]

In comparison with similar studies performed by Fried et al[12] and Fives et al,[1] we found that tumor size > 4cm was a poor prognosticator compared to tumors < 4cm without invasion, but there was no significant difference in survival between cases of <4 cm with or without invasion. This indicates a principal role of tumor size rather than invasion in survival, which is supported by the results of Fried et al[12] and our finding that tumor size was a univariate predictor of survival.

We examined the influence of tumor differentiation through histologic grade and found significance in univariate but not multivariate analysis of survival, and there was a significant impact on distant but not locoregional recurrence. Okura et al[14] showed similar findings in a study of 345 patients with lower gingival SCC, but more conclusive studies argue against the significance of grade.[3,4,6,10] Further studies with increased sample sizes may be able to further investigate this finding.

We were surprised to find that while 63 patients had pathology findings meriting recommendations for adjuvant therapy, only 26 actually underwent RT or CRT. We found a number of reasons why the other 37 patients did not receive therapy. Seven had undergone prior irradiation to the oral cavity or oropharynx and were not deemed to be candidates (3 remain alive with no recurrence, 2 developed recurrences, 1 died of a carotid blowout a month later, and 1 was lost to follow-up). Eight other patients with advanced stage disease and multiple risk factors died in the 3-month postoperative period from medical and/or surgical complications including dehydration, malnutrition, failure to thrive, and sepsis from infection of non-healing wounds; 3 of these had already experienced recurrences by the time of their deaths. Similarly, 5 patients were regarded as too frail to withstand adjuvant therapy; all 5 recurred by 24 months. Three patients had a positive margin as the sole criterion but did not receive adjuvant therapy; 1 of these had a local recurrence at 20 months successfully salvaged, and all 3 are alive. Finally, 4 patients with multiple risk factors declined the recommended adjuvant therapy and all 4 recurred by 6 months.

Patients at high risk for postoperative medical or surgical complications (based on nutrition status, comorbidities, history prior RT) may be faced with delays in initiating adjuvant therapy. Other patients may present for adjuvant therapy with poor performance status, which may be present prior to surgery or may develop in the postoperative period. In those cases, when multiple high-risk features are present, prognosis appears to be quite grim. Likewise, when patients with multiple high-risk features decline therapy, the outlook seems to be dismal. Efforts should be made to reduce the likelihood of complications including proper optimization of patients in the preoperative setting[15] and postoperative care pathways.[16] Patients with advanced stage tumors, especially with nodal disease, should be counseled as to the dismal outcomes following surgery alone, and should clearly understand preoperatively the notion of multidisciplinary care and the need for adjuvant therapy.

Our analysis faces several limitations. This study is at risk for the inherent bias present in retrospective reviews and its single-institution manner leads to potential sampling bias such as the underrepresentation of cases of cortical bone invasion. The small number of patients reduces the power to determine statistical significance. Furthermore, the inclusion of patients with recurrent tumors, a history of head and neck cancer or radiation, and patients undergoing maxillectomy limits the intended applicability to cases with primary tumors potentially invading the mandible. Strengths of this study include the blinded nature of the pathologic slide review for depth and extent of invasion and the rigorous statistical analysis for both survival and recurrences.

Conclusion

This single-institution retrospective study demonstrates that the strongest prognostic factor in oral SCC requiring bone resection is nodal stage rather than patient factors, pathologic findings such as tumor stage, or the extent or type of surgical resection. For patients with multiple high-risk features who do not undergo indicated adjuvant therapy, prognosis is grim.

Disclosures

No financial support given. The authors report no conflicts of interest.

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Original Science

A Longitudinal Ultrasound Curriculum for Emergency Medicine First Year Residents Improves Skill Acquisition and Resident Satisfaction Compared to Block Rotation

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Abstract

Education in point of care ultrasound for entering emergency medicine residents has traditionally been delivered over a 4-week block rotation which we have associated with several drawbacks. A longitudinal postgraduate year-1 (PGY-1) point of care ultrasound (POCUS) rotation was developed to address these deficiencies and compared to our block rotation. The primary objective is to observe the effect that a longitudinal ultrasound curriculum has on knowledge acquisition and practical ultrasound scanning skills. The secondary outcome is resident stated preference for a curriculum format. This is a prospective case control study. From July 2016 to July 2018 30 PGY-1 Emergency Medicine residents participated. Residents entering in 2016 (n=15) participated in our traditional block 4-week rotation and residents entering in 2017 (n=15) participated in a 28-week longitudinal rotation during Emergency Department rotations. In January of the PGY-1 and July of the PGY-2 year the faculty performed direct observation testing (DOT) of echocardiogram (ECHO) and Focused Assessment of Sonography in Trauma (i.e., FAST) examinations. Residents also completed a demographic and self-assessment survey. Residents in the longitudinal rotation had higher DOT scores at both assessment periods versus the block rotation (June: 13.4 vs 16.7, p= 0.04; July: 17.8 vs 20.7, p=0.02). Knowledge based quiz scores were not significantly different. Eighty-nine percent of all surveyed residents preferred a longitudinal curriculum. Our pilot data suggests a longitudinal POCUS rotation may be superior to the traditional block rotation in developing POCUS skills as illustrated by higher DOT scores for ECHO. This longitudinal approach provided a more consistent POCUS education experience that was preferred by the residents and should be considered when planning a residency curriculum.

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Introduction

Formal training in Point of Care Ultrasound (POCUS) has been a Residency Review Committee requirement for graduates of allopathic emergency medicine (EM) training programs since 2016.[1] POCUS as a component of EM residency training has been increasingly incorporated into residency programs over the past few decades. Published descriptions of these EM ultrasound curricula are few and serve primarily as guidelines. In 1998 Cook and Roepke published a report of the prevalence of established EM residency ultrasound curricula. At that time only one-half of the responding ninety programs had ultrasound curricula.[6] The Council of Emergency Medicine Residency Directors established guidelines in 2008 in order to provide minimum education

standards for EM residency ultrasound training.[7] Presently, all EM residency programs must incorporate POCUS into the curriculum and the Accreditation Council for Graduate Medical Education (ACGME) has defined a sub competency milestone related to EM residency ultrasound training.[1,8] Despite the wide implementation of resident training in ultrasound very little has been written about how that education curriculum should be delivered.

Anecdotal evidence suggests that the primary structure for this training is a single 4-week rotation during intern year. This traditional anesthesia-ultrasound rotation combines a morning experience with anesthesia staff practicing airway management and an afternoon session with EM ultrasound faculty completing didactic and bedside instruction in POCUS. Since 2004, our PGY-1 ultrasound instruction was delivered within this anesthesia-ultrasound block model. Annual feedback from our EM residents has shown recurrent challenges with block curriculum contributing a negative impact on their ultrasound experience. A longitudinal PGY-1 ultrasound rotation was developed to address these deficiencies and compared to our block rotation.

To our knowledge, there is no published data regarding longitudinal-based ultrasound rotations for PGY-1 EM residents. Numerous studies in the medical school literature support longitudinal ultrasound curriculum, however it has yet to be studied in residency programs. 3-5 Boulger et. al.[2] have recently described an advanced track curriculum for EM house staff with a special interest in ultrasound delivered over the course of three years. There have been few studies performed regarding optimal curricula designs. Cartier et al.[9] surveyed residents participating in one particular POCUS course and found residents favored small group format with live demonstrations and, most importantly, hands-on scanning however no details were provided on scheduling.

With residency growth from 10 residents per class in 2006 to 15 residents per class in 2014, our residents and ultrasound faculty have found this block scheduling to be unsatisfactory. The most troublesome aspect of block scheduling has been that at least half of the class receives less structured ultrasound education until the second half of the academic year. Affected residents universally described this as a negative aspect of their training. Residents were also unequally affected by seasonal scheduling factors that reduced the number of supervised bedside scanning shifts such as the December holiday schedule or the summer vacation season. Our resident complement directly contributes to an unequal teaching environment as several blocks must accommodate two residents for the entire rotation. Ultrasound faculty found the block schedule problematic as residents that require additional ultrasound instruction or remediation sometimes are not identified until later in the academic year, when opportunities to schedule additional instructional time are limited. Furthermore, in the block model it is difficult to ensure that residents progress efficiently through the curriculum when each learner may be at a different point.

To address these challenges, we developed a longitudinal ultrasound rotation for our PGY-1 residents. We hypothesized that this longitudinal rotation would optimize content delivery by maintaining instruction content and timing uniform throughout the academic year. Our residents would participate in bedside teaching and complete our didactic curriculum continuously over their entire PGY-1 year. To accomplish this, we assigned shifts during every ED block rotation for the PGY-1 residents to participate in bedside ultrasound instruction with faculty in groups of 2 residents. This allowed for at least the same amount of bedside instruction as the block rotation it replaced. Residents were able to complete our standard online didactic and knowledge assessment evaluations at a self-directed pace (Figure 1). In order to reduce the clinical shift load during the EM block the PGY-1 resident is required to work clinical shifts in the ED during the anesthesia rotation.

Methods

The data presented are the results from a case-control observational study based on our internal QI data collected to assess the efficacy of the longitudinal rotation. Data was collected prospectively from July 2016 to July 2018. All PGY-1 residents were eligible to participate. Participants were informed of the goals of the assessments and general expectations for the rotation at the beginning of each academic year. The study was reviewed and approved by our institutional review board and determined to be exempt.

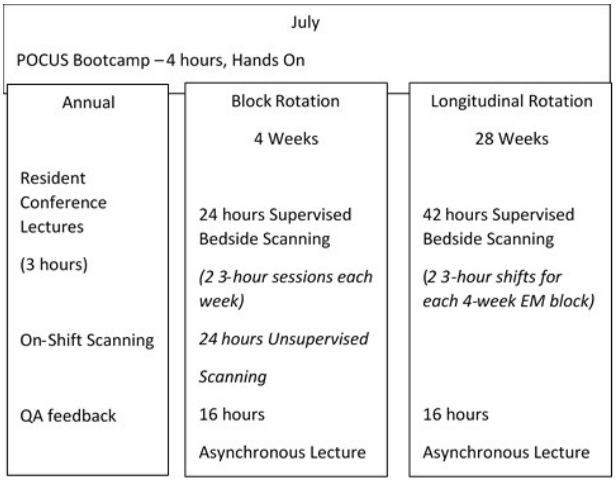

Figure 1. Comparison of Block Curriculum and Longitudinal Curriculum

The primary emergency department setting for our training program is a 120,000 annual visit ED with an on-campus Pediatric ED and an annual US volume of >6000 educational, diagnostic, and procedural studies. Additionally, >95% of faculty are credentialed to perform POCUS examinations. PGY-1 residents entering training in July of 2016 and completing our traditional block rotation serve as the control group. These residents completed 8 three-hour supervised bedside scanning shifts as well as 8 three-hour unsupervised scanning shifts over a 4-week rotation. They were required to complete an online curriculum of lectures and quizzes during the block. PGY-1 residents entering training in July of 2017 and completing the longitudinal ultrasound rotation and comprise the intervention group. The longitudinal rotation included two three-hour supervised ultrasound shifts during each of seven 4-week EM blocks. In quarterly intervals they completed the same assigned ultrasound lectures and quizzes as the control group. Both classes participated in an Introduction to Ultrasound boot camp that took place during the first week of residency with a focus on core examinations including abdominal aorta, cardiac, Focused Assessment with Sonography of Trauma (FAST), biliary ultrasound, and ultrasound guided IV placement.

At the conclusion of each intern ultrasound rotation residents completed a voluntary survey about their ultrasound curriculum experience. The intern Ultrasound Curriculum Evaluation Survey (Appendix 1) was completed by both groups. The survey questions are developed annually by our ultrasound faculty to obtain feedback to prepare for the following year. The goal is to collect data on previous ultrasound training, curriculum preferences, and self-reported knowledge and performance of core EM ultrasound modalities.

To compare the longitudinal curriculum to the block curriculum the groups completed direct-observation testing in January of the PGY-1 and July of the PGY-2 year. During the testing, participants were asked to complete a limited bedside echocardiogram and a FAST examination on the same adult male patient from our standardized patient pool. These modalities were chosen because they are recognized as core scans in the clinical training and practice of EM, encompass thoracic, abdominal and pelvic scanning techniques, and require different probe options. The decision of which ultrasound modalities would be tested was not shared with the residents prior to the testing. It was strictly communicated that they be prepared for testing on any one of the core EM ultrasound modalities.

The resident performance was scored on a standardized direct observation score sheet by two ultrasound faculty with the average score utilized (Appendix 2). The standardized scoring rubric has not been published previously and was initially developed and tested on residents from a different EM residency program in 2014. Feedback from this experience allowed for adjustments to provide an objective scoring assessment of image acquisition. Scores for each standard view ranged from 0 to 3. An image score of 3 was awarded if the learner could demonstrate to the examiner the correct target anatomy (1 point), use the correct axis with complete dimensions of the anatomical structure (1 point), and use of adequate depth, resolution and gain settings (1 point). For example, a score of 0 was given if no identifiable image of target anatomy was obtained such as bladder not visualized in the pelvic FAST view. A score of 1 was given if image showed incorrect axis or did not show entire target region such as inability to visualize left atrium in subxyphoid view. A score of 2 was provided if entire target region visualized with poor resolution and gain or adjustment required, but not performed; for example, an apical four chamber view if

all four chambers visualized with septum in vertical axis, but the image was significantly hypoechoic. A score of 3 was given if excellent view of entire target region with no adjustments in gain or depth required.

The data was analyzed using SAS 9.4 (Cary NC). Comparisons of instructor score ranks were made using Wilcoxon Rank Sum tests. Alpha of < 0.05 was used for statistical significance.

Results

All residents successfully completed the PGY-1 academic year. Twenty-eight residents completed the curriculum survey (13 control, 15 intervention) with a survey response rate of 93.3%. Ultrasound training prior to residency was similar between the groups with 40% and 33% of the control and intervention groups respectively reporting no US education prior to residency and 26% and 20% reporting >20 hours of US education. On a 5-point Likert scale there were no significant differences in self-reported knowledge retention, skill retention, or application specific skills (eFAST, Cardiac, Aorta, US guided needle placement, first trimester ultrasound, and renal ultrasound). The intervention group reported significantly increased skill progress (3.3 v. 4.4, $p = 0.01$) with the longitudinal curriculum and self-reported modality specific skill improvement with the gallbladder examination (2.7 v 3.4, $p = 0.02$).

Table 1. Direct Observation Testing and Quiz Results

	Control	Intervention	P value
N	14	15	
January			
ECHO	6.1 ± 3.2	8.2 ± 1.8	0.04
FAST	7.3 ± 2.2	8.5 ± 1.4	0.09
Total	13.4 ± 4.7	16.7 ± 2.6	0.03
July			
ECHO	8.4 ± 1.8	10.6 ± 1.7	< 0.01
FAST	9.4 ± 0.8	10.1 ± 1.3	0.10
Total	17.8 ± 2.2	20.7 ± 2.4	0.02
Interval Improvement	4.4 ± 4.1	4.0 ± 3.0	1.00

Direct observation ultrasound skills were better among the intervention group than the control group in both January and July (Table 1). In January the mean DOT scores for the intervention group were 8.2 and 8.5 for ECHO and

FAST respectively compared with 6.1 and 7.3 for the control group. On repeat testing in July the DOT scores for the intervention group were 10.6 and 10.1 for ECHO and FAST respectively compared with 8.4 and 9.4 for the control group. Both the ECHO ($P = 0.04$, $P < 0.01$) and total ($P = 0.03$, $P < 0.02$) scores for the intervention group were statistically higher. One resident in the control group (N=15) did not complete the standardized DOT during the July session, therefore data for that resident was not included in the direct observation data analysis.

Performance among applications was unequal, with more improvement seen in cardiac ultrasound skills than in the FAST examination assessment. Although both groups saw similar overall improvement during the year, the higher achievement level among the intervention group persisted in July. Mean quiz scores were similar between the groups (89% v. 87%, $p = 0.13$).

Discussion

Emergency physician use of POCUS in current emergent care is ubiquitous and it is considered a core skill. Presently, all EM residency programs must incorporate POCUS into the curriculum and the ACGME has defined a sub competency milestone related to EM residency ultrasound training.[1,8] Despite the wide implementation of resident training in ultrasound very little has been written about how that education curriculum might be delivered.

There is an emerging body of literature describing medical school longitudinal ultrasound education with hands-on simulation training on models and standardized patients. Several institutions have described positive feedback from medical students with regards to a progressive POCUS curriculum through 4 years of training. Typically, these include web-based lectures, hands on peer instruction and practice, instructor-led demonstrations, and skill assessments.[3-5] The emerging success of these curricula continues to be studied, but suggests similar adoption in

EM training programs, where residents would potentially benefit from longitudinal rather than traditional block ultrasound rotations.

We found that converting the resident experience to a year-long format allowed us to deliver more hours of bedside instruction with the same amount of faculty time. A number of competing factors may affect a program's ability to create similar curricula such as ED clinical responsibilities, required off-service rotations, and the availability of teaching staff. Our rotation structure is innovative because it allows teachers to evaluate the skills of an entire class over the course of a year as a cohesive whole. Any member of the PGY-1 class can easily be compared to the progress of their peers or prior classes to see if they are falling behind in skill acquisition or didactic completion. As a result, poor performers are identified early and have opportunities for remediation. When compared to the traditional block schedule, all residents have equal access to the training needed to participate in POCUS examinations when off-service and on clinical shifts.

Our trainees in the longitudinal rotation equaled or exceeded the performance of their peers over the academic year. We also discovered that the longitudinal rotation facilitates more meaningful supervised scanning time. The importance of supervised, regular scanning sessions cannot be overstated. As discussed by Noble et al.10, there was greater improvement in POCUS knowledge when participating in a proctored ultrasound training rotation, rather than relying on independent scanning for the majority of study acquisition. This curricular intervention promoted frequent, repetitive exposure to core didactic content and continuous skills training. There is considerable literature describing the benefits of spaced learning theory in a wide range of educational applications. Curricular design should utilize spacing and encourage learners to distribute their study time.11 The deployment of this learning strategy in medical education has also been described in recent work. The spacing effect, or "distributed practice" promotes more durable learning with repeated exposure to material over time.[12,13] Dolan et al.[14] demonstrated better knowledge retention and improved care quality at 10 months among residents randomized to a curricular intervention with repeated practice. These findings are consistent with our results in which the intervention group reported significantly increased skill progress and self-reported skill with the gallbladder exam. Observed ultrasound skills were also better among the intervention group than the control group.

Test-enhanced learning theory suggests that tests given often and spaced out in time require effortful recall which promotes retention of clinical knowledge.[15] Distributive spacing and interval testing is associated with better knowledge retention especially when assessments are conducted in retrieval format (ie., short answer) and not recognition format (i.e., multiple choice).[16] Available data to inform optimal spacing intervals is limited. Cepeda et al.[17] suggest optimal timing to be 5-10% of the duration the information is desired to be retained (i.e., monthly testing for a 1-yr retention goal). Our learners underwent direct observational summative testing at regular 6-month intervals. More frequent ultrasound knowledge testing and skills assessment is a focus for future study.

Limitations

This is a small pilot study at a single institution. We would have liked to be able to randomize assignment to the block schedule or the longitudinal schedule but the logistics of scheduling our house staff prevented this. Neither group nor the instructors were blinded to the intervention at any point, potentially introducing bias. Our sample sizes were small and limited to two classes of residents; it is possible that unique individual characteristics had a cofounding effect on the results. Interestingly the control group included two residents who graduated from medical schools offering an integrated ultrasound curriculum. We were unable to perform a power calculation and sample size estimation as there was no prior research in this area on which to base the calculations. It would be ideal to repeat this study as a multi-center study, with the current study serving as the pilot.

The observed clinical examination was performed in a setting that is unlike the general ED setting for POCUS studies and it is possible that the test environment and nature of the test affected the results. We attempted to control for variability in faculty assessment of skills by using two assessors. The unique direct observation scoring rubric utilized has not been published previously. In addition, our results do not

address how trainees may use ultrasound after the PGY-1 year or completion of their residency training, two outcomes which most ultrasound instructors would find important.

A key outcome of the study is the rotation format preference among residents and some may find this measure too subjective. While resident preference by itself should not be the cornerstone of any training program, we believe it is an important consideration when designing curricula. Incorporating resident feedback can help both motivate the resident for the experience and be the stimulus for making change. In our experience, it was the resident dissatisfaction with the block rotation that was an important consideration when we were designing our curricular modification.

Conclusion

Pilot data on the longitudinal POCUS rotation suggest it may be superior to the traditional block rotation in developing and improving ultrasound skill set throughout EM PGY-1 year. This was demonstrated by higher DOT scores for ECHO and combination scores, along with resident preference for the longitudinal curriculum. Although the longitudinal curriculum is associated with scheduling challenges, it provides a consistent POCUS education experience that has the potential to significantly improve the effectiveness of ultrasound training for resident learners.

Disclosures

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Appendix 1. Intern Ultrasound Curriculum Evaluation Survey

What resident graduation year are you?

What ultrasound training experience did you have prior to starting residency?

Throughout your intern EM year how well did you feel that you retained POCUS knowledge?

Throughout intern year how well did you feel you retained POCUS skill set?

Overall, how well did your POCUS education progress throughout intern year?

Based on your experience would you prefer a single block of dedicated ultrasound experience or a longitudinal experience spread throughout intern year?

How strongly does the POCUS education lecture series enhance your POCUS education?

How strongly does the bedside teaching sessions enhance your education?

How would you rate the ultrasound scanning shift scheduling throughout intern year?

Do you feel the biannual direct observation testing motivated you to maintain your POCUS knowledge and skill-set?

Rate your own E-FAST exam performance:

Rate your own cardiac echo exam performance:

Rate your own aorta ultrasound exam performance:

Rate your own ultrasound needle guidance performance:

Rate your own first trimester pregnancy ultrasound performance:

Rate your own gallbladder ultrasound performance:

Rate your own renal ultrasound performance:

Please provide further feedback on your intern POCUS experience:

Appendix 2. Direct Observation Testing Scoring Rubric

Cardiac

*For each core view a score of 0 to 3 was given based upon if the learner could demonstrate: the correct target anatomy (1 point), use the correct axis with complete dimensions of the anatomical structure (1 point), and use of adequate depth, resolution and gain settings (1 point).

Patient position adjustments only if needed to improve views.

View	*Points*				*Comments*
Parasternal long axis	*0*	*1*	*2*	*3*	
Parasternal short axis	*0*	*1*	*2*	*3*	
Apical four-chamber view	*0*	*1*	*2*	*3*	
Sub-xiphoid view	*0*	*1*	*2*	*3*	
IVC view	*0*	*1*	*2*	*3*	

FAST exam

*For each core view a score of 0 to 3 was given based upon if the learner could demonstrate: the correct target anatomy (1 point), use the correct axis with complete dimensions of the anatomical structure (1 point), and use of adequate depth, resolution and gain settings (1 point).

Patient position adjustments only if needed to improve views.

View	Points				Comments
Right upper quadrant (liver-kidney interface)	0	1	2	3	
Left upper quadrant (spleen-kidney interface)	0	1	2	3	
Pelvic view (transverse/ sagittal)	0	1	2	3	
Pelvic view (transverse/ sagittal)	0	1	2	3	
Sub-xiphoid (all 4 chambers visualized)	0	1	2	3	

Case Reports

Stanford Type A Aortic Dissection in COVID-19 Patient — Do the Risks of Surgery Outweigh the Benefits?

Karanpreet K. Dhaliwal, M.S.[1] and Neal D. Kon, M.D.[1]

Abstract

Stanford Type A aortic dissections are a surgical emergency. When a patient with an acute ascending aortic dissection preoperatively tests positive for COVID-19, operative planning becomes more complex. We present a case of a 76-year-old female with a history of hypertension, hyperlipidemia, COPD, and known COVID-exposure who presented to outside hospital with dyspnea and equivocal chest pain. The patient was found to have a Stanford Type A/DeBakey Type II aortic dissection and transferred to our institution for management. After learning of her positive COVID-19 test, we elected to continue with surgical repair due to the high mortality associated with the disease. The procedure was successful and she recovered well postoperatively. In conclusion, a careful risk-benefit analysis must be performed when deciding operative management of a COVID-positive patient. We believe that surgical repair of a Type A aortic dissection in a COVID-positive patient should and can be safely performed

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Introduction

As of August 20th 2020, there have been over 5 million reported cases of and 170,000 deaths from the COVID-19 pandemic.[1] An early study conducted in New York, the first American epicenter of the outbreak, found a significant decline in the number of surgical cases due to acute type A aortic dissection as compared to the prior year.[2] This trend is widely thought to be secondary to public avoidance of health care facilities in an effort to limit possible COVID-19 exposure. However, type A aortic dissections remain an operative emergency and should be treated as such, even in the setting of a COVID-positive patient. Therefore, we present a case of a COVID-positive patient transferred to our institution for operative management of a Stanford type A aortic dissection.

Case Report

A 76-year-old female with a history of poorly controlled hypertension, hyperlipidemia, COPD and current tobacco use of 20 pack-years presented to our hospital as an emergency transfer for operative management of aortic dissection. She presented at outside hospital (OSH) with dyspnea and an equivocal history of chest pain after known COVID-19 exposure. Computed tomography (CT) was performed due to clinical suspicion of pulmonary embolism, and this revealed a Stanford Type A/DeBakey Type II aortic dissection (Figure 1). The patient was transferred to our

hospital, directly to the operating room. She was awake and alert on arrival. During surgical evaluation, our team received a call that the patient had tested positive for COVID-19 at OSH. This brought about the question of whether or not to intervene with shared decision-making between the patient and surgical team. Because of the emergent nature and high mortality of the disease process, we elected to proceed with operation. The heart was exposed via median sternotomy per usual. The ascending aorta and proximal aortic arch were dilated, with grossly normal coronary anatomy. Intraoperative transesophageal echocardiography (TEE) demonstrated left ventricular ejection fraction (LVEF) > 55% without significant valvular abnormalities. Aortic repair was performed under deep hypothermic circulatory arrest (DHCA) using a 24x8 mm Gelweave graft (Terumo Aortic). A large dissection flap was noted on the anterolateral surface of the ascending aorta (Figure 2). Also, chronic thrombotic formation was noted above the non-coronary sinus just above the sinotubular junction. The diseased segment and thrombus were removed. The times for cardiopulmonary bypass, aortic cross clamp, and DHCA were 71, 46 and 13 minutes, respectively. Post-procedure TEE demonstrated LVEF > 55% with no significant valvular abnormalities. The patient tolerated the procedure well and was transported to the intensive care unit (ICU). The patient was extubated on post-operative day (POD) 0. No further COVID-19 testing was performed at our institution. She remained hemodynamically stable for her hospital stay. Given her COVID-19 infection and history of COPD, she was treated with a 10-day course of Dexamethasone. Chest tube and pacemaker wires were discontinued on POD4. She was discharged on POD5 in good condition.

Discussion

Stanford type A aortic dissection remains a highly lethal pathology with mortality historically described as 1-3% per hour in the first 48 hours.[3] Recent guidelines in light of the COVID-19 pandemic define an ascending aortic dissection as an emergency which should be treated as such.[4] However, several considerations must be made when the patient is COVID-positive. These include the presence of subclinical or clinical pulmonary manifestations, increased operative risk, personal protective equipment availability, and risk of exposure. Further, reports continue to emerge regarding the broad cardiac manifestations of COVID-19 which range from heart failure and cardiogenic and vasoplegic shock to myocarditis and coronary disease.[5] Therefore, the choice to proceed with operative management is difficult – it requires shared decision making and a careful analysis of patient

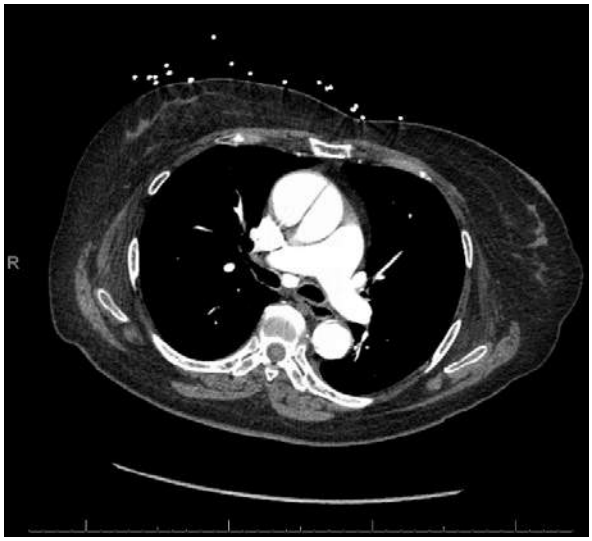

Figure 1. CT performed for clinical suspicion of pulmonary embolism that demonstrated a Stanford Type A/DeBakey Type II aortic dissection.

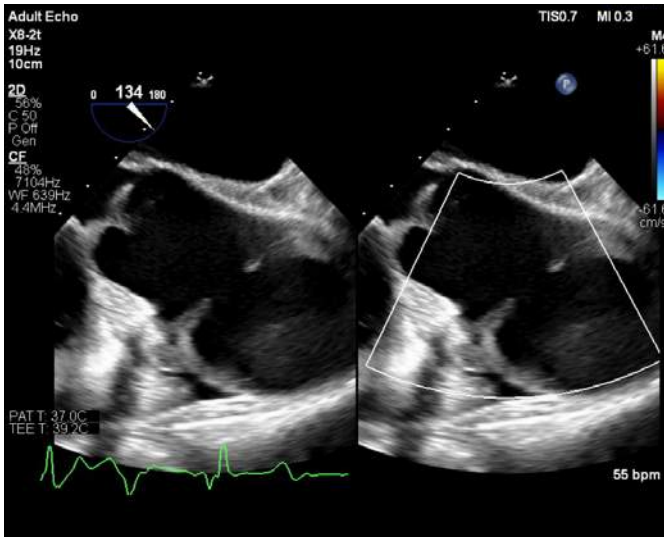

Figure 2. TEE notable for large dissection flap was noted on the anterolateral surface of the ascending aorta.

comorbidities and of the surgical risks versus potential benefits. If surgery poses less risk than the natural history of the disease process, the team should elect to proceed with definitive operative management. In our opinion, there are seldom any situations in which case a COVID-related illness would warrant the delay of surgical intervention for acute ascending aortic dissection.

While safety and infection control are the principal concern during aerosolizing procedures such as tracheal intubation in COVID-19 patients, cardiovascular manifestations of the disease require consideration during surgical planning. A broad range of cardiac manifestations can result from COVID-19 infection. These may be caused by an excessive inflammatory response which leads to hypercoagulation, the release of proinflammatory cytokines and direct virus-mediated myocardial injury.[6-7] Anesthesia itself may induce an inflammatory response in surgical patients, and this response is exaggerated in cardiac surgery which necessitates cardiopulmonary bypass.[6] Further, because COVID-19 can cause severe and sudden cardiopulmonary collapse, the team must be prepared to engage in ECMO services when appropriate.[8]

There have been few case reports detailing operative management of type A aortic dissections in COVID-positive patients.[9-12] An early case was described in which a patient underwent successful aortic repair but was found to have worsening respiratory status in the ICU and subsequently diagnosed with COVID-19; this patient passed away within one week of positive testing.[6] Other reports have described successful management in acute ascending aortic dissections, though these patients did not necessarily have positive testing prior to procedure. Our case describes a successfully managed cardiovascular surgical emergency in a known COVID-19 patient without major morbidity and mortality. Further, no one exposed from this case/patient has developed symptoms.

Therefore, we conclude that surgical repair of a type A aortic dissection in a COVID-positive patient can be safe and should be performed in certain instances emergently due to the high mortality associated with non-operative treatment.

Disclosures

No financial support given. The authors declare no conflicts of interest. IRB approval was not required for this case report. Oral consent was obtained.

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Case Reports

Hypocalcemia Presenting as a Code Stroke: A Case Report

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Abstract

Cerebrovascular accidents (CVA) present in many ways, and many other pathologies mimic CVAs. This case details a 43-year-old female who presented as a "Code Stroke" due to loss of function of her upper extremity, facial asymmetry, and speech difficulties. After detailed work up, she was found to have hypocalcemia. Her symptoms were muscular tetany interpreted as inability to use her arm, facial changes and slurred speech. Anchoring on the initial data presented, she was assessed for a perfusion abnormality. After careful review of this case, the final diagnosis of hypocalcemia was made. Having heard the description of the patient by emergency medical services (EMS), anchoring bias caused the providers to focus in on CVA and not necessarily consider other causes in the differential. Providers must broaden the differential regardless of how classic the presentation in order to not miss diagnoses and to provide timely and accurate intervention.

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Introduction

"Code Stroke" is a common emergency medical services (EMS) alert in most Emergency Departments (ED), typically indicating that a patient will be arriving to the ED with an acute neurologic deficit that is within a time frame for intervention.[1] Many diseases can mimic stroke symptoms, such as metabolic derangements[2], intoxications, complex migraines[3], post-ictal states of seizures[4], intracranial lesions, and psychiatric disorders. An emergency provider must simultaneously determine, in a timely manner, if there is an acute vascular occlusion or hemorrhage upon which one can intervene or if there is another cause of the patient's presentation.

This process often begins with the EMS providers' report, and based on that information, the ED provider determines whether to activate a "Code Stroke." It is not always possible to get a full history from the patient or family for many reasons: patient condition, unknown circumstances, waxing and waning symptoms, and rapidity of the evaluation. Cognitive errors often occur in emergent, fast paced decision making, especially when the "diagnosis" fits. Anchoring early based on limited or misinterpreted information can delay or cause inappropriate treatment. For example, in this case the patient's symptoms were not caused by the occlusion of a cerebral artery. This patient had hypocalcemia, causing neuromuscular irritability. This metabolic disturbance is capable of causing symptoms that could easily be mistaken or interpreted as stroke-like symptoms.

This case presentation will highlight 1) the cognitive errors that occurred as well as what biases were present and 2) discuss the final diagnosis of hypocalcemia.

Case Report

The patient is a 43-year-old female with a history of hypertension, hyperlipidemia, type 2 diabetes, anxiety, and depression. Her family called EMS for onset of speech trouble, inability to use her left upper extremity, and facial changes. Emergency medical services personnel reported inability to use the left arm, facial asymmetry and slurred speech, as well as tachypnea and a very anxious state. Further history taking on arrival noted that she had gradual onset of symptoms after waking up 2 hours prior. Symptoms included bilateral arm tingling and weakness that eventually progressed to the inability to use the left arm, facial droop, and slurred speech. The symptoms had resolved just before arrival.

Computed tomography (CT) imaging with CT angiography and perfusion studies were unremarkable, point of care glucose was within normal limits, and the patient had a normal neurologic exam with no subjective symptoms upon arrival. While the patient was waiting for her evaluation to be completed, she had another episode of speech difficulty and inability to use her left upper extremity similar to her previous episode. She had return of her symptoms due to the blood pressure cuff inflating, causing tetany, not flaccidity, in that arm and tapping on her facial nerve produced the facial asymmetry due to tetany, not flaccidity of the muscles. An ionized calcium was sent based on the clinical findings, and it was 0.73 (1.00-1.30mM/L). Other laboratory results revealed normal renal and liver function but with a few other electrolyte abnormalities. Her potassium was 3.1 (3.5-5.2mM/L), Magnesium was 0.7 (1.5-2.5mg/dL), and calcium was 7.1 (8.5-10.2mg/dL). The patient's ECG showed a prolonged QT interval but was otherwise unremarkable. The patient's electrolytes were replaced, and she was admitted to the Internal Medicine service. All symptoms resolved with correction of her electrolyte abnormalities.

Discussion

This case illustrates two issues. The first issue is how anchoring and other cognitive biases lead to a belief that the symptoms were from a stroke instead of developing a broad differential for the symptoms. Although it is of paramount importance to evaluate for a stroke rapidly, a detailed history in this case showed that the symptoms were not actually consistent with stroke. The second issue is how a constellation of symptoms known to be caused by hypocalcemia presented as transient stroke-like symptoms. A literature search for similar presentations was only successful in finding reports of how electrolyte derangements predispose patients with cerebrovascular accident (CVA) to worsening outcomes.

The road to the final diagnosis was filled with many common biases that physicians face routinely. EMS teams gather key information and provide life-saving treatments while transporting patients. However, anchoring too much on the EMS report will inhibit the provider's ability to develop a wider differential diagnosis list. Anchoring is prematurely keying in on a single diagnosis based on a few important features in the initial presentation. It is easy to hear "cannot use arm," "slurred speech," and "facial asymmetry," and assume stroke. Noting the gradual onset of symptoms which were not timed together, the anxiety with bilateral hand and leg tingling, as well as defining what "cannot use arm" meant would have directed this patient encounter in a different manner, or at least widened the differential. This also might be considered a form of diagnosis momentum in which a diagnostic label has been assigned and it is difficult to view the presentation in another light.

Availability bias is an assumption that the disease that most readily comes to mind is the most relevant. Certainly, stroke is a more common presentation than hypocalcemia for this constellation of symptoms. Keeping a wide differential will help prevent this. Confirmation bias is searching for certain findings that support your original diagnosis, often ignoring findings that do not. Employing an objective way of working through a differential by comparing and contrasting all the

findings (signs and symptoms) to the disease process on the differential will help prevent this bias. Finally, premature closure is acceptance of a disease as the diagnosis before it has been fully proven.[5] Once the diagnosis of stroke was presumed, all differential thinking stopped and only the workup of stroke continued until it was negative.

Other key learning points involve this patient's pathology of hypocalcemia. Serum calcium is found in several forms: free (or ionized), bound to proteins, and bound to other organic and inorganic compounds. The majority of calcium is in its free, metabolically active form. The level is primarily regulated by parathyroid hormone (PTH) and Vitamin D.[6] Symptoms of hypocalcemia usually do not occur until the calcium level is below 8 mg/dl. Common causes of hypocalcemia include hypoalbuminemia, hypoparathyroidism, hypomagnesemia, and Vitamin D deficiency. Neuromuscular symptoms may occur, including numbness or tingling of the peri-oral area or digits, muscle cramps that may lead to spasm, voice changes due to laryngospasm, and dysphagia.

Hypocalcemia itself will cause muscle tetany secondary to changes in the membrane potential of the axons of nerve cells. Free calcium affects muscles by binding and allowing the actin myosin chains of skeletal muscle to interact and cause contraction.[7] Hypocalcemia affects the nerves by putting them in a hyperexcitable state. When calcium drops low enough, the sodium channels become activated, the resting potential is much closer to zero, as opposed to very negative. This makes the cells spontaneously discharge and can cause a prolonged contraction or tetany.[8] The Trousseau's sign elicited in this case, blood pressure cuff inflating causing carpal spasm, was cause by decreased blood flow to the extremity, further worsening neuron excitability and inappropriate firing of motor signals.[9] Chvostek Sign, the facial tetany, is caused by external stimulation of the facial nerve.[10] These findings can also be exacerbated by hyperventilation.[11] Hyperventilation, in this case in the setting of anxiety, can further induce the symptoms of hypocalcemia. Respiratory alkalosis secondary to the hyperventilation raises blood pH. Elevated blood pH increases the binding of free calcium to blood proteins thus transiently lowering ionized calcium.[12] This patient had a baseline hypocalcemia, so the hyperventilation served to exacerbate her symptoms.

Diagnosis: Hypocalcemia is diagnosed with laboratory findings and corresponding appropriate exam findings. One can test the serum calcium level as well as the free metabolically active calcium level. Free calcium is often part of a rapid point of care test that can be obtained very quickly. Diagnosing the cause of the hypocalcemia would involve investigating the causes (as listed above).

Treatment: Treatment for hypocalcemia involves initial treatment with calcium supplementation to reverse symptoms and then management of the underlying disease responsible. Correcting other electrolyte derangements may also correct the hypocalcemia when they help maintain calcium homeostasis, such as magnesium. For severe cases, boluses of calcium gluconate/chloride can be given intravenously. If needed to maintain acceptable free calcium levels (~1mM/L) one can chose to start a calcium infusion and then admission to a monitored setting with continuous telemetry is recommended. Finally, physicians should beware of venous injury and dysrhythmia as potential consequences of uncontrolled or rapid infusion of calcium.[13]

Conclusion

Certainly this case describes a less common mimic for presentation of stroke like symptoms — hypocalcemia causing neuromuscular excitability resulting in tetany. This caused facial spasm during panic and hyperventilation, which was communicated as facial changes and speech difficulty. Inability to use the arm was due to spasm at rest and with the BP cuff inflating. Electrolyte disturbances can have varying effects on the body; in particular calcium has the ability to manifest neuromuscular symptoms. Anchoring, diagnosis momentum, availability bias, and premature closure were cognitive errors and biases that affected the initial evaluation of the patient. Awareness of biases and initiation of cognitive de-biasing strategies may help prevent their influence on patient care.

Disclosures

No financial support given. Authors report no conflicts of interest.

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Case Reports

Clinically Significant Progression of Median Arcuate Ligament Syndrome

Katelyn Madigan, M.D.[1], Chi-Cheng Huang, M.D.[2]

Abstract

Median arcuate ligament syndrome (MALS) is a poorly understood condition characterized by compression of the celiac artery by a fibrous ligament connecting the diaphragmatic crura. Severe compression on the celiac artery can contribute to abdominal pain, commonly chronic and located in the epigastric region. This clinical vignette describes a 54-year-old woman with a history of sleeve gastrectomy and provoked pulmonary embolism who presented to an outside hospital for recurrent chronic abdominal pain of unclear etiology. On arrival at Wake Forest, the patient was found to have severe lactic acidosis and later imaging findings concerning for MALS. The patient underwent further evaluation with a vascular doppler ultrasound to assess respiratory variation, which aided in evaluating the severity of the impingement on the celiac artery. Given the severity of her debility, the patient was medically optimized before scheduled surgery for the treatment of her suspected MALS.

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Introduction

The median arcuate ligament is commonly cephalad to the origin of the celiac artery, although it is estimated to cross over a proximal portion of the celiac artery in 10-25% of patients (as depicted in Figure 1).[1] Severe stenosis of the celiac artery is predicted to affect 1% of patients with imaging findings of MALS.[1] In these cases, patients often develop collateralization between the celiac artery and the superior mesenteric artery (SMA) to alleviate the risk for visceral ischemia.[2] Unfortunately, these collateral vessels can often induce shunting of blood away from the SMA to these smaller vessels. This form of "vascular steal syndrome" reduces vital blood supply to the gastrointestinal organs that may go unrecognized and lead to chronic ischemia.[3] This clinical vignette describes a patient with severe lactic acidosis in the context of unexplained chronic abdominal pain, nausea, vomiting, and syncopal symptoms and was found to have a clinical evaluation consistent with MALS.

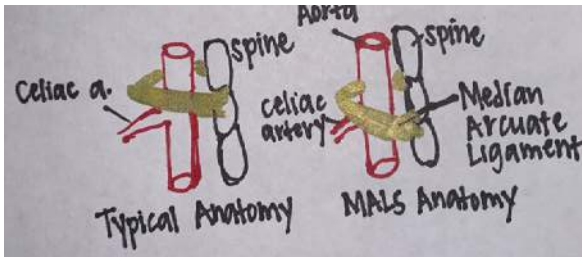

Figure 1. Anatomic comparison of typical anatomy and compression in median arcuate ligament syndrome.

Case Report

A 54-year-old female with a history of sleeve gastrectomy and provoked pulmonary embolism presented to an outside hospital with severe epigastric abdominal pain, nausea, and syncopal symptoms. On arrival at Wake Forest Baptist Medical Center, the patient was afebrile, tachycardic to 121, and normotensive. Labs were notable for lactic acid of 9.8 mmol/L, bicarbonate 12 mmol/L, and anion gap 19 mmol/L. Physical exam upon admission was significant for diffuse epigastric tenderness with radiating numbness reported to her knees bilaterally. The chronic waxing and waning achy upper abdominal pain was most severe post-prandially, with no other well-defined aggravating or alleviating factors from history gathered on positional changes, medications, or nutritional status. Associated symptoms included nausea, vomiting, syncopal symptoms, and intermittent loose, non-watery, non-bloody diarrhea. The patient was aggressively hydrated with lactated ringer solution with slow improvement in her lactic acidosis, yet had persistence of epigastric pain. The patient's report of persistent leg discomfort led to concern for a vascular etiology and subsequently computed tomography angiography (CTA) revealed impingement superior to the celiac trunk. With concern for MALS, duplex vascular ultrasound was performed to evaluate respiratory variation on arterial imaging (Figure 2). Multiple collateral arteries were noted with turbulence noted in the area of the proximal celiac artery. This patient's velocities of 247 cm/sec. These velocities reduce to 86 cm/sec with inspiration. Our patient exhibited compression of the celiac artery accentuated during expiration as the median arcuate ligament moved cranially, which was relieved during inspiration. In coordination with

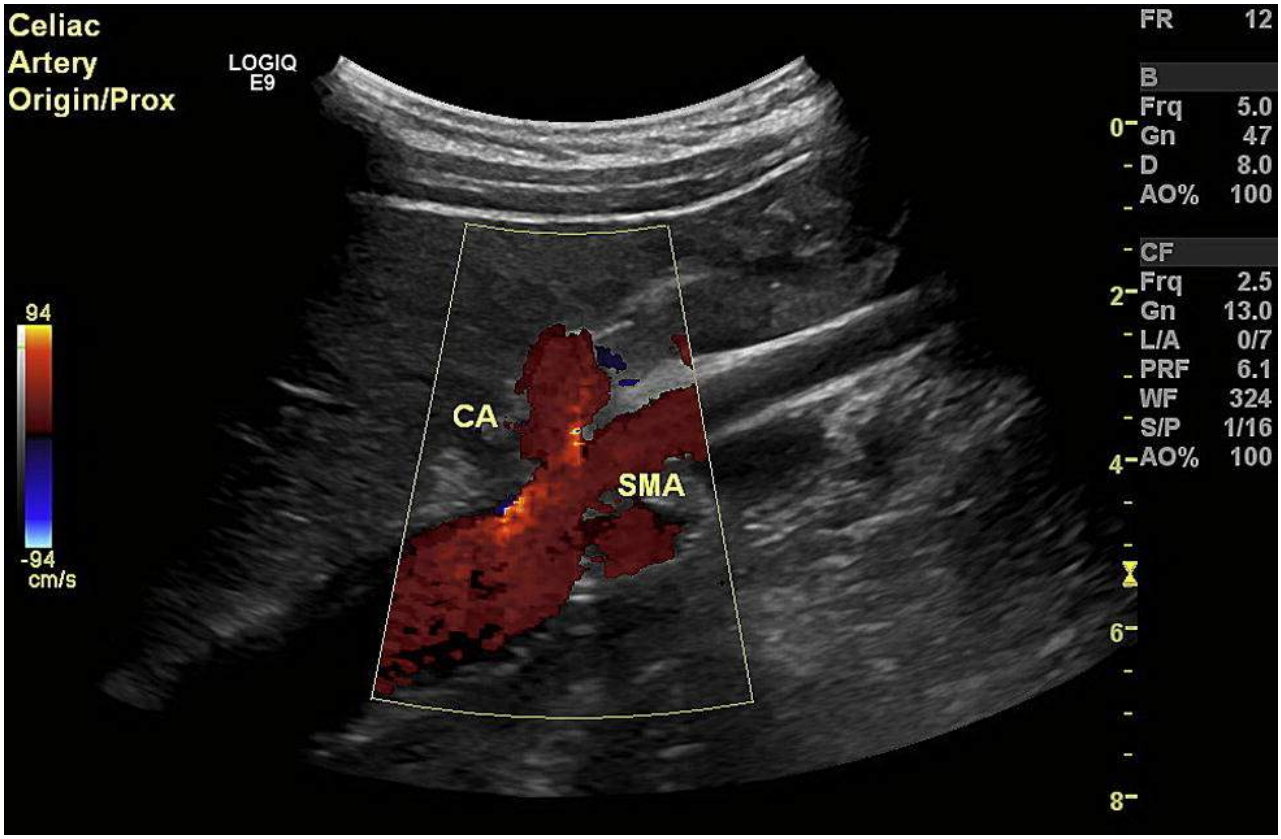

Figure 2. Color duplex of the common origin of the celiac and superior mesenteric artery from the aorta.

the care team, the patient had continual supplementation for her numerous vitamin and mineral deficiencies, including total parenteral nutrition to optimize the patient before later surgical intervention for the treatment of MALS.

Discussion

This case outlines a complex patient presenting with chronic abdominal pain who required urgent medical care in treatment evaluation of her severe lactic acidosis, which may have been induced by chronic ischemia secondary to MALS. The broad differential for unspecified abdominal pain without concerns on CT imaging includes, but is not limited to: arterial or venous thrombosis, arterial embolism, vasospasm, or extrinsic compression. This patient completed 6 months of anticoagulation for previous pulmonary embolism and was no longer taking anticoagulation. Recognition of MALS as a potential etiology in the diagnostic evaluation of abdominal pain is of growing clinical importance. Increased bariatric surgery incidence leads to a higher prevalence of patients with rapid weight loss: a major risk factor for the development of MALS.[4,5] The celiac nerve plexus impingement in MALS can lead to a broad distribution of abdominal pain, such as further hepatic, gastric, splenic, and pancreatic plexuses. Lipshutz et al. first described MALS in 1917 with only a few later cases documented, such as in 1963 and 1965;[4,6] interestingly, epidemiologic review of cases revealed higher incidence in females (4:1), notably between the ages of 40 and 60 years old.[1]

However, challenges in diagnosis include the nonspecific symptoms seen in the triad commonly associated with MALS: epigastric pain, weight loss, and abdominal bruit.[2,3] A review per Jimenez found abdominal bruit present in only 35% of patients, with auscultation often difficult due to body habitus.[3] Custati et. al found the most predominant symptoms of nausea and vomiting (56% of patients), with other symptoms less prevalent.[3] Thorough history and physical exam should precede medical evaluation with blood work, imaging including abdominal ultrasound, with later CTA or doppler ultrasound aid in the diagnosis.[1] Doppler vascular ultrasound to evaluate respiratory variation can help determine if compression is clinically significant and may be contributing to abdominal pain.[7] Our patient did not have imaging prior to sleeve gastrectomy to discern if she was at increased risk for post-operative complications. Rarely used and more invasive additional testing include gastric tonometry (to determine arterial PaCO2 levels before and after exercise) or a percutaneous celiac ganglion nerve block (may be diagnostic as well as therapeutic).[3]

Disclosures

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Case Reports

Intentional Use of Carbapenem to Treat Valproic Acid Overdose: New Fad or Flawed Treatment

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Introduction

Valproic acid (VPA) overdose most commonly presents with gradations of central nervous system (CNS) depression, but in the most severe forms can lead to fatal cerebral edema and coma.[1-3] Typical management includes supportive therapy and consideration of carnitine supplementation or dialysis. We present a case of massive VPA overdose that was managed using a combination of standard of care therapies with an unusual therapy, meropenem. We then discuss the risks and benefits of using meropenem for VPA toxicity.

Case Report

A 28-year-old male (58 kg) with a history of seizure disorder status post ventriculoperitoneal (VP) shunt, depression, anxiety, atrial fibrillation, and prior overdose presented to the Emergency Department (ED) due to altered mental status and possible overdose. He was found unresponsive at his homeless shelter with empty bottles of VPA and levetiracetam. Review of the patient's medical record found that he had also previously been prescribed fluoxetine (20 mg QD) and gabapentin (300 mg TID).

The patient presented unresponsive with a GCS of 8. His initial vitals were blood pressure 124/81 mmHg, heart rate 116 beats/minute, respiratory rate 19 respirations/minute, oxygen saturation 100%, and glucose 76 mg/dL. He had an elevated ammonia concentration of 99 µmol/L (ref range 6-47 µmol/L), lactic acid concentration of 3.5 mmol/L (ref range 0.9-1.7 mmol/L), and VPA concentration of 984 mcg/mL (reference range 50-100 mcg/mL). Other pertinent labs included a normal comprehensive metabolic panel (CMP), undetectable acetaminophen and salicylate concentrations, a negative urine drug screen, and an ethanol concentration of 16 mg/dL (ref range <10 mg/dL). His chest x-ray and CT head were negative for significant findings. His electrocardiogram revealed no significant abnormalities.

The patient was intubated due to CNS depression and inability to maintain his airway. Poison Control, the ED pharmacy team, the medical intensive care unit (MICU), and nephrology were consulted. He received 50 g activated charcoal via nasogastric tube (NG), 2 g meropenem intravenously (IV), 6,300 g L-carnitine (IV), and emergent hemodialysis.

He required norepinephrine due to progressively worsening hypotension that persisted after being intubated. He had mean arterial pressures (MAP) ranging from

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48-60. He received a bolus of D10 via IV. Approximately 40 minutes after this hypotensive episode, his vitals stabilized with MAP consistently greater than 100. He was given 2 mg of IV lorazepam and 2 mg of IV midazolam due to seizures. Sixteen hours after his presentation, his VPA concentration was therapeutic at 62 mcg/mL and at 19 hours he was extubated. Upon discharge from the MICU, he was transferred to the psychiatry service.

Discussion

Valproic acid acid is a branched chain carboxylic acid used for treating seizures, mania, bipolar disorder, and migraines. Reported mechanisms of action include blocking voltage gated sodium channels, increasing brain GABA concentrations, and inhibiting T-type calcium channels.[4] Patients who ingest more than 200 mg/kg and/or have serum concentrations greater than 180 mcg/mL are at risk for CNS effects and metabolic derangements.[4,5] Significant CNS depression can lead to respiratory depression and hypoventilation, potentially requiring intubation and mechanical ventilation.[5,6] Other life-threatening complications from VPA overdose include cerebral edema and hemorrhagic pancreatitis, although these occur infrequently.[6] Metabolic derangements associated with VPA overdose include anion gap metabolic acidosis, hypernatremia, hypocalcemia, and hyperammonemia.[5,7,8]

VPA is metabolized via three primary methods, including glucuronidation, beta-oxidation in the mitochondria, and cytochrome P450. Glucuronidation is the primary route, accounting for nearly 50% of total metabolism.[9] In-vitro studies of human liver microsomes have identified a host of enzymes that are responsible for glucuronidation of VPA, thereby enabling its excretion by converting it to its water soluble form (VPA-G).[9,10] VPA is a fatty acid, and therefore undergoes similar metabolism as free fatty acid (FFA). This occurs in the mitochondria via beta-oxidation and accounts for roughly 40% of VPA metabolism. The remaining 10% of VPA metabolism is through the CYP-450 system and is considered a minor pathway. Some of the mitochondrial metabolites generated in this process are hepatotoxic.[9]

VPA decreases the concentration of carnitine by increasing urine excretion, decreasing tubular reabsorption, reducing endogenous synthesis, inhibiting carnitine transporters into the cell, and inhibiting carnitine storage.[11,12] With reduced carnitine available for fatty acid metabolism, hyperammonemia ensues.[13] This occurs because carnitine is an essential cofactor in the metabolism of long-chain fatty acids. Specifically, carnitine plays a key role in transporting fatty acids to the mitochondrial matrix, where beta-oxidation occurs. Therefore, reduced carnitine availability will lead to an accumulation of unmetabolized fatty acids that disrupt the urea cycle.[13] Prior research has established an association between decreased carnitine levels and VPA associated hyperammonemia.[14,15]

Traditional overdose therapies include gastrointestinal decontamination, supplementation with carnitine, and consideration for dialysis. Researchers theorize that supplementing depleted carnitine levels may improve VPA associated encephalopathy (VPE) by mitigating hyperammonemia.[11] This is believed to occur by restoring the carnitine transport chain needed for beta-oxidation of VPA and thereby reducing the accumulation of cytosolic fatty acids that interferes with the urea cycle.[11] Bohles et al. identified 14 patients with hyperammonemia who were undergoing treatment with VPA. They had ammonia concentrations greater than 50 µmol/L. They were treated with L-carnitine 500 mg/m^2 twice daily and experienced normalization of serum ammonia.[16] A 2010 systematic review concluded that it is reasonable to use L-carnitine in patients with VPA overdose and CNS effects.[17]

As for the use of hemodialysis in treating VPA-induced hyperammonemia, this mechanism has been well researched by the Extracorporeal Treatment in Poisoning (EXTRIP) workgroup and these studies have found that VPA is moderately dialyzable.[18,19] A systematic review of 79 articles found that patients with VPA-induced hyperammonemia experienced clinical improvement in regard to mental status, respiratory depression, and hemodynamics.[19] In recent years, the interaction of carbapenem antibiotics and VPA serum concentration has been explored.[20-23] While this research provided the foundation for using carbapenems for VPA overdose, it is also important to consider the associated risks. As such, we reviewed the available evidence to better understand the benefits and risks of this emerging therapy.

Carbapenem antibiotics, specifically meropenem, are a novel treatment for VPA overdose as they lower VPA concentration.[20-23] This occurs because carbapenems inhibit acylpeptide hydrolase. Acylpeptide hydrolase, located in the hepatocytes, removes the glucuronic acid group from VPA-G. In doing so, VPA-G is converted back into its active form, VPA, thus reducing its excretion in urine and bile.[20,24] Without this enzyme, the recycling process is inhibited and more rapid elimination occurs. Wu et al. recorded VPA concentrations before and after carbapenem administration. These patients were receiving maintenance anti-epileptic treatment primarily for seizure prevention (79% of patients) and antibiotic therapy for pneumonia (54%). This study found that VPA concentrations were subtherapeutic in 90% of subjects within 24 hours.[23] In another study, researchers analyzed VPA levels of patients receiving both VPA and meropenem and saw a reduction of > 70% of VPA levels compared to values before initiating meropenem.[21] Another retrospective analysis of 36 patients found that the mean reduction of serum VPA levels was > 80% after starting meropenem.[22] These findings suggest that carbapenem antibiotics may play a role in the management of VPA overdose.

Given that L-carnitine, hemodialysis, and supportive care demonstrated adequate results in treating VPA overdose, the addition of meropenem requires careful consideration as there are associated risks.[1,11,17,19,25] The primary concern with the use of meropenem in serum VPA concentration reduction revolves around the prolonged inhibition of acylpeptide hydrolase.[26] This inhibition increases the risk of seizure-like activity in patients on VPA for anti-epileptic purposes, as the therapeutic serum levels are not maintained due to decreased recycling of the VPA.[23,27] As a result of the reduction in serum VPA concentration after carbapenem administration, one study found that 48% of patients being treated for epilepsy with maintenance VPA experienced increased seizure frequency.[27]

This study demonstrated the potential effect of carbapenem on VPA concentration and the resulting clinical outcome. Therefore, providers must weigh these risks against the existing treatment modalities that have demonstrated effectiveness. On one hand, meropenem has been shown to reduce VPA concentration by 50-80% within 24-48 hours.[21,23,27] However, when hemodialysis alone was used, valproic serum half-life was markedly reduced, and clinical improvement was rapid.[19] These studies support the theory that hemodialysis is an effective treatment, thus raising the question of the need for an intervention which may have uncertain consequences.

In the case being reviewed above, the patient had reduction of VPA levels from 984 mcg/mL to 109 mcg/mL over 7 hours after 1 course of hemodialysis and 2 g of meropenem. During this time, the patient's clinical status improved. However, it is uncertain which treatment method contributed more to the changes in the patient's status. With this in mind, it is important to consider the risk profile of each intervention. There are risks to the use of hemodialysis in all patients, including blood pressure changes, metabolic derangements, access site complications, and several others. Although after reviewing the EXTRIP guidelines, there were no specific risks for hemodialysis in VPA overdose patients.[19] As such, hemodialysis may be considered the safer option. Conversely, there is data to support the risk of precipitating seizure-activity with the use of carbapenems.

In summary, this case raised the question of whether the addition of meropenem to an already proven VPA overdose treatment regimen was worth the ongoing risk of precipitating seizure activity. While studies have not been done to specifically examine this question, it is a valuable consideration when determining the best course of treatment for a patient.

Conclusion

Emergency Medicine physicians must be able to diagnose and manage toxicologic emergencies, such as VPA overdose. Additionally, they must be able to lead and collaborate with multidisciplinary teams in order to weigh the risks and benefits of therapies, including L-carnitine, meropenem, and emergent hemodialysis for VPA overdose. Future research is needed to better understand the role, if any, of using meropenem for VPA overdose among patients with a known seizure disorder.

Disclosures

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Case Reports

E-Cigarette, or Vaping, Product Use-Associated Lung Injury: A Diagnosis Not to 'MIS-C'

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Abstract

In the past year, two novel diagnoses with similar clinical manifestations have been characterized: E-cigarette, or vaping, product use-associated lung injury (EVALI) and multisystem inflammatory syndrome in children (MIS-C). Throughout Fall 2019, popular media and scientific journals rapidly published articles regarding EVALI as cases were identified across the Unites States. With the acceleration of the COVID-19 pandemic in late Winter and early Spring 2020, popular and scientific focus shifted quickly to disseminating information regarding sequelae of COVID-19, including MIS-C. Changing community disease prevalence, increasing popular media focus, and a high volume of scientific publications all contribute to clinicians readily considering a novel diagnosis. EVALI and MIS-C are novel diagnoses with similar presentations and, though there is substantial cultural focus on the COVID-19 pandemic, when evaluating a pediatric patient with pulmonary or respiratory pathology, clinicians should include both illnesses in their differential diagnosis. This case report outlines the challenge of differentiating between EVALI and MIS-C in the context of the COVID-19 pandemic.

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Case Report

A 17-year-old male was transferred to the pediatric emergency department (ED) from an outside hospital due to fever, shortness of breath, nausea, vomiting and diarrhea.

Four days prior to presentation, the patient accidentally inhaled "a bunch of" motor fumes; he then reported shortness of breath, chest tightness, headache, and subjective fever. His mother noted that he was breathing fast and took his temperature, which was reported to be 101.4 °F. Over the next few days, the patient remained febrile and developed abdominal pain, nausea, vomiting, and diarrhea. The patient and his mother reported that one episode of emesis may have contained blood, but they were unsure.

The patient's mother contacted his pediatrician, who obtained a chest x-ray, which showed bilateral consolidations. The patient was tested for COVID-19 (negative) and influenza (negative). At the pediatrician's office, oxygen saturation was reportedly 76% on room air, and he was transferred to a local ED.

In the outside hospital ED, the patient had an oxygen saturation of 88% and was placed on 4L of oxygen via nasal cannula. His D-dimer was significantly elevated, and a chest computed tomography angiography (CTA) was obtained to assess for pulmonary emboli. The CTA showed "no acute pulmonary emboli" and "extensive bilateral airspace disease consistent with severe pneumonia." Due to the concern

for severe pneumonia, the patient was started on empiric antibiotics (ceftriaxone, vancomycin, azithromycin) and transferred to the children's hospital ED.

In the pediatric ED, the patient was documented as "ill-appearing" on physical exam and required 4L oxygen via nasal cannula to maintain an oxygen saturation of 95%. He temporarily required a non-rebreather mask while in the ED.

Per departmental protocols, ED staff ordered in-house COVID-19 testing (Simplexa COVID-19 Direct Assay), COVID-19 antibody testing, and lab work indicated by the local MIS-C protocol. Laboratory testing showed elevated ESR, CRP, D-Dimer, and fibrinogen. PT and PTT were both elevated. Transferrin was decreased. A white blood cell count was elevated and demonstrated neutrophilia and lymphopenia (Table 1). The chest x-ray obtained in the ED (Figure 1) showed widespread airspace and interstitial opacities, concerning for severe viral or atypical pneumonia.

Past medical history was significant for a seizure disorder, asthma, chronic back pain, anxiety, and attention deficit hyperactivity disorder. Home medications at presentation included escitalopram oxalate, levetiracetam, and tizanidine.

Two and a half months prior to presentation for this acute concern, the patient was also transferred to the pediatric ED from an outside hospital due to fever, shortness of breath, nausea and vomiting. A COVID-19 test and Respiratory Virus Panel (RVP) were both negative at that time. The patient was treated for atypical pneumonia and discharged after 1 day.

Social history was notable for vaping both marijuana and tobacco, cocaine use, and hydrocodone use, but no intravenous drug use.

The patient was admitted to the general pediatrics floor due to respiratory distress and requirement for supplemental oxygen to maintain goal SpO2 >90%. The admitting team ordered a Respiratory Virus Panel, Gastrointestinal Pathogen Panel, blood culture, sputum bacterial culture, sputum fungal culture, and sputum acid fast culture. All were negative or showed no growth.

Infectious Diseases (ID) was consulted to assist in evaluation for possible MIS-C or atypical etiologies of pneumonia. Per ID, the patient was asked about any specific history of exposure to agitated soil (e.g. dirt biking, mud runs, spelunking, excavation), which he did endorse. Consequently,

Table 1. Laboratory Values as of patient's initial presentation, especially notable for elevated D-Dimer, ESR, CRP and neutrophil count

Blood/Serum Test	Value	Reference Range
WBC	13.1 x 103/uL	4.8 - 10.8 x 103/uL
Neutrophil	94%	40% -60%
Lymphocyte	4%	20%-40%
Eosinophil	0%	0%-6%
Neutrophil abs	12.3x 103/uL	1.6 - 7.3 x 103/uL
Lymphocyte abs	0.5 x 103/uL	1.0 - 5.1 x 103/uL
Ferritin	265 ng/mL	30-300 ng/mL
Transferrin	144 mg/dL	212 - 360 mg/dL
CRP	384.8 mg/L	<5.0 mg/L
ESR	110 mm/hr	0 - 20 mm/hr
D-Dimer	3960 ng/mL	190 - 500 ng/mL
PT	14.3 sec	8.9 - 12.1 sec
PTT	36.2 sec	<=30.0 sec
INR	1.34	<5.00

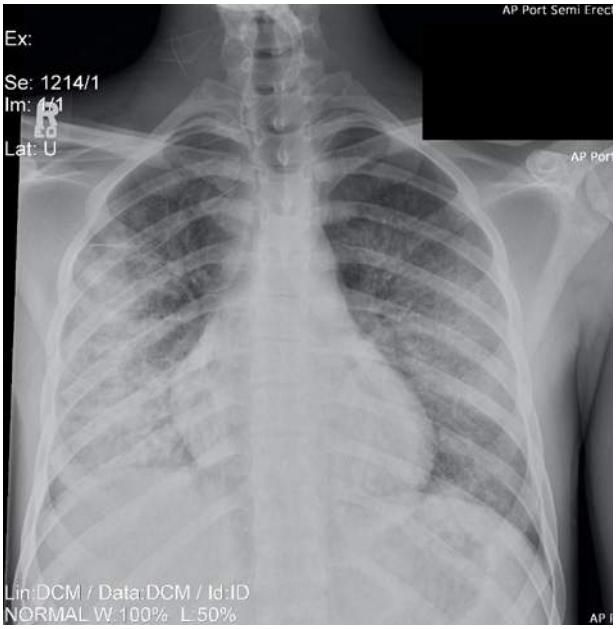

Figure 1. Figure 1. Chest X-Ray taken in the Emergency Department on initial patient presentation.

infection with Histoplasma or Blastomyces were added to the differential diagnosis. Due to the combination of respiratory and gastrointestinal symptoms on presentation, Legionella pneumonia was also considered. Urine antigen tests for Histoplasma, Blastomyces, Legionella, and Streptococcus pneumoniae were sent to an outside lab for evaluation. The patient was empirically treated with vancomycin, azithromycin, and ceftriaxone before ultimately being discharged on oral doxycycline for a 7 day total antibiotic treatment of community acquired atypical pneumonia.

Pulmonology was consulted to evaluate a possible vaping-related lung injury due to the patient's social history of vaping both nicotine products and marijuana. The consulting pulmonologist agreed that EVALI should be included on the differential. A repeat chest x-ray was recommended if the patient showed worsening clinical status. The consultant also noted that patients with EVALI can deteriorate rapidly, so close monitoring of respiratory function was a critical part to treatment.

Rheumatology was consulted as part of the institutional protocol for evaluation of possible MIS-C. Additionally, there was concern for a potential underlying rheumatologic condition due to the patient's multisystem involvement and reported chronic back pain. Rheumatology ordered laboratory tests inpatient, and planned to follow up with the patient after discharge regarding results.

Cardiology was not consulted on this case in the context of a noncontributory echocardiogram on the day of admission.

The patient clinically improved both objectively and subjectively over his 4 days in the hospital. This clinical improvement, amidst ongoing concern for possible infectious etiology, was the justification for not treating with steroids, even with his concerning initial presentation. The patient was gradually weaned from supplemental oxygen and was discharged after maintaining an SpO_2 > 92% on room air for 24 hours. By discharge, inflammatory markers normalized; neutrophilia and lymphopenia resolved. The patient reported resolution of gastrointestinal symptoms and significant improvement in respiratory symptoms.

All tests for infectious causes were negative, elevating MIS-C and EVALI as the two most likely diagnoses. Due to two negative COVID-19 tests, a negative COVID-19 antibody test, and clinical improvement without MIS-C interventions (e.g. IV Ig, steroids), MIS-C was felt to be less likely. EVALI was the best explanation for the patient's presentation and hospital course. The patient was counseled by multiple providers on both the general pediatrics and pulmonology teams on the risks of vaping. He was encouraged to quit vaping and informed there was no level of vape use that could be considered safe. Additionally, the patient was offered the option to speak with a psychiatrist, which he declined. The patient was discharged with scheduled follow-up appointments with pulmonology, rheumatology, and his PCP.

Discussion

EVALI and MIS-C are non-infectious causes of acute lung injury that have been brought to the attention of the medical community in recent months. EVALI is defined as respiratory failure within 90 days of electronic cigarette use with no evidence of infection or alternate causes of respiratory failure.[1] Pulmonary infiltrates are noted on chest imaging, and the vast majority of patients (95%) present with cough, chest pain, and shortness of breath.[2] Other common symptoms (85%) are fever, chills, and weight loss; slightly less common (77%) are abdominal pain, nausea, vomiting, and diarrhea.[2] It is also notable that a significant proportion of patients (86%) reported using electronic cigarettes containing THC.[3] In addition to containing THC, these cartridges commonly incorporate vitamin E acetate, an agent that has been linked to EVALI.[1,2] Epidemiologically, most patients are white males younger than 35, although most of the deaths (25%, compared to 2% of total cases) occur in patients older than 65.[3]

The lack of diagnostic criteria for EVALI makes it a diagnosis of exclusion.[4] The CDC has created an algorithm that outlines the necessary workup to rule out other causes and make the final diagnosis.[4] In summary, the patient needs to have a history of electronic cigarette use, symptoms consistent with those of other EVALI patients, and no apparent infectious etiology present upon evaluation. Infectious workup for suspected EVALI is relatively exhaustive—if a case is severe enough to warrant inpatient admission, the CDC recommends common respiratory evaluations (influenza testing, chest X-rays, etc.) as well as more involved analyses (such as

bronchoalveolar lavage or CT scan even with a normal chest X-ray). Bronchoalveolar lavage specimens often show a cell count with neutrophilic predominance, although lipid-laden macrophages and eosinophils have also been seen.[1,2] Surgical lung biopsies reveal a wide range of pathologies from mild and nonspecific inflammation to interstitial and peribronchiolar granulomatous pneumonitis.[2] Patients who are diagnosed with EVALI tend to have leukocytosis with neutrophilic predominance as well as elevated inflammatory markers, but these are relatively nonspecific findings.[1] Radiographic findings are more conclusive, with four discrete radiographic patterns identified in EVALI: acute eosinophilic pneumonia, diffuse alveolar damage, organizing pneumonia, and lipoid pneumonia.[1] The most common findings on chest X-ray and CT are bilateral ground-glass infiltrates with basilar predominance and sub-pleural sparing.[1] In concordance with the radiographic findings, EVALI's clinical course involves progressive hypoxemia progressing to acute respiratory distress syndrome (ARDS) in 22% of patients.[2] The significance of the histopathological and radiographic findings with respect to disease course and severity has not been ascertained. Consequently, the clinical course has been the most commonly used marker to track patient status. Patients with oxygen saturations greater than 89% on room air are deemed safe to discharge.[2] If a patient presents with an oxygen saturation above 95% or minimal respiratory distress, outpatient management of EVALI can be considered.[4]

Outpatient management of EVALI is largely supportive, with emphasis placed on discontinuation of electronic cigarette use and continued monitoring for infectious etiology. Although all infectious etiologies must be ruled out, patients may be treated with antibiotics before the diagnosis of EVALI is made.[2] The influenza vaccine should also be administered if not previously received.[4]

For patients with a severe disease course, the current proposed treatment for EVALI is respiratory support and administration of systemic glucocorticoids. With this treatment protocol, clinical improvement was documented in 65% of cases.[1] No guidelines for dosage or course have been established. Unfortunately, steroids must be used with caution before the diagnosis has been established.[4] Steroid treatment can worsen respiratory infections and, in the case of a fungal infection, may cause significant morbidity. For the patient discussed in this case, glucocorticoids were not administered due to ongoing concern for possible infectious etiologies and improvement in the patient's clinical appearance.

The wide spectrum of EVALI presentation and its relative lack of characterization unfortunately make diagnosis and treatment guidelines difficult to establish. Awareness of the range of clinical, laboratory, and imaging findings are of the utmost importance in assessing and treating patients with suspected EVALI.

MIS-C is even more novel than EVALI, with the diagnosis only recently described during the current SARS-CoV-2 pandemic. Unfortunately, as with EVALI, the diagnostic criteria for MIS-C are poorly characterized. The diagnosis is made based off the following case definition from the Centers for Disease Control and Prevention.[5]

- An individual aged < 21 years
- Clinical criteria,
  - A minimum 24-h history of subjective or objective fever ≥ 38.0 °C, AND
  - Severe illness necessitating hospitalization, AND
  - Two or more organ systems affected
- Laboratory evidence of inflammation,
  - One or more of the following: an elevated CRP, ESR, fibrinogen, procalcitonin, D-dimer, ferritin, LDH, or IL-6; elevated neutrophils or reduced lymphocytes; low albumin
- Laboratory or epidemiologic evidence of SARS-CoV-2 infection,
  - Positive SARS-CoV-2 testing by RT-PCR, serology, or antigen OR
  - COVID-19 exposure within 4 weeks prior to onset of symptoms
- And, no alternative diagnosis.

Notable parallels have been drawn between MIS-C and Kawasaki disease, but MIS-C can also present as a pneumonitis-like process lacking the hallmark vasculitis features of Kawasaki disease. A study of 186 patients found Kawasaki-like features in 40% of cases and an overall mortality rate of 2%.[6] Systems commonly involved were gastrointestinal (92%), cardiovascular (80%), hematologic (76%), mucocutaneous (74%), and respiratory (70%). Although many children with MIS-C have respiratory involvement, a primary concern for

these patients is development of cardiac dysfunction during their illness. Pulmonary infiltrates seen on chest X-ray in suspected MIS-C are often consistent with acute left heart failure, although cases of MIS-C-related ARDS have also been reported.[5,6] In the series examined by Nakra et al., 50% of patients presented with cardiovascular shock necessitating vasopressor or inotropic support.[5] Similar to Kawasaki disease, this disease process raises concern for coronary artery aneurysm, so cardiac monitoring is emphasized for MIS-C patients. In contrast, pulmonary dysfunction is the primary concern with EVALI, so respiratory support and monitoring is more critical to treatment than cardiac monitoring.

Treatment for MIS-C is also analogous to treatment for Kawasaki disease. The mainstays of treatment for Kawasaki disease are intravenous immunoglobulin (IVIG) therapy and aspirin. MIS-C has demonstrated responsiveness to IVIG therapy, but compared to Kawasaki disease, MIS-C is more likely to require adjunctive steroid therapy.[7] In addition to IVIG and steroids, IL-1 and IL-6 antagonists, have reported efficacy in MIS-C treatment.[6,7] The hospital course for MIS-C patients tends to be fairly intense, with a median duration of hospitalization at 7 days; in one series of inpatients, 80% received intensive care, 20% required mechanical ventilation, and 48% received vasoactive support.[6] Epidemiologically, MIS-C seems to predominantly affect adolescents and children older than 5 years.[6] In addition, reports from the UK and France suggest increased incidence in patients of Afro-Caribbean descent, whereas no Kawasaki-like MIS-C cases have been reported from Asian countries as of 4 June 2020.[7] This may imply a genetic predisposition to the development and severity of MIS-C, although this hypothesis will require more research before definitive conclusions are drawn.

Of note for this case, MIS-C remained a part of the differential diagnosis even in the context of multiple negative PCR COVID tests. This patient presented relatively early during the COVID-19 pandemic when little was known about the disease course for MIS-C. It was unclear if MIS-C occurred only during active infection that could be detected by PCR, or if it occurred in the absence of PCR detected infection. Consequently, MIS-C was considered in a patient with negative PCR tests.

Clinicians' relative unfamiliarity with EVALI and MIS-C make diagnosis and treatment challenging, especially as their presentations and patient populations often overlap. In addition, both syndromes are diagnoses of exclusion, requiring extensive workup before either diagnosis is finalized. This case outlined points of differentiation between the two syndromes with an emphasis on the hallmark subjective and objective elements of the clinical course that may inform clinical decision-making.

Conclusion

There is a wide differential for adolescent patients presenting with systemic inflammatory symptoms. The prevalence of SARS-CoV-2 virus should not preclude the consideration of other novel etiologies, notably in this case EVALI. Both MIS-C and EVALI may have overlapping features on presentation including shortness of breath and gastrointestinal symptoms. The course and treatment for MIS-C and EVALI, however, can vary considerably. As such, awareness of the distinguishing factors in each condition as well as thorough history-taking and further workup are necessary to ensure patients are treated appropriately. EVALI and MIS-C, as relatively new phenomena, both require further investigation to establish definitive case criteria and treatment guidelines.

Disclosures

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Case Reports

Thirteen Syndrome: A Case Report and Review of the Literature

Benjamin P. Rardin, M.D.[1], Kamran Ahmed, M.D.[1], and Timothy Martin, M.D.[1]

Introduction

Horizontal gaze abnormalities have a variety of etiologies, including lesions to the abducens nucleus/paramedian pontine reticular formation (PPRF), medial longitudinal fasciculus (MLF), or a combination of the abducens nucleus/PPRF and MLF. The latter was initially described as a one-and-a-half syndrome by Dr. Fisher and comes from the gaze palsy representing "1" and the internuclear ophthalmoplegia representing "1/2"[1]. A unilateral lesion to the PPRF and/or abducens nucleus results in impaired ipsilateral gaze and preserved contralateral gaze while the one-and-a-half-syndrome results in impaired ipsilateral gaze plus impaired adduction of the ipsilateral eye with contralateral gaze. Abduction of the contralateral eye is preserved but exhibits nystagmus[1,2]. Additionally, there are a spectrum of related disorders that involve damage to additional cranial nerve nuclei/fascicles/nerves, such as cranial nerves 5, 7, and/or 8 in addition to a gaze palsy or one and a half syndrome. A curious method of nomenclature has arisen building on the "one and a half syndrome", such as "eight-and-a-half syndrome", so named because the affected patient exhibited a one and a half syndrome in addition to cranial nerve seven palsy (1.5 + 7 = 8.5). This system of naming, which has far more teaching value than practical application, has resulted in a number of reported syndromes, and we add to this list by reporting a patient with "13 syndrome".

Case Report

A 72-year-old right-hand dominant woman with a history of poorly controlled hypertension presented to Wake Forest Eye Center as a referral for a chief complaint of intermittent, horizontal, binocular diplopia. At presentation, she was found to have left upper and lower facial weakness. Her ocular alignment showed esotropia of the left eye in primary gaze, and she preferred a left head turn. She had normal right gaze but had a left gaze palsy with neither eye being able to move past midline (Figure 1). No ptosis was present, and pupils were normal without an afferent pupillary defect. In the left eye, the patient had 13 mm lagophthalmos with gentle closure which decreased to 8 mm with forced closure and a positive Bell's phenomenon. The patient had marked decreased corneal sensitivity as well as significant punctate epithelial erosions of only the left eye due to exposure keratopathy but no pain or irritation. Additionally, she had subtle decrease to soft touch and pinprick of the left upper and lower face compared to the right. She first noticed diplopic symptoms three months prior when being admitted to the hospital for a left pontine intraparenchymal hemorrhage with intraventricular extension secondary to malignant hypertension requiring IV nicardipine drip. CT and MRI showed a left dorsal pontine hemorrhage

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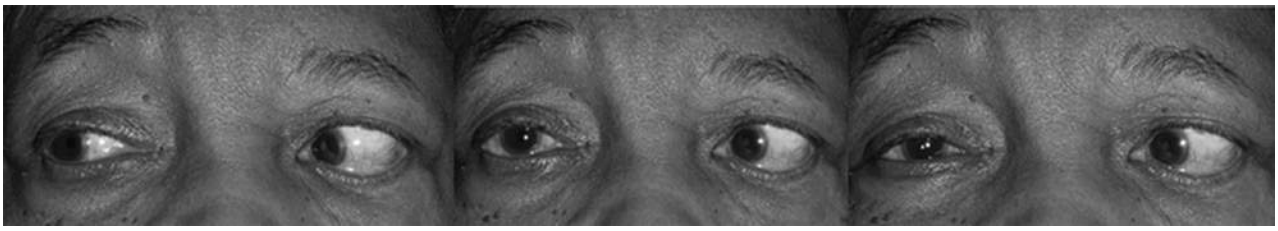

Figure 1a-c. Patient showing left facial weakness with attempted gaze from L to R (a): normal right gaze (b): primary gaze showing left esotropia (c): attempted left gaze showing left gaze palsy.

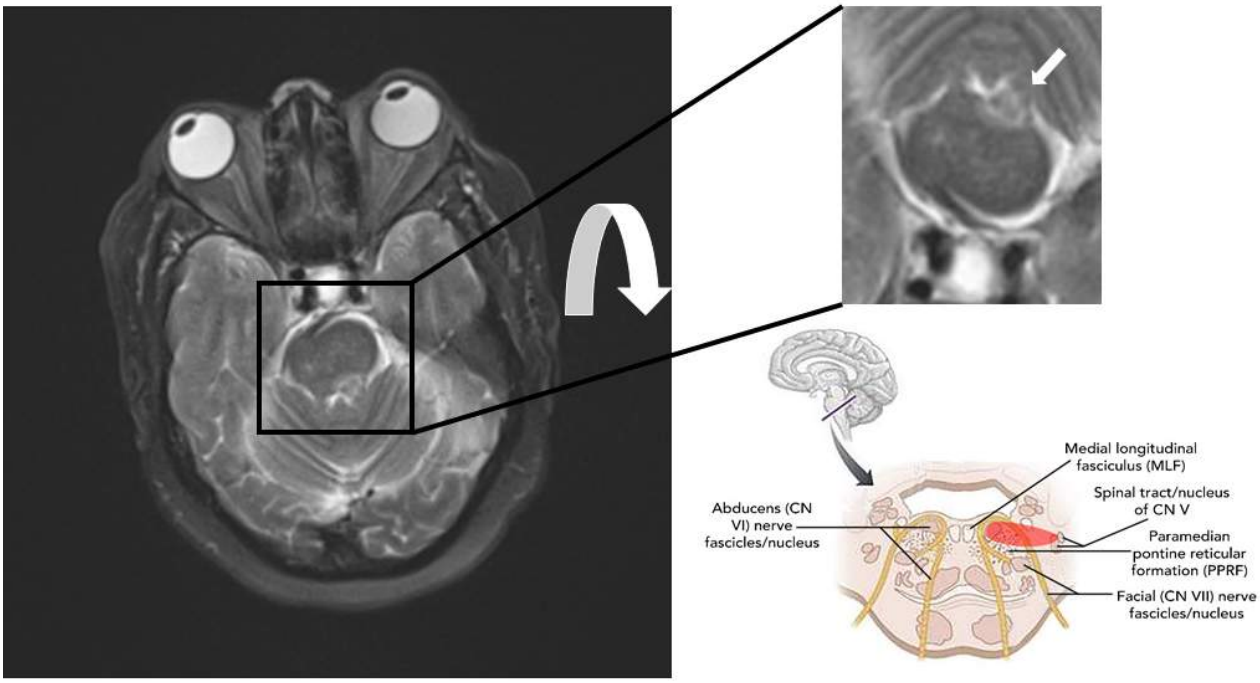

Figure 2. MRI Brain T2 Axial demonstrating left dorsal pontine hemorrhage with comparison brainstem anatomy figure highlighting correspondence of MRI hyperintensity (white arrow) with known locations of CN 5, CN 6 and CN 7. Redrawn with permission from Dr. Timothy Martin, MD.

with mild surrounding vasogenic edema, without underlying enhancement (Figure 2). The MRI also displayed extensive chronic microvascular ischemic changes and evidence of prior microhemorrhages in a distribution consistent with hypertensive etiology.

Discussion

Past case reports have described the combination of one-and-a-half syndrome with additional deficits arising from pontine lesions. These include eight-and-a-half syndrome (1 ½ syndrome + CN7 palsy)[2], nine syndrome (1 ½ syndrome + CN7 palsy + ipsilateral ataxia)[2,3], and thirteen-and-a-half syndrome (1 ½ syndrome + CN7 palsy + CN5 palsy)[2,4] among others[2,5]. Most commonly, these disorders are due to pontine infarction and hemorrhage, but can also be attributed to demyelinating processes, infection, or tumors[2,5].

This case is unique in that it is believed to be the first described incidence of what we term thirteen syndrome: the combination of left gaze palsy (representing "1"), CN5 palsy (corneal and facial sensation defect), and CN7 palsy (upper and lower facial weakness). There has been a recent reported

case of eight-syndrome consisting of ipsilateral gaze palsy and facial nerve palsy[5], but none demonstrating the addition of a trigeminal nerve palsy as seen in this case. As such, this case expands the known spectrum of pontine-cranial nerve disorders to include thirteen syndrome.

This case also serves as an important lesson in the utility of a comprehensive neurologic and ophthalmologic physical exam paired in the setting of suspected CNS lesions. When considering the patient's positive exam findings of a left gaze palsy, facial weakness, and decreased corneal and facial sensation, a working knowledge of neuroanatomy localizes the patient's lesion to the left dorsal pontine region demonstrated on MRI. Furthermore, this example of a patient with unilateral neurologic deficits also serves as an important teaching point regarding the clinical manifestations and physical exam findings of brainstem lesions. It is traditionally taught that the hallmark of brainstem lesions are 'crossed findings', or sensory/motor deficits that manifest on one side of the face in conjunction with deficits occurring on the contralateral body. This example of thirteen syndrome serves as an important example of an exception to this rule when comparing the patient's MRI findings with known locations of brainstem tracts. With this patient's lesion localizing to the dorsal pons, it notably spares the spinothalamic and medial lemniscus tracts (located just ventral to the lesion) as well as the corticospinal tract (located even further ventral to the lesion)[6]. In sparing these long tracts within the brainstem, this case serves as a useful example of the fact that the lack of crossed findings on neurologic exam does not preclude brainstem pathology.

Disclosures

No financial support given. The authors report no conflicts of interest.

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Case Reports

An Atypical Presentation of NMOSD in a Young Adult with Visual Hallucinations

Syndey Thomas, B.A.[1], George R. Tamula, M.D.[2], Emily Pharr M.D.[2]

Case Report

A previously healthy 18-year-old African American female presented to an outside hospital (OSH) with a one week history of acute-onset visual hallucinations, abnormal behavior, and malaise. Urine toxicology screen was negative, and lumbar puncture demonstrated leukocytes of 72 x 10*3/μL with a monocyte predominance, protein of 70 mg/dL, and glucose of 50 mg/dL. She was admitted to the OSH with concern for infectious meningoencephalitis and was started on ceftriaxone, vancomycin, and acyclovir. These were discontinued following negative cultures and viral PCR studies. During her hospitalization, she was noted to have left hemiparesis. MRI Brain demonstrated increased T2/fluid attenuated inversion recovery (FLAIR) signal within the bilateral thalami extending to the right aspect of the midbrain, hypothalamus, and bilateral occipital lobes without diffusion restriction (Figures 1-2). While specific imaging of the orbits was not obtained, there was no optic nerve enhancement on the contrasted MRI Brain. Magnetic resonance venography (MRV) was negative for venous sinus thrombus and routine electroencephalogram (EEG) was normal. She was transferred to our hospital for further evaluation.

On our initial examination, the patient's eyes opened to voice. She intermittently followed commands but did not verbalize. Her cranial nerves were intact and reflexes were unremarkable. She had weakness in her left upper extremity (4/5) and left lower extremity (3/5) with full strength in the right hemi-body.

Continuous video EEG revealed mild, diffuse encephalopathy. Her symptoms, MRI findings, and negative infectious workup suggested an autoimmune process, such as anti-NMDA-receptor (NMDAR) encephalitis. Although the risk of exacerbating psychosis was considered, IV steroids (methylprednisolone 1,000 mg) was ultimately administered[1]. The patient became persistently tachycardic in spite of treatment. Cardiology evaluation favored tachycardia secondary to an underlying central nervous system (CNS) process. The patient later developed bradycardia (heart rate approximately 30 bpm); repeat transthoracic echocardiogram (TTE) was significant for global hypokinesis. The patient became hypothermic with a rectal temperature of 88°F and worsened encephalopathy. She now no longer followed commands. She was transferred to the intensive care unit (ICU).

The acute change in mentation and autonomic instability suggested a systemic process. Given the lack of response to steroids, plasmapheresis was initiated. CT chest/abdomen/pelvis with contrast was unremarkable for lesions suggestive of malignancy, including ovarian teratoma.

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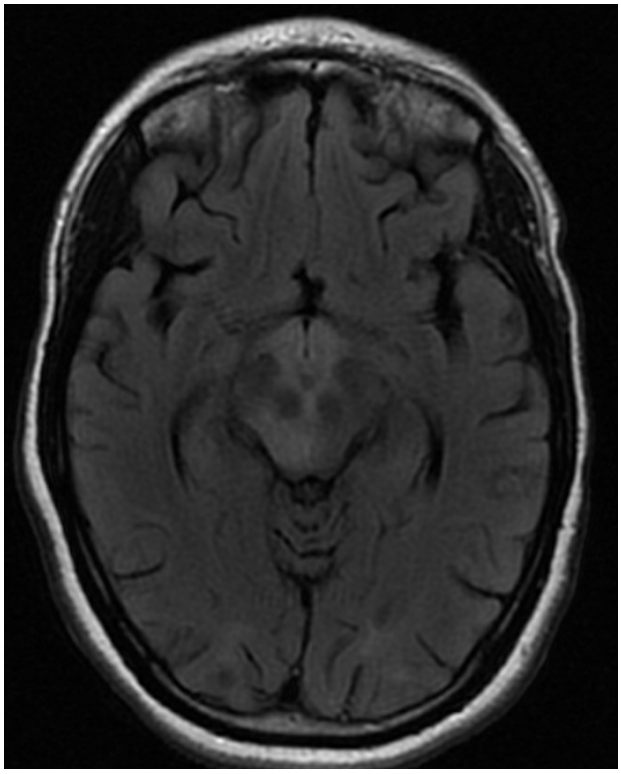

Figure 1. T2/FLAIR hyperintense signals within the right midbrain, hypothalamus, and subcortical bilateral occipital lobes.

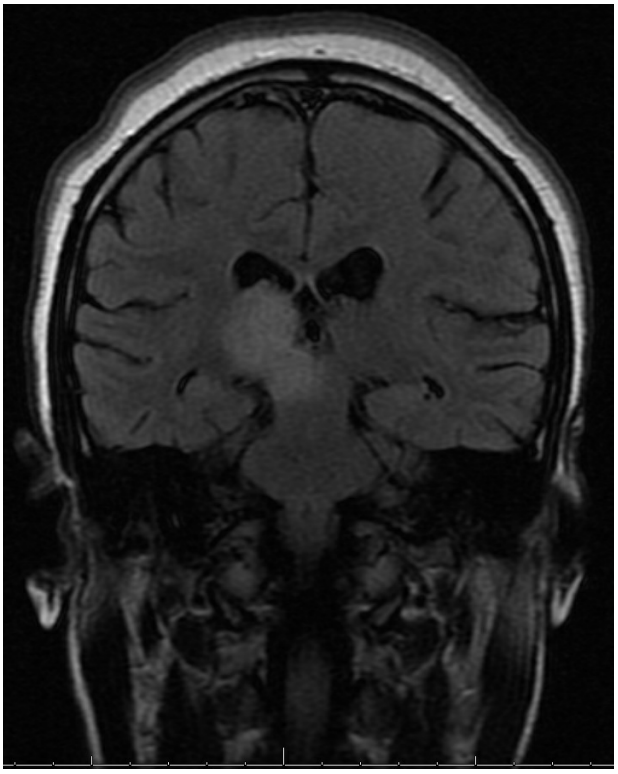

Figure 2. Thalamic and hypothalamic T2/FLAIR hyperintense signals.

Throughout her six pheresis treatments, the patient's neurologic exam, particularly mentation, waxed and waned. She slowly improved to answering questions with short phrases. Her autoimmune panel, including anti-NMDAR antibodies, returned negative. Twelve days after admission, her serum anti-AQP4 antibodies resulted positive (via Mayo Clinic Laboratories NMO/AQP4-IgG Fluorescence-Activated Cell Sorting [FACS] Assay). Given these findings, the patient was diagnosed with neuromyelitis optica spectrum disorder (NMOSD). She was started on prednisone and received Rituximab (1,000 mg).

She eventually began to move her left upper extremity to commands but still was unable to move her left lower extremity. MRI of the cervical and thoracic spine was negative for demyelinating lesions. She received a second dose of rituximab two weeks later and was transferred to an inpatient rehabilitation facility. At three-month follow up, her mother reported she was nearly back to baseline, able to converse and perform ADLs independently. Repeat MRI at five-months demonstrated some resolution of the T2/FLAIR signal changes (Figure 3).

Differential Diagnosis

In a young female with acute encephalopathy and visual hallucinations, one must consider schizophrenia, drug abuse, seizures, anti-NMDA-receptor (NMDAR) encephalitis, and Hashimoto's encephalopathy[2]. With an MRI demonstrating T2 hyperintensities extending into the hypothalamus, one should consider neuromyelitis optica spectrum disorder (NMOSD), a chronic inflammatory central nervous system disorder characterized by immune-mediated demyelination that primarily affects the optic nerves and spinal cord.

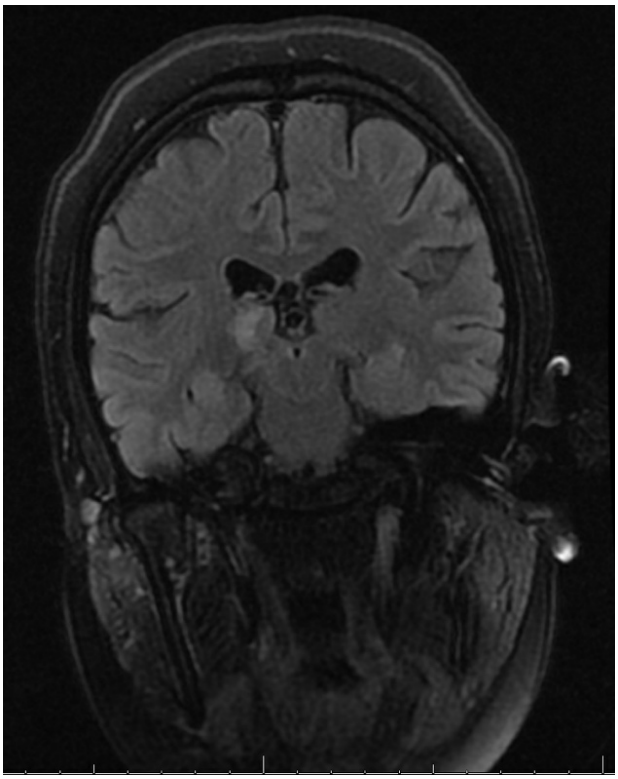

Figure 3. Five-month T2 FLAIR partial resolution post-rituximab infusion.

The history was not suggestive of underlying psychiatric co-morbidities or emotional stressors. Drug abuse was less likely due to negative toxicology. Neither the routine EEG nor the continuous video EEG monitoring demonstrated seizures. After initial evaluation, one could obtain a thyroperoxidase (TPO), thyroglobulin (TG), and anti-myelin oligodendrocyte (MOG), anti-Aquaporin-4 (AQP4) antibodies, and an autoimmune panel including Sjogren's syndrome, systemic lupus erythematosus (SLE), and anti-NMDAR antibodies.

Discussion

The International Consensus Diagnostic Criteria (ICDC) defines six core clinical characteristics of NMOSD: optic neuritis, acute myelitis, area postrema syndrome, acute brainstem syndrome, symptomatic narcolepsy or acute diencephalic clinical syndrome with NMOSD-typical diencephalic MRI lesions, and symptomatic cerebral syndrome with NMOSD-typical brain lesions. With the absence of transverse myelitis and optic neuritis, this case demonstrates a very atypical presentation[3].

This patient's chief complaint was visual hallucinations. Few reported cases have demonstrated symptoms of psychosis in patients with NMOSD[4]. Two previous case reports have noted hallucinations in patients with established NMOSD but to our knowledge, this is the first to describe visual hallucinations at presentation[5]. The MRI showed bilateral occipital lobe involvement, which could have contributed to her visual hallucinations.

Apart from enhancement of the optic nerves, a MRI brain is normal at presentation in up to 84% of patients with NMO[6]. In this patient, bilateral thalamic and hypothalamic involvement was present on admission with clinical signs of hypothalamic instability throughout her admission. In a retrospective analysis, hypothalamic-axis involvement in anti-AQP4 antibody-positive NMO was frequently observed, with bilateral involvement in 90% of these patients[7]. This is in accordance with the high expressions of AQP4 channels in this area. Another study speculated that the proximity of the hypothalamic region to the visual pathways typically involved in NMO may explain the occurrence of hypothalamic lesions and dysfunction in some patients[8].

Anti-AQP4 antibodies demonstrate a 94-99% specificity for NMOSD[9]. A link between NMOSD with anti-AQP4 antibody positivity and autoimmune connective tissue disorders has been previously documented[3]. An array of autoimmune testing for conditions such as SLE, Sjogren's syndrome, and rheumatoid arthritis were obtained in our patient and should be assessed in NMOSD patients.

This patient demonstrated a CSF pleocytosis. This has been previously reported in NMOSD, though it is a nonspecific finding, as one study demonstrated only 50% of patients showing a CSF pleocytosis[10].

NMOSD can present across a broad spectrum and is potentially debilitating. In young women with hypothalamic symptoms or psychosis, NMOSD should be high on the differential with early use of high-dose steroids to prevent long-term disability.

Disclosures

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