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The editors of *MSRJ* are excited to announce the publication of our Winter 2017 issue, the first issue of the new academic year. We continue to be amazed by the creativity and ambition of the authors of our submissions. This issue contains thought provoking articles on a wide variety of topics written by authors from Tulane University, University of Louisville, University of Alabama, Harvard, Yale, Central South University, Northeast Ohio Medical University, Creighton University, and Michigan State University.

We would like to thank everyone for waiting patiently during our brief hiatus. Since the release of our last issue we have been working diligently to retool our publishing process and we are delighted to announce the result of this work. All articles accepted for publication in *MSRJ* will now be featured as an electronic publication ahead of appearing in our print issue. Throughout the year we have been working diligently to streamline our new publication process in an effort to best serve not only our readers but our submitting authors as well. It is our belief that this new process provides a great benefit to our authors as it allows them to see the fruits of their labor in published form as soon as possible. This change will also provide a great benefit to our readers as we are now able to disseminate the findings of our authors in a timelier manner.

Our journal staff continues to grow year after year and we have been extremely lucky to have an ever expanding pool of talented and dedicated medical students that make this journal what it is. While we were unable to publish a print issue during our brief hiatus last academic year we had an incredibly dedicated group of Executive Editors who shepherded our journal through its transition to our new publication process. We were fortunate to have Kaitlyn Vitale serve as our Executive Editor in Chief during this time, she was an extremely capable leader with a wonderful vision for our journal. After the completion of the 2015-2016 academic year she began her residency in Neurology at the University of Michigan. Rama Salhi was another indispensable member of our

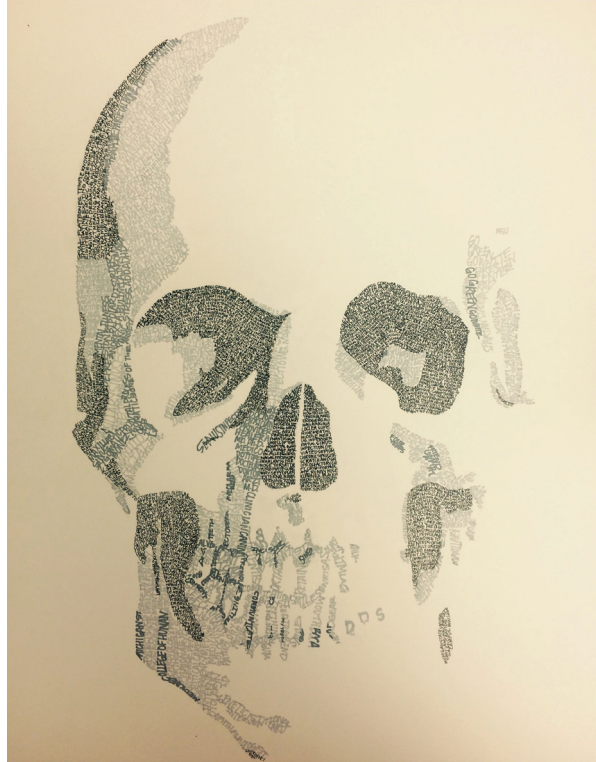
editorial staff in her capacity as an Executive Editor. Rama is currently training in Emergency Medicine at the University of Michigan. We would like to extend a sincere thank you to both Kaitlyn and Rama without whom *MSRJ* would not be in the position it is today. We here at *MSRJ* wish them the best in all of their future endeavors. The leadership of the journal for this year includes James Polega, Danny Yau, and Garrett Roe. James and Garrett are fourth year students at MSU College of Human Medicine and Danny Yau is a third year student. James Polega is excited to step into the role of Executive Editor in Chief after serving as an Executive Editor last year. Garrett Roe and Danny Yau join our executive team after working their way through various editorial roles within the journal. We are looking forward to implementing the fresh ideas and direction that this group is bringing to the *MSRJ*.

As always, we would like to thank the Michigan State University College of Human Medicine for their continued support. In addition, we would like to acknowledge the hard work of our talented staff; without them, this journal's success would not be possible. We hope that our readers will continue to follow the progress of the *MSRJ* both on Facebook and Twitter, and on our website at <http://www.MSRJ.org>. Please continue to send your manuscripts to us; we welcome reading all of the amazing work from our fellow colleagues. Sincerely,

James Polega
Executive Editor – *MSRJ* 2016–2017

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Human Skull Word Cloud

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The relationship between a physician and a patient is a dynamic and sacred one. There are an infinite number of factors that contribute to this relationship, and every single one of them is important. Expressing this relationship through art was not an easy task.

I asked fellow students, family members, physicians, and teachers for the words that they would use to describe the relationship between a physician and patient. Their responses, along with anatomy terms, translations of the words doctor and student, diseases, procedures,

MSU CHM's mission statement, fun facts, and the always necessary "GO GREEN, GO WHITE" all come together to make an image that is recognizable by everyone—a human skull. For me, the different words coming together from so many diverse sources to create something that everyone can relate to shows both how complex this relationship is, and how so many small things come together as the framework for something bigger.

Combating Obstacles to Empathy: A Replicable Small-Group Discussion Series for Medical Students

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Background: The expression of humanism in patient encounters is a core component of the medical profession and evolving national medical student curriculum. Growing evidence suggests that empathetic care improves patient outcomes and diagnostic accuracy while decreasing physician stress and rates of litigation. Unfortunately, multiple recent studies using different scales and survey tools have consistently shown empathy to decrease during the third and fourth years of medical school.

Methods: We developed a replicable, case-based, student and expert-driven, small-group discussion series designed to address this decline. Over 2 years, the series included four separate discussions over controversial topics seldom addressed by formal courses (Chronic Pain Management vs. Prescription Drug Abuse, Balancing Business and Medicine, and Domestic Violence). We utilized pre- and post-session surveys to qualitatively and quantitatively evaluate the program.

Results: Our results demonstrated significant improvement in participants' comfort with the subject matter and desire to approach faculty and peers regarding humanistic patient care.

Conclusion: Future and more frequent interactions, combined with optimization of the format could further uncover the utility of this program. Ultimately, we believe our discussion series could be replicated on other medical campuses.

Keywords: medical humanities; bioethics; curriculum; student-led; empathy; medical education; pre-clinical

INTRODUCTION

A variety of recent studies using different scales and survey tools have consistently shown empathy to decrease during the third and fourth year of medical school.^{1–5} Various explanations have been proposed for this decline, including long work-hours and sleep deprivation, dependence on technology, and decreased bedside interaction.^{1,6}

Dating back to Hippocrates, humanism has been considered a component of leadership and professionalism in medicine.^{7–10} Patient outcomes, quality of life, and diagnostic accuracy are very likely improved by empathetic and humane care.^{1,11–13} Empathy allows the physician to gain the perspective of the patient. Furthermore, it improves the quality of data taken in the patient history, which can improve diagnostic ability and decrease miscommunication. Patients themselves desire 'humaneness' as the highest rated preference in a physician. This trait fosters good communication,

partnership, and makes it more likely that a patient's autonomy will be protected.¹⁴ Empathetic physicians can improve the trust, health literacy, and compliance of their patients.^{13,15} Moreover, objective health outcomes and quality of life are improved across a variety of diagnoses.¹² From the standpoint of the physician, those deemed as humanistic doctors have described their careers as more satisfying, less stressed, and having lower rates of litigation.^{16,17}

With professional development and patient outcomes at the forefront, both international and US medical schools have focused on incorporating ethics, humanism, and moral reasoning into the medical curriculum. There is growing evidence that clinical empathy as a medical skill can be taught via medical humanities.¹⁸ The Association of American Medical Colleges (AAMC), the Accreditation Council for Graduate Medical Education (ACGME), and the American

Board of Internal Medicine (ABIM), among others, state the study of ethics and its relation with humanistic physician behavior must be included in the curriculum.^{19–21} Perhaps most evident for the need for humanistic physicians is a new feature of the Electronic Residency Application Service (ERAS). Medical students applying for residency for the 2016 match will now have a chance to indicate their membership in the Gold Humanism Honor Society (GHHS). According to Lynn White, MD, the director of GHHS, 'The addition of the GHHS checkbox sends a strong message that humanistic, caring physicians are both desired and needed in medical training programs'.²²

This national trend, however, has encountered many obstacles. Factors interfering with expressions of humanism range from but are not excluded to sporadic care, shortage of time, interruptions, litigation and defensive care, and occupational burnout.¹⁵ A gap between theory and practice may also develop when constructing curriculum aimed to promote ethics and humanistic medicine. Often there are assumptions that the humanism and medicine content are unequal in quality, practicality, and a need for further proof of efficacy.²³ Furthermore, funding itself is lacking, with 52% of surveyed medical schools reporting no funding for curricular development in ethics.²⁴

Another basic and fundamental issue is the lack of comprehensive and critical analysis of medical education in ethics and humanities. There are some efforts to combat this. A recent national workshop, The Project to Rebalance and Integrate Medical Education (PRIME), developed broad recommendations stemming from expert panel discussions during this workshop.²⁵ Three recommended themes emerged from this gathering: to focus on cultivating professional conduct, the need for academic support, and the importance of clear and realistic goals.

In an effort to face the obstacles of cultivating ethics and medical humanities education, the University of Louisville School of Medicine (ULSOM) has provided several solutions oriented to medical students' needs. Programs, such as the GHHS (instated at ULSOM in 2009), a Master's degree (dual MD/MA) offered in Bioethics and Medical Humanities, and a specific committee, HEART: Humanism in Medicine, are helping to address these problems and better fulfill the themes that ACGME and PRIME delineate.^{5,7}

HEART is an acronym for Humanistic, Empathetic, Altruistic, Relationship-centered Team. The HEART committee consists of a group of faculty, students, and administrators at the ULSOM committed to creating

opportunities for the medical school community to value quality patient care through empathetic, compassionate relationships. Near-peer (peer-assisted) learning has been shown to be an effective adjunct to traditional teaching, especially where questions are discussed in a group setting.²⁶ With this in mind, one of the projects through HEART, entitled 'HEART-to-Heart (HtH)', was created, led, and implemented by medical students. HtH began as an initiative to bring students and faculty together to discuss topics in ethics and humanism in medicine. These topics, while relevant to physicians, were underrepresented in the formal curriculum. Since its initiation, HtH has held four formal, small-group discussions. The outline consisted of: introduction of a topic, an expert panel presentation, and a small-group interactive discussion over cases and relevant issues. The program aimed to provide interactive experiences and partly address the previous barriers in humanistic teaching. We hypothesized that participating in HtH would increase the student's knowledge of the topic matter, improve their ability to confront situations related to the discussion topic, and provide them with more confidence in teaching others about the need for a humanistic approach in such situations as those presented.

METHODS

This discussion series was designed to provide students and faculty with a structured and novel educational experience related to humanistic and ethical considerations in medicine seldom covered by the formal curriculum. The program consisted of four 1-h discussion sessions: 1) Chronic Pain Management vs. Prescription Drug Abuse: Can we find the balance?; 2) Making a Business out of Medicine: Balancing the Hippocratic Oath with Practicality; 3) Health Practitioners Role in Identifying and Reporting Domestic Violence; and 4) Health Practitioners Role in Identifying and Reporting Child Abuse. First- through fourth-year students were recruited via an email invitation to attend each session. Additionally, posters were hung around campus to promote the event. Attendance was optional. Each session was designed to maximize medical student attendance by providing a realistic length (1 h during weekday lunch) and location (close proximity to lecture halls). Each had a similar outline (Table 1).

The pre- and post-session surveys were intended to assess whether: 1) attendees believe humanism and ethics are a sufficient portion of their formal education, 2) attendees feel HtH sessions are effective, satisfying,

Table 1. General outline for small-group discussion series

Discussion Series Timing and Structure

00:00–00:05	– Attendees receive food, are seated, and asked to complete an anonymous pre-session survey
00:05–00:15	– Brief introduction to the discussion topic by a student leader
00:15–00:35	– Guest speakers deemed experts in their field/patients with experience on the topic, comment on their personal experiences and give any recommendations they may have for physicians or medical students
00:35–00:50	– Attendees are given patient case(s) related to the discussion's topic and form into small groups of 6–8 to discuss ethical issues, points to consider involving patient's care, and personal experiences.
00:50–00:55	– Returning to the large group, each group briefly shares their discussion and how they would manage the given patient situation. Guest speakers give their remarks.
00:55–01:00	– Attendees asked to complete post-session survey.

and useful, 3) attendees feel comfortable discussing difficult patient situations with faculty, and 4) such sessions give the perception that the attendees are better prepared to care for patients.

SPSS (IBM SPSS, 2012) version 21.0 was used to analyze the quantitative data. Percentages, means, or standard deviations are reported for all analyses. The pre–post Likert scale data were analyzed using the Wilcoxon signed-rank test. All p values were two-tailed. Statistical significance was set by convention at $p < 0.05$. Qualitative data were analyzed using a variation of Glaser and Strauss's grounded theory, using independent reviewers to identify comment categories, code replies, and synthesize summaries based on reviewer consensus.²⁷

The Institutional Review Board at the ULSOM approved this study.

RESULTS

Quantitative Data

One hundred and thirty-four students completed the surveys (86 first-year students, 38 second-year students, 6 third-year students, and 4 fourth-year students). The comparison of students overall pre- and post-scores on the five humanism Likert scale questions shows a significant increase on all items except for one. Students' pre-to-post scores increased on their agreement that 'participating in group conversation about humanism and ethical dilemmas is an effective way to prepare for difficult patient situations' (pre, mean = 4.40; post = 4.56, $p = 0.001$); their comfort in 'approaching faculty and attendees with concerns about a patient's care' (pre, mean = 3.99; post = 4.29, $p < 0.001$); the belief that 'their school's residency/department's curriculum encourages humanism in medicine' (pre, mean = 4.10; post = 4.23, $p < 0.001$); and the 'feeling of being adequately prepared to care for patients with a more humanistic approach' (pre, mean = 3.45; post = 4.10, $p = 0.001$). The item addressing 'if students see a connection between understanding humanism

in medicine and improving clinical practice' showed no statistical increase in scores; however, 96% of the students initially agreed with this statement. Hence, scores had limited ability to improve (see Table 2).

For students who had attended a previous HtH session within this series, pre- and post-scores were also compared to see if reinforcement of the humanism content would continue to increase scores. Scores increased on two out of four items (One item, 'I felt adequately prepared to care for patients with a more humanistic approach', was only used during the first session, and therefore could not be analyzed.). Scores significantly increased in this subsample for the items 'I think participating in group conversations about humanism and ethical dilemmas is an effective way to prepare for difficult patient situations' ($p = 0.003$), and 'I felt comfortable approaching faculty and attendings with concerns about a patient's care' ($p = 0.001$). The items 'I can see the direct connection between understanding humanism in medicine and improving clinical practice', and 'my school's residency/department's curriculum encourages humanism in medicine' did not achieve significant increase; however, these initial scores were relatively high (see Table 3).

Overall, students thought the HtH session was a valuable use of their time (mean = 8.86, SD = 1.07) and enjoyed the experience (mean = 9.03, SD = 1.03) based on a 10-point rating scale where 10 indicates the most positive rating. The pre- and post-Cronbach alpha scores on the five-item instrument for this sample were 0.45 and 0.87, respectively. The increase in this reliability coefficient from unacceptable to good indicates that the instructional session may improve student's understanding of the concept of humanism as it relates to medicine.

Qualitative Data

Participants were asked to describe two goals they wanted to achieve by attending an HtH session.

Table 2. Pre- and post-humanism agreement items where columns represent the sample size, the percentage responding to a response option(s), the mean and standard deviation, and the *p* value for the comparison of pre- and post-item responses

		n	Strongly disagree/disagree (1 or 2)	Neutral (3)	Agree/strongly Agree (4 or 5)	Mean (SD)	P
I can see the direct connection between understanding humanism in medicine and improving clinical practice.	Pre	134	0%	4%	96%	4.67 (0.55)	0.319
	Post	134	0%	1%	99%	4.72 (0.47)	
I think participating in group conversation about humanism and ethical dilemmas is an effective way to prepare for difficult patient situations.	Pre	134	0%	5%	95%	4.40 (0.59)	0.001
	Post	134	0%	1%	99%	4.56 (0.51)	
I feel comfortable approaching faculty and attendings with concerns about a patient's care.	Pre	133	4%	21%	76%	3.99 (0.80)	<0.001
	Post	133	2%	6%	92%	4.29 (0.65)	
My school's residency/department's curriculum encourages humanism in medicine.	Pre	134	3%	8%	89%	4.10 (0.66)	<0.001
	Post	134	1%	7%	92%	4.23 (0.64)	
I feel adequately prepared to care for patients with the issues discussed today with a more humanistic approach.	Pre	29	17%	31%	52%	3.45 (1.02)	0.001
	Post	29	0%	24%	76%	4.10 (0.77)	

Pre-survey data demonstrated six common goals outlined (see Table 4). A majority of the students wished to gain more competency on the topic discussed (37%, 76/207), as well as learn practical application of the material (27%, 55/207). When asked to respond 'yes, somewhat, or no' to if the session achieved their goals, post-survey results show that a majority of participants' goals were achieved after having attended the session. Specifically, 88% responded 'yes', and 12% responded 'somewhat'. No participants responded 'no'.

Participants were also asked how the HtH sessions could be improved (see Table 4). A majority of the responses cited 'time' as an area of improvement. Most

participants wished that there was more time for the group, case-based discussions, while others stated a need for more time to hear from the expert speakers. Twenty-four percent of participants stated that the 'structure' of the sessions could be enhanced, some citing that having the opportunity to prepare for the sessions ahead as an option. Lastly, some participants cited no need for improvement (22%, 14/207).

DISCUSSION

Our hypothesis that these sessions would be efficacious was based on others' experience and supportive literature. They suggest educational efforts to teach

Table 3. Pre- and Post-humanism agreement items for students who have previously attended a HEART-to-Heart session where columns represent the sample size, the percentage responding to a response option(s), the mean and standard deviation, and the *p* value for the comparison of pre- and post-item responses

		n	Strongly disagree/disagree (1 or 2)	Neutral (3)	Agree/strongly agree (4 or 5)	Mean	SD	P
I can see the direct connection between understanding humanism in medicine and improving clinical practice.	Pre	47	0%	4%	96%	4.73	(0.54)	1.000
	Post	47	0%	2%	98%	4.72	(0.50)	
I think participating in group conversation about humanism and ethical dilemmas is an effective way to prepare for difficult patient situations.	Pre	47	0%	4%	96%	4.40	(0.58)	0.003
	Post	47	0%	0%	100%	4.66	(0.48)	
My school's residency/department's curriculum encourages humanism in medicine.	Pre	47	2%	4%	94%	4.23	(0.63)	0.206
	Post	47	0%	6%	94%	4.32	(0.59)	
I feel comfortable approaching faculty and attendings with concerns about a patient's care.	Pre	47	2%	28%	70%	3.96	(0.81)	0.001
	Post	47	0%	11%	89%	4.26	(0.64)	

Table 4. Qualitative Analysis – Suggestions for Improvement where columns represent the frequency, percentage, and an open-ended response justifying the suggestion for improvement

Improvement	Frequency	%	Examples
Structure	15	24	'I think the case discussions could be used to lead the presentation so present the case at the beginning and walk through it giving teaching points as you go along'.
More time for experts	13	21	'I would enjoy listening to more stories of actual patients and possibly new problems that were discovered and how they were dealt with'.
More time for group discussion	21	23	'If we could secure a longer period of protected time we could discuss further'.
No improvement	14	22	'Excellent, good perspectives, very pragmatic and practical'.
	63	100	

humanism in the curriculum can decrease the natural decline of empathy in the later years of medical school.^{5,10,28–30}

Importantly, the more active the student is in the process, the more they take away. HtH differentiates itself from other lecture series by including small-group discussions over case studies and challenging topics. In place of passive absorption, students interactively reflect on the material. Recently, residency programs have adopted similar small-group reflections with positive feedback on their impact on resident's well-being and sense of community with peers.³¹ Their work further strengthens rationale for using the small-group format.

Drawing further on the finding that role models have significant influence on attitudes and behaviors, HtH provides several expert speakers in each discussion.²⁹ These are physicians or health-care workers in the field related to the subject matter, which provide their narrative. We also have actual patients provide their perspective and strengthen practical lessons for students. Finally, due to the nature of clinical student's work schedules, most of the students attending are in first or second year. This ensures that we can emphasize the importance of humanism and ethics and impact attitudes before they have a probabilistic chance to decline.⁵

After participating in an HtH session, participants' scores regarding positive thoughts about group discussions, approaching faculty and peers about patient

care, and curriculum encouraging care for patients with a more humanistic approach significantly improved. These findings support the idea that participating in the program is an effective approach for teaching medical ethics and humanities curricula.

For students who had previously attended an HtH session, an interesting finding emerged. This subgroup acknowledged that they 'agree/strongly agree' with 'feeling more comfortable approaching faculty and attending with concerns about patient care', by demonstrating higher pre- and post-test scores for this question item (pre = 70%, post = 89%). Pre- and post-scores for this same question item showed that for participants who had not previously attended HtH, the scores for 'agree/strongly agree' improved from 52% (pre) to 76% (post). This finding shows that participating in the HtH program may have made a long-term impact in this subgroup.

Qualitative data demonstrated that a majority of students achieved their desired goals by participating in HtH. The goals were categorized and quantitated to determine common themes important to students. These themes showed participant's interests ranged from gaining competency in the subject matter to learning practical applications and improving communication skills. Suggestions for improvement in the sessions mainly focused on time limitations. Most participants wished for more time to hear from experts or more time for group case-based discussions. Other than time, the structure of the program was cited as an

area for improvement. Specifically, students suggested that the cases used in the discussion groups be sent out before the HtH session and that the speakers utilize the cases to provide more practical feedback. Additionally, over 40% of the participants suggested more time for discussion and expert presentation on the subjects. Previous studies have determined that in order to significantly increase moral reasoning skills in students they must engage in small-group discussion for at least 20 h.³² This lends support to increasing the frequency of HtH sessions to several times a semester. Another student suggestion was choosing the best time logistically to encourage the most participants. Lunch hour was found to be optimal; however, as indicated it was limited to a 1-h period, flanked by the commute time to and from class. This inherently put a rush and compression on the activities. Many participants suggested at least an hour and a half for proper discussion and development of idea exchange. Future discussion would need to find a time that fits these competing influences. Finally, it may be beneficial to widen the umbrella and incorporate more clinical students and residents as an effort to engage participants at this level in re-evaluating a humanistic perspective after gaining clinical experience.

General limitations of this study were that the program took place at only one institution over two academic years, and the survey instrument, although devolved with expert advice to establish face validity, had not been piloted.

CONCLUSIONS

There are future improvements and obstacles to acknowledge to advance the efficacy of this discussion series. There can be a subjective character to evaluating (defining and operationalizing) baseline and end-point qualities like compassion and professionalism.³³ The qualitative theory and participant survey structure were carefully selected to best approach this barrier. While the results from our study are encouraging, we recognize that our conclusions are based on a small amount of exposure time. The data from the four sessions have served as a productive initial study to demonstrate that students value and benefit from the HtH program. We hope to use these data to expand the HtH program to more frequent sessions with protected time for adequate discussion.

Patients and their physicians benefit from empathetic medicine. If this trait declines naturally during medical education, gaps in curriculum should be supplemented with effective efforts to combat that tendency. HtH uses

case-based, expert-driven, small-group discussions led by medical students that interactively stimulate and improve upon understanding humanistic-centered patient care. It establishes clear goals and helps teach professional conduct, thus aligning with the national PRIME recommendations. It tackles the controversial and faces the informal curriculum head on. The format is engaging, flexible to students' schedules, and creative. Most importantly, our preliminary data help to substantiate these claims. We believe our discussion series could be translated and improved in medical campuses across the country.

Conflict of interest and funding: The authors declare that the Arnold P. Gold Foundation funded this project.

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Does Traditional Chinese Medicine Matter? Medical Choices of Rural Diabetic Patients in Changsha, China

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Introduction: With an aging, urbanizing population, China is home to the world's largest number of adult diabetics. Although more diabetic patients currently live in cities, the prevalence of prediabetes is greater in the rural population due to changing dietary and physical habits, as well as the relative poverty. This demographic is thus an important target for public health intervention. As Traditional Chinese Medicine (TCM) is viewed in China as useful for treating chronic diseases and widely accepted, we sought to explore its use for rural diabetic patients.

Methods: The study population included 63 diabetic patients and 2 village doctors from four rural villages near Changsha, China. An initial survey was orally conducted with all 63 participants to collect demographics, financial situation, health-seeking behaviors, treatment beliefs, and medical expenditure. Three focus groups of six rural patients each were subsequently held at village health centers. For analysis, questionnaire data were summarized using means and standard deviations, or medians and quartiles. Focus group sessions were voice-recorded, and transcripts were coded for thematic analysis.

Results/conclusions: Questionnaire data revealed that for the majority of participants, seeing a doctor is costly in terms of time and money. Patients often do not have the luxury of choosing their medical provider. Despite the benefits of TCM, its slow speed and cumbersome preparation methods do not fit a need for immediate results. Furthermore, TCM doctors are not as available or accessible as Western medicine (WM) doctors. As such, although 20% of the rural patients rated higher trust in TCM than WM, no patient solely used TCM for their treatment. Instead, almost 40% of the patients try to use both TCM and WM. Village practitioners similarly believed that although diabetes treatment should go toward integrative treatment, TCM's development is hindered by its slow onset and inconvenience coupled with a more systemic lack of TCM infrastructure and research in China. In summary, the continued trust that rural patients place in TCM supports further research for better understanding the true economic, social, and health benefits of having combined TCM–WM treatment be part of diabetes standard of care.

Keywords: Traditional Chinese Medicine; health-seeking behaviors; Rural China; diabetes

INTRODUCTION

Almost half of the health care in China is based on Traditional Chinese Medicine (TCM).¹ To understand the importance of TCM among the Chinese, one needs to understand its 3,000-year history. Rooted in Taoist philosophy, the goal of TCM is to maintain balance and harmony in the bodily forces. Just as no person is separate from his or her relationship with society, no symptom can be analyzed separate from its relationship with the body.² By considering the multi-system effect of disease, TCM treatment often focuses on behavioral and preventative interventions that make it particularly relevant for chronic and undiagnosed illnesses. Western medicine (WM), in contrast, is viewed as more effective for treating acute and etiologically understood diseases. With traditional medicine and WM practiced and accepted side-by-side, China is perfectly situated to address the intersection of both practices.¹

Diabetes mellitus, a hallmark example of chronic disease, is a good model to explore the role of TCM in China. Patients with chronic diseases often turn toward TCM because of perceived quality, lower cost with better safety profiles, and cultural and historical trust.^{3,4} China has the world's largest number of adult diabetics: over 92 million (9.7% of the population) were believed to have diabetes in 2010, with 60.7% of these cases undiagnosed.⁵ The exact reason for this sharp increase is multifaceted, involving a dynamic interaction between the social and behavioral facets of an aging and urbanizing population experiencing changing diet and physical activity habits. Prompt public health and policy responses in sparking lifestyle modifications are thus needed not only because of the heavy disease burden on the individual but also because of the large economic weight on society;

it was estimated that the direct medical cost of treating type 2 diabetes and its complications was more than 18% of China's total health expenditures in 2007.⁶

There is a handful of articles on the treatment of diabetes with Chinese herbs^{2,7} and acupuncture. Systematic review of 66 randomized trials for herbal treatment of type 2 diabetes showed generally favorable hypoglycemic results, despite low methodological quality of the trials.⁸ In TCM, diabetes is attributed to *yin-yang* imbalance, and the treatment relies on replenishing both *yin* and *yang* by promoting blood circulation and invigorating the organs to strengthen the body.⁹ TCM focuses on treating and preventing diabetes complications in addition to lowering blood glucose with a combination of ingredients tailored to the particular symptoms and clinical presentation of the patient.¹⁰

In often overlooked, resource-poor communities of rural China, mortality rates are particularly high due to noncommunicable diseases such as diabetes.¹¹ As one of TCM's largest benefits to the population is its relative low cost to efficacy,^{4,12,13} it is particularly relevant for the rural population as medical expenditures and lack of insurance coverage are main causes of impoverishment.¹⁴ As many rural patients neglect seeing doctors until their disease progresses to far costlier stages,¹⁵ prevention thus becomes a keystone in improving welfare. Although there are presently more diabetic patients in cities than the countryside, the higher prevalence of prediabetes in the rural population makes this demographic an important target for public health intervention.⁵

To date, there are no patient-centered studies inquiring why individuals with diabetes pursue TCM for treatment. This project endeavors to understand what factors influence the medical care diabetic patients in rural China choose. In addition, we interviewed rural village doctors, who typically receive rudimentary WM training from local institutions. Despite the paucity in evidence for TCM treatments for diabetes, it is not the intent of this study to judge efficacy but rather determine the motivations of rural patients in using TCM. With patient-centered interviews and focus groups, we elucidate the extent to which TCM is used by rural diabetic patients and describe the reasons behind their choices for treatment.

METHODS

This study was approved by the Human Investigation Committee of Yale University (HIC protocol #

1204010079) and the Independent Ethics Committee Institute of Clinical Pharmacology of Central South University (Project # CTXY-120028).

Selection and Description of Participants

A total of 98 diabetic individuals were previously identified using a novel screening instrument from three villages in the Xingcheng and Qiaoyi townships of Wangcheng District in Hunan, China¹⁶; 10 of whom had passed away. The remaining 88 individuals were contacted by telephone; 13 individuals denied being diabetic and 30 either refused to participate or could not be reached after two phone calls on separate days. Eighteen additional subjects were recruited with the assistance of a village doctor in Xingcheng township. A final total of 63 subjects were interviewed from four villages (Supplementary Fig. 1).

Survey Collection

Interviews were conducted in Mandarin and the local Changsha dialect by two graduate students (LQ and XG), who introduced themselves as researchers from the Xiangya School of Public Health.

For the initial interview, subjects were contacted by telephone for individual meetings at their respective village health centers. A 39-question survey was given orally by XG and LQ to collect demographics (age, sex, education level, marital status), financial situation (average yearly family/individual income), health-seeking behaviors (symptoms at diagnosis, duration, therapies used), treatment beliefs (belief in WM or Chinese medicine on a scale of 1 to 10 with 1 being complete trust in WM and 10 being complete trust in TCM), and medical expenditure (amount spent on treatment and therapies). The survey was created by XG with content validated by five professors in the Social Medicine department of Xiangya School of Public Health. A pilot interview was performed on six rural diabetic inpatients in Xiangya Hospital to monitor flow and understanding of the questionnaire, as well as to gauge duration. This initial survey collection period took approximately one hour per person.

Interviews

After the initial survey collection, XG contacted subjects from each village to participate in a focus group interview located at their village health center. Three focus groups of six subjects each were conducted within three villages (18 participants total), lasting approximately 30–45 min. All subjects consented at the onset of the interview to be voice

recorded; each subject was further informed of the anonymity and confidentiality of their answers and told that they can skip any question or withdraw from the interview at any time. Individual interviews were also conducted by XG and LQ with one village doctor each from Xingcheng and Qiaoyi townships (Table 1). Similar procedures of informed consent were performed with the doctors; interviews were voice recorded and lasted 20 min each.

Questions for each focus group were adapted from questions used by Xu et al. (2006), who explored patient perspectives on TCM use in cancer care. XG and LQ conducted interviews in Chinese and the local Changsha dialect using a list of open-ended questions for guidance (Table 1). Discussion was not limited to the listed topics and participants were allowed to freely discuss their experiences with the illness. Although both researchers took notes about the behaviors of the group, no effort was made to connect responses to specific respondents.

Table 1. Questions for patient focus group interviews (A) and one-on-one interviews with village doctors (B)

A. Regarding treatment for patient focus groups

1. Why and when did you seek Traditional Chinese Medicine (TCM) or Western medicine (WM)?
2. What did you expect of your chosen treatment?
3. What type of treatment did you seek and receive?
4. What are the strengths and weaknesses (what do you like and dislike) regarding the chosen treatment?
5. Are there any barriers or facilitators for you to seek/receive your chosen treatment?
6. How much do you spend per month on either TCM or WM?
7. How much do you spend per month on your diabetes treatments as a whole?
8. What is your monthly income?

B. Regarding treatment for village doctors

1. What is the place of TCM in diabetes care in China?
2. Under what situations will patients seek TCM or Western therapy?
3. What type of TCM or Western therapies do you propose? Why?
4. What are the potential benefits and risks to patients, or advantages and disadvantages of using TCM or WM?
5. Are there any barriers or facilitators to the use of TCM or Western therapy?
6. What do you see being the trend of use for diabetes treatment?
7. Explain the potential collaboration on clinical research between the two types of medicine.

Data Analysis

Paper questionnaire data were entered into Excel with no participant identifying information and summarized using means and standard deviations, or medians and quartiles. Data were analyzed via medical belief (measured on a scale of 1 to 10, with 1 being full trust in WM and 10 being full trust in TCM) and type of medical care sought/used (a score of >6.5 was considered as trusting TCM, 4.5 to 6.5 as trusting both, and <4.5 as trusting WM; see Fig. 1). These groups were compared with regards to age, sex, education, duration of illness, family income, expenditure (both lifetime and 3-month), and medical belief. Categorical data were analyzed using chi-squared or Fisher's exact as appropriate, while continuous data were analyzed using one-way ANOVA or unpaired two-tailed *t*-tests. Significance was set at $p < 0.05$.

Focus group and village doctor interviews were transcribed verbatim and translated by XG (bilingual native English speaker) and LQ (bilingual native Chinese speaker), then back-translated for accuracy by SYX, a professor of Social Medicine. Thematic analysis was conducted with each focus group interview by examining the translated text for themes and trends while using the interview questions and notes for guidance. After creating several thematic categories, transcripts were subsequently coded. The categories for the patient focus groups included the following: reasons for seeking care; expectations of care; strengths, weaknesses, and differences between TCM and WM; barriers or obstacles to seeking care; and rural patient's special needs. The categories for the village doctor interview included the following: recommendation for diabetes care; factors hindering TCM development; and trend for future diabetes care.

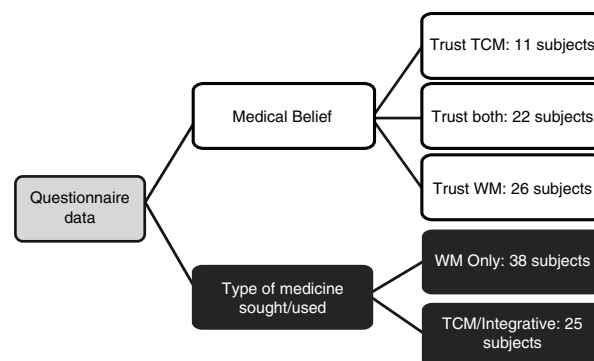


Figure 1. Delineation of questionnaire data from all interviewed subjects in medical belief and type of medicine sought/used.

RESULTS

Demographics

Of the 63 diabetic subjects, 15 (24%) were male and 48 (76%) were female (age range: 37–79; average: 58 ± 8.3). The duration of diagnoses of patient’s diabetes ranged from 1 month to 36 years, with a median duration of 5 years. Fifty five (87%) were married and 40 (63%) had the equivalent of a primary school education or less. The annual family income ranged from 840 RMB (US\$134) to 160,000 RMB (US\$25,575) with a median of 15,000 RMB (US\$2,398), while mean 3-month expenditure on medical care (including medications) ranged from 0 to 9,000 RMB (US\$1,438), with a median of 600 RMB (US\$96) (Supplementary Table A). The 18 subjects who participated in the focus groups were representative of the subject pool (Supplementary Table B).

Health-Seeking Behavior

Fifty-nine subjects ranked their medical belief on WM and TCM; 11 (18.6%) trust TCM more than WM, 26 (44%) trust WM more than TCM, and 22 (37.2%) trust both equally (Table 2). There were no significant differences between the groups in any demographic variables, including age, sex, education, or duration of disease (Table 2). Of the 63 subjects, 38 (60.3%) used only WM, while 25 (39.6%) used both TCM and WM. Users of combined TCM and WM have had diabetes for a significantly longer duration ($9.0 \text{ years} \pm 7.8 \text{ years}$ compared with $5.3 \text{ years} \pm 4.0$; $p = 0.02$) and have greater relative belief in TCM compared with WM (Table 3).

Reasons for seeking care

The most commonly stated reason by the 18 interviewed rural subjects for initially seeking care was lack of energy. Of the 18 interviewees, 15 stated that they

consulted a doctor because they did not have enough *jin* (‘劲’), loosely translated as energy, vigor, or strength.

I had no energy to walk, and was walking slower than others and needed to be carried. I had no jin for a while.
My diabetes isn’t the same as theirs. No dry mouth or a large need for urination. Just that I had no jin . . . I didn’t have other obvious diabetes symptoms.
I really liked to eat, and had a severe lack of jin. Other people realized I lost a lot of weight and suggested I undergo a checkup for diabetes.

For four subjects, diabetes was diagnosed during routine checkups or as an incidental finding during a doctor’s visit for a separate problem.

I went with my loved one together for checkup . . . My body was itchy. I was uncomfortable. Eyes were swollen in the morning.
I was just losing weight, and my husband told me to go get a checkup.
I was working, every time I ate a meal, I had to go to the bathroom four times. So I thought that was a problem.

Expectations for care

When asked about expectations from treatment(s) they were receiving, all interviewees unanimously agreed that the overarching goal was to control or lower blood sugar. The conversation often regressed to solely about numbers, where subjects exchanged the fluctuations of their blood glucose readings (stated in mmol/L) as an indication of suffering.

In the morning on an empty stomach, it is 9-point-something. Two hours after meals, it is 11-point-something. Last time I checked blood sugar it was 14.5 . . . Basically, it is never been 5- or 6-point-something.

Table 2. Demographics of participants by medical belief

		TCM (n = 11)	WM (n = 26)	Combined (n = 22)	χ^2 (p)
Sex	Male	2	5	6	0.656 (0.754)
	Female	9	21	16	
Education level	Elementary or below	5	17	16	2.534 (0.2816)
	Middle school or above	6	8	6	
Continuous variable: mean (SD)					F (p)
Age in years		54.4 (8.9)	60.0 (7.3)	58.4 (7.6)	0.3350 (0.8001)
Duration in years		3.8 (2.3)	6.0 (5.0)	7.2 (4.4)	1.945 (0.1534)
Family income in RMB		19,500 (10,583)	16,225 (14,180)	28,424 (43,107)	0.5059 (0.6793)
3-month expenditure in RMB		373.6 (529.4)	1,879 (2,385)	1,364 (1,868)	1.4676 (0.2252)

Table 3. Demographics of participants by type of therapy used

		Combined (n = 25)	WM only (n = 38)	p-value or χ^2 (p)
Sex	Male	3	12	0.1291
	Female	22	26	
Education level	Below elementary	6	11	2.428 (0.657)
	Elementary	8	15	
	Middle school	9	8	
	High school and above	2	3	
Continuous variable: mean (SD)				<i>p</i>
Age in years		55.1 (13.3)	58.9 (7.1)	0.1594
Duration in Years		9.0 (7.8)	5.3 (4.0)	0.0206
Family income in RMB		20,661 (24,568)	23,428 (30,704)	0.7569
3-month expenditure in RMB		1,781 (2,720)	1,039 (1,099)	0.1579
Belief in TCM versus WM ^a		5.1 (2.3)	7.1 (2.2)	0.001

^aLower score connotes greater belief in TCM.

When asked to explain the disease in their own words, no subject was able to provide an explanation beyond that of symptomology.

I know everything, I just do not remember, do not know how to explain. If others say it I would know. I just know in my heart.
I know it's "three more one less" [Hypertension, hyperglycemia, hypercholesteremia, and hypoinsulinemia] ... *Otherwise, no memories at all.*
It's that you cannot eat much. If you see anything you want to eat, you cannot eat it. When a person gets old, you want to eat some good stuff sometimes. But then you have to control yourself, and think: Even though I'm old I cannot enjoy the good stuff, only the bad stuff.

Three subjects compared diabetes with an entity ingrained into their individual identities.

It cannot be cured, only controlled. A cancerous type of disease, you cannot do what you want to, cannot eat what you want to. Your health is not as good as [the health of] others.
I do not know what type of disease diabetes is. It only represents myself.

In all four focus groups, the conversation regarding the nature of diabetes inevitably led to a discussion about the immense cost of medication.

Diabetes is not a good disease. Medication ... is unaffordable. If you start with good medication, you cannot go to cheap medication later. I just think: What can I do? I have no more money.

Beliefs and attitudes toward TCM and WM

Focus group members agreed that WM's main benefit is its speed and convenience, while its major

drawbacks include numerous side effects and an ability to only address the symptomology rather than the cause of a disease.

WM comes to effect quickly. But it only treats symptoms and not the root problem.
[Regarding side effects of WM:] Sometimes I feel psychologically uncomfortable. Anxious.

Conversely, while participants said that TCM would treat their diabetes in a balanced, holistic manner without hurting their internal organs, its slow onset and cumbersome preparation methods are immense drawbacks.

TCM medication is better than WM medication. Everyone's disease is different, so you need to treat it differently.
TCM does not simply treat diabetes ... it is whole-body oriented. TCM treats the root of the problem.
When I take WM, my blood sugar drops faster. Taking TCM, it's slower and the effects are not very evident.

Furthermore, a particular drawback noted by a few participants against TCM use was its unclear etiology and mechanism.

Even though I have used TCM medications, I do not know if [they] are good or not.
Sometimes you do not know what exactly goes into a concoction. They might use other herbs instead.

When asked about the defining differences between TCM and WM, participants evoked the end-goals of each class of medication: WM controls blood sugar; TCM balances the body. Thus, the general consensus was for integrative WM–TCM use when possible to

balance the positives and negatives of each style of medicine.

I believe it still should be TCM-WM treatment together . . . because WM has too many side effects. WM can control blood sugar, but it cannot adjust the balance of the body.

Everyone says it is good to use TCM [even though] you cannot really tell what's good about it. But it does not hurt your internal organs. . . And no side effects. . . But you cannot take TCM for a long time.

TCM helps heal the damage done by WM.

Barriers/obstacles to seeking care

All participants were eager to discuss China's medical care issues. At every site, the discussion would cover basic problems with Chinese health care, such as physician bribery and long wait times.

In China, there is influence when you know people. Some people, if they know people, won't need to stand in line, and even cut the line to see a doctor.

Finance was also a huge concern. Many interviewees self-prescribe cheaper medications from local pharmacies and would only consult a doctor when their symptoms become overwhelming.

[On whether the interviewee knew diabetic patients in her village] Many older individuals, above 60, but they do not see doctors. It is basically an economic problem. [Their diabetes] cannot be treated, so the older you get, the sicker you get. You need to take very good medication to achieve an effect. And you cannot get reimbursement for any medication.

These medicines are all about the same, so I just bought medicine by myself to take. I had two types of medicine, and when I felt my body was fine I stopped taking them.

Although the national government offers rural residents financial assistance, the consensus was that despite a theoretical benefit, the programs are impractical in use. Many interviewees also believe that city residents have a better quality of life due to preferential governmental policies.

Rural areas have economic difficulties. At the health center, the medications that can be reimbursed are not good medications. Good drugs you cannot reimburse. In the city, medical conditions are better, doctor skills are high, and they have specialized diabetic divisions. In the countryside, it is even hard to buy medications.

When you come from the countryside and they [doctors

in the city hospitals] give you medicine, you take what you are given.

When asked about barriers to seeing WM or TCM doctors, interviewees described a lack of availability to TCM practitioners. In both village health centers and city hospitals, WM predominates and skilled TCM doctors are difficult to find.

Those from rural areas cannot just pick up and go to Changsha to see a doctor. Village health centers only have WM doctors, so everyone goes to WM doctors.

I asked [the doctor] to prescribe me TCM but he would not.

There is a lack of TCM around. . . In the countryside, you cannot wait for that long. You want something simple. You do not even take side effects into consideration.

Finally, all focus group members stated they would see a TCM doctor if given the choice to do so.

Of course, if there was the option of course we would go . . . But there are no TCM doctors. No choice.

I just listen to what others say to take . . . For rural people, there's not much choice.

Perspectives of the village doctors

In the experience of the two village doctors we interviewed, the majority of diabetic patients use WM, particularly those newly diagnosed and those with higher blood sugars. However, a significant minority of patients – those with lower blood sugars or those for whom WM's side effects are too overwhelming – will use TCM.

When patients first discover their diabetes, most use WM because WM acts quickly. After buying the medicine, they can just take it, without the hassle of TCM. You need to personally cook TCM and spend a lot of time. However, WM has side effects. TCM is more expensive than WM. Some patients cannot tolerate the side effects of WM so use TCM, with certain effect.

Both the doctors recommended integrative medical care. In general, TCM conditions the whole body and has fewer side effects but is inconvenient, slow, and has unclear scientific evidence; on the other hand, WM is fast in effect and has good theoretical support but also has adverse side effects and only addresses symptomology.

If blood glucose levels are high, they first use WM to control blood glucose to normal levels, and then use TCM

to condition. If blood glucose levels are not too high, they can use effective TCM prescriptions to control their blood sugar. In general, TCM-WM combined treatment is the best for treating diabetes.

Factors hindering the use and development of TCM are threefold: patients cannot wait for TCM to come into effect, TCM has limited research and inadequate scientific foundation, and WM is more pervasive than TCM, especially in large hospitals. However, both the doctors believe that there is an eventual place for TCM in diabetes care in China:

WM will still continue for a long period of time as being the mainstream treatment of diabetes, but there will be progression towards integrative care, finally reaching a balance between WM and TCM.

DISCUSSION

This patient-centered study is one of the first to explore the health-seeking behaviors of rural diabetic patients in China. Although our data set was not powered to reliably determine quantitative interactions between medical beliefs and expenditures, we obtained a myriad of information via interviews on rural patients' perceptions of TCM use in their diabetes management. Focus group findings revealed that for most rural individuals, doctor visits are too expensive and time consuming; thus, patients only seek help when they absolutely must and will travel directly to the large city hospitals run by predominantly WM-trained doctors. Although patients agreed on the many benefits of TCM, they also concurred that its slow onset of therapeutic activity and inconvenience in preparation do not fit a need for immediate results. Furthermore, patients stated that TCM doctors are not always as available or accessible as WM doctors.

Given that the nearest hospital is between 3 and 30 km away from all four villages we visited, village doctors serve as the first line of medical care for the majority of the interviewed rural residents. Interviews with the two village doctors mirrored those of the patients and with literature on the beliefs of Chinese doctors; the crux of diabetes treatment should go toward integrative treatment rather than pure blood glucose control.⁹ Our interviews highlighted the village doctors' belief that TCM's development is hindered by its innate drawbacks coupled with a more systemic loss of TCM personnel, infrastructure, and research. They further explained that finance plays an important factor in what their patients can choose. Although more than 90% of rural individuals are currently covered under

China's National Cooperative Medical Scheme (NCMS) through their local governments, disease and financial burden may have increased rather than getting decreased due to high deductibles; moreover, as the NCMS does not cover folk medications, it follows that rural citizens have been decreasing their utilization of TCM.¹⁷

Although diabetes is a chronic disease with a complex standard of care, it is well documented that appropriate monitoring, treatment, and lifestyle changes can improve morbidity. However, the high costs of medications and the unfortunate fact that diabetes commonly arises amidst a myriad of other diseases such as hyperlipidemia, hypertension, obesity, and heart disease, maintaining patients' quality of life remains a difficult issue. In our sample, although almost 20% of the subjects placed higher trust in TCM than WM, none of those interviewed uniquely sought TCM care. This is consistent with findings from a recent national sample of diagnosed diabetic individuals, where less than 15% used lifestyle interventions that are major components of holistic TCM.⁵ The question whether TCM is still important for rural diabetic patients in China is difficult to answer and highly multifaceted. From one perspective, it is not important; our hypothesis that TCM will decrease financial burden was unsupported. Not only is TCM often more expensive than WM, but it is unavailable to most of the rural patients we interviewed. On the other hand, TCM is still widely regarded as a bridge toward overall health and well-being. Deeply ingrained in Chinese culture and mentality, TCM is consistently viewed as positive. It is favored by both rural patients and village doctors given its holistic approach to care and fewer side effects. In fact, every person we spoke to felt that an integrative approach would be their medicine of choice.

There are several limitations to this study that preclude a full generalization of the results. In addition to a relatively small sample size, not all participants answered all questions, leading to an even smaller data set. We also did not have information on the type of diabetes each patient had, although type 2 (adult-onset) is more likely due to the common etiological risk factor of poor lifestyle and diet. Moreover, our focus groups did not include any participants who lacked formal education even though this cohort composed of more than a quarter of our study pool; this was an unintentional outcome, and future studies should increase efforts for outreach to this potentially more underserved population. Finally, our results may not apply to patients living in urban or suburban areas.

It would be interesting to replicate this study in other provinces or administrative regions in China to fully elucidate how health-seeking behaviors are similar or different depending on geographic and cultural influences.

Doctor visits are costly in terms of time and money, and rural patients often do not have the luxury of choosing their medical provider. As long as research and development of TCM and WM are not in balance, it will be difficult to gauge the full benefit and influence of TCM. This study serves as an initial foray into the perspectives of a rising proportion of China's ill: rural diabetic patients. Sino-Western collaborations are beginning to emerge for the evaluation of TCM–WM combination in the treatment of diabetes, such as the Beijing Chaoying Diabetes Hospital, a joint venture by China and the UK.¹⁰ Cross-sectional studies are further showing that integrative medicine use leads to better glycemic control in diabetics.¹⁸ Coupled with the trust that rural patients continue to place in TCM, further research using larger data sets are important for exploring the true economic, social, and health benefits of having combined TCM-WM treatment be part of diabetes standard of care.

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Time to Neurological Deterioration in Ischemic Stroke

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Background: Neurological deterioration (ND) is common, with nearly one-half of ND patients deteriorating within the first 24 to 48 h of stroke. The timing of ND with respect to ND etiology and reversibility has not been investigated.

Methods: At our center, we define ND as an increase of 2 or more points in the National Institutes of Health Stroke Scale (NIHSS) score within 24 h and categorize etiologies of ND according to clinical reversibility. ND etiologies were considered nonreversible if such causes may have produced or extended any areas of ischemic neurologic injury due to temporary or permanent impairment in cerebral perfusion.

Results: Seventy-one of 350 ischemic stroke patients experienced ND. Over half (54.9%) of the patients who experienced ND did so within 48 h of last seen normal. The median time to ND for nonreversible causes was 1.5 days (interquartile range (IQR) 0.9, 2.4 days) versus 2.6 days for reversible causes (IQR 1.4, 5.5 days, $p = 0.011$). After adjusting for NIHSS and hematocrit on admission, the log-normal survival model demonstrated that for each 1-year increase in a patient's age, we expect a 3.9% shorter time to ND ($p = 0.0257$). In addition, adjusting for age and hematocrit on admission, we found that for each 1-point increase in the admission NIHSS, we expect a 3.1% shorter time to ND ($p = 0.0034$).

Conclusions: We found that despite having similar stroke severity and age, patients with nonreversible causes of ND had significantly shorter median time to ND when compared with patients with reversible causes of ND.

Keywords: acute ischemic stroke; neurological deterioration; latency; time to event analysis.

INTRODUCTION

Neurological deterioration (ND) following acute ischemic stroke (IS) is common, occurring in up to 40% of acute IS patients.¹ While various definitions of neurologic deterioration have been utilized throughout the literature with no consensus reached,² our center has defined neurologic deterioration as an increase in the National Institutes of Health Stroke Scale (NIHSS) score (stroke severity score, with higher scores representing more severe strokes) by 2 or more points within a 24-h period during hospitalization.³ As we and others have shown, even a small worsening in NIHSS (as few as 2 points) has been associated with poorer prognosis when compared with patients who do not deteriorate.^{3,4}

Previous studies have shown the association between ND occurrence and stroke severity on admission,^{5,6} the presence of large vessel occlusion,^{7–9} history of coronary artery disease or myocardial infarction,^{1,7} diabetes mellitus,^{1,7,9,10} acute or chronic hyperglycemia,^{1,7,11–13} elevated blood pressure,^{13,14} as well as early recurrent IS¹⁵ and symptomatic intracranial hemorrhage (sICH).^{11,16}

While it has been shown that nearly one-half of ND patients deteriorate within the first 24–48 h of the stroke,^{1,17–19} no study has described time to ND or investigated factors affecting time to ND. The primary objective of this study was to evaluate time to ND in IS

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patients and to elucidate factors affecting time to ND. Our secondary objective was to determine if time to ND differed between patients with nonreversible and reversible causes of ND.

METHODS

Study Population and Data Source

Our hospital is a tertiary care referral center located in New Orleans which manages local patients in southern Louisiana as well as referred patients from facilities throughout the southeastern United States. All patients admitted to our center from June 2008 to December 2010 were screened via a prospective stroke patient registry as previously described.²⁰ This included direct hospital admissions, emergency department admissions, and transfers to our center from other hospitals. Only White and Black patients with IS were included, as they represented the overwhelming majority of our center's patient population. For the purposes of this study, patients with an unknown time of last seen normal (LSN) or LSN over 48 h prior to arrival, who experienced an in-hospital stroke or who had incomplete time data were excluded. Patients who met inclusion criteria were monitored until the time of discharge for ND.

Variable Selection and Definition

We examined baseline characteristics, past medical history, home medication use, clinical presentation, stroke severity as measured by NIHSS, and laboratory findings, first by ND status and then by reversibility of ND etiology as part of a post hoc analysis of one previous investigation.³ At our center, NIHSS on admission is determined during the first clinical encounter by the neurology resident (certified in NIHSS scoring) while subsequent NIHSS scores are determined daily by the neurology resident (and corroborated by the neurovascular attending) during morning rounds. If an episode of clinical deterioration is witnessed by other house staff, nursing staff, or other hospital team members, the event is recorded in the patient medical record along with an updated NIHSS score. To be classified as having an IS, patients had to meet both clinical and imaging (tissue-based) criteria. ND was defined as an increase of 2 or more points on a patient's NIHSS within a 24-h period, as previously described since this threshold has been associated with several poor outcome measures including discharge disability and death.³ We used previously described etiologies as defined by Siegler et al.²¹ Patients with ND secondary to progressive stroke, new stroke, or intracerebral hemorrhage

were classified as having nonreversible ND due to the fact that these etiologies may produce or extend any areas of ischemic neurologic injury from temporary or permanent impairment in cerebral perfusion (in keeping with our prior definitions).^{6,21} Patients with ND secondary to edema; fluctuation in symptoms; seizure; extubation; sedation; or any hemodynamic, toxic, metabolic, or infectious etiology were classified as having a reversible cause of ND.²¹ Several etiologies of clinical deterioration after stroke have been previously investigated,^{2,22,23} but these do not encompass all potential causes of ND. Selected etiologies of ND for this investigation have been previously described at our center, classified as reversible or nonreversible, and were defined in a codebook prior to data abstraction from medical records in order to reduce the potential for bias.^{6,21} Stroke etiology was defined according to the Trial of Org 10172 for Acute Stroke Treatment (TOAST).²⁴ Vascular risk factors were defined in keeping with previous definitions.²⁵

Statistical Analysis

Categorical variables were compared using Pearson chi-square or Fisher's exact test where appropriate. Continuous variables were compared using the Wilcoxon Rank Sum test. We used Akaike information criterion (AIC), Bayesian information criterion (BIC), probability plots, and Cox-Snell residual plots to determine the best-fitting parametric model. Once deemed appropriate, we then used log-normal distribution to determine the median time to ND and to determine which covariates significantly affected time to ND. In addition, a multivariable Cox proportional hazards regression model was performed to evaluate median time to ND accounting for covariates. Kaplan-Meier analysis was used to estimate the time to ND for nonreversible and reversible causes. The log-rank test was used to compare time to ND for ND resulting from any nonreversible cause and ND resulting from any reversible cause. The log-normal distribution was also used to compare time to ND in nonreversible and reversible etiologies. As this was an exploratory analysis, no adjustments were made for multiple comparisons.²⁶ Two-sided *p* values of ≤ 0.05 were considered statistically significant. This study was approved by our center's Institutional Review Board.

RESULTS

During the 31-month period, 350 IS patients were screened, of which 299 met the inclusion criteria. A comparison of patients who did not experience ND to

Table 1. Demographics and clinical presentation of patients who did not experience ND compared with patients who experienced ND

	No ND <i>n</i> = 228	ND <i>n</i> = 71	<i>p</i>
Age, median years (range); IQR	62 (19–97); 53, 74	73 (39–92); 61, 81	<0.001
Gender, No. female (%)	94 (41.2)	30 (42.1)	0.878
Race, No. (%) patients			0.649
Black	154 (67.5)	50 (70.4)	
White	74 (32.5)	21 (29.6)	
Past medical history, No. (%)			
Stroke	92 (40.4)	25 (35.2)	0.438
Carotid artery stenosis >50%	38 (17.5)	17 (27.0)	0.096
Atrial fibrillation	21 (9.3)	8 (11.4)	0.607
Hypertension	169 (74.4)	58 (82.9)	0.147
Diabetes	71 (31.3)	27 (38.6)	0.257
Hyperlipidemia	101 (44.9)	27 (38.6)	0.352
Coronary artery disease	38 (16.7)	16 (22.5)	0.262
Systolic heart failure	19 (8.4)	4 (5.7)	0.612
Home medications, No. (%)			
Anti-platelet agent	87 (38.7)	33 (46.5)	0.242
Anti-hypertensive agent	145 (64.4)	51 (75.0)	0.105
Oral diabetes medication	46 (20.3)	16 (23.5)	0.562
Lipid-lowering agent	90 (39.8)	27 (39.7)	0.986
Active smoker, No. (%)	72 (31.9)	18 (25.7)	0.329
SBP, median mmHg (range); IQR	159 (96–280); 139, 185	173 (107–234); 145, 200	0.019
DBP, median mmHg (range); IQR	94 (54–180); 83, 107	93 (60–179); 82, 118	0.221
Admission NIHSS, median (range); IQR	5 (0–29) 3, 10	12 (0–29); 5, 20	<0.001
Admission glucose, median mg/dL (range); IQR	113 (70–569); 95, 143	120 (78–391); 102, 148	0.055
Treatment, No. (%)			
IV t-PA	78 (34.5)	26 (36.6)	0.746
IAT	7 (3.1)	6 (8.5)	0.054
LDL, median mg/dL (range); IQR	103 (17–540); 77, 128	120 (29–540); 72, 150	0.149
HbA1c, median % (range); IQR	5.8 (5.0–14.0); 5.4, 6.6	6.1 (5.0–13.0); 5.7, 6.5	0.027
24-h NIHSS, median (range); IQR	2 (0–29); 1, 6	13 (1–42); 5, 21	<0.001
TOAST, No. (%)			0.301
Cardioembolic	59 (25.9)	21 (29.6)	
Large vessel	52 (22.8)	22 (31.0)	
Small vessel	45 (19.7)	15 (21.1)	
Cryptogenic (>1 cause)	7 (3.1)	2 (2.8)	
Cryptogenic (no cause)	55 (24.1)	8 (11.3)	
Other	10 (4.4)	3 (4.2)	

ND, neurological deterioration; IQR, interquartile range; SBP, systolic blood pressure; DBP, diastolic blood pressure; NIHSS, National Institutes of Health Stroke Scale; IV t-PA, intravenous tissue-plasminogen activator; IAT, intra-arterial thrombolysis; LDL, low-density lipoprotein; HbA1c, hemoglobin A1C; TOAST, Trial of org 10172 in acute stroke treatment.

those that had ND is depicted in Table 1. Patients who experienced ND were significantly older (73 vs. 62 years, $p < 0.001$), had higher systolic blood pressure on admission (173 vs. 159, $p = 0.019$), higher NIHSS on admission (12 vs. 5, $p < 0.001$), higher admission glucose (120 vs. 113, $p = 0.055$), and higher HbA1c levels on admission (6.1 vs. 5.8, $p = 0.027$).

A total of 71 patients experienced ND. The remaining 228 patients were categorized as censored (76.3%).

Over half (54.9%, 39/71) of the patients who experienced ND did so within 48 h of LSN, with 25.4% (18/71) occurring within the first 24 h. As shown in Figure 1, the observed mean time to ND for the 71 patients that experienced ND was 20 days. By 5.5 days, 25% of the sampled patients had experienced ND. Of all potential covariates, only age, NIHSS on admission, and admission hematocrit (Hct) were significant predictors of time to ND in univariate analysis. After adjusting for

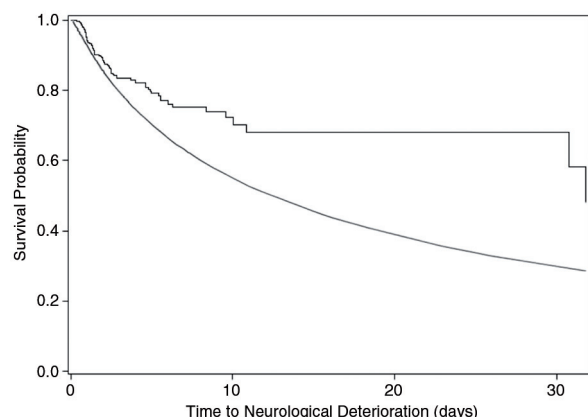


Figure 1. Log-normal (parametric) survival curve demonstrating time to neurological deterioration with Cox proportional hazards curve overlaid. Figure demonstrates the time to neurological deterioration using two separate models.

NIHSS and Hct on admission, survival analysis using the log-normal model demonstrated that for each 1-year increase in a patient's age, we expect a 3.9% shorter time to ND ($p = 0.0257$). In addition, adjusting for age and Hct on admission, we found that for each 1-point increase in the admission NIHSS, we expect a 3.1% shorter time to ND ($p = 0.0034$). After adjusting for age and NIHSS on admission, Hct on admission did not reach statistical significance ($p = 0.0738$).

Table 2 contrasts patients who experienced ND from nonreversible causes (i.e., new stroke, stroke progression, hemorrhagic transformation) and reversible causes (e.g., edema, toxicity, metabolic disorder, infectious disease). Patients who experienced reversible ND were more frequently black (85.2% vs. 59.0%, $p = 0.030$) and reported higher rates of prior stroke (48.1% vs. 23.1%, $p = 0.034$) and dyslipidemia (57.7% vs. 25.6%, $p = 0.009$), while patients who experienced ND from nonreversible causes were more frequently treated with IV t-PA (46.2% vs. 22.2%, $p = 0.047$). Two-thirds of patients with ND from a nonreversible cause experienced ND within 48 h of LSN (66.7%, 26/39), with 13 of these events occurring within 24 h (33.3%, 13/39). Over one-third of the patients who experienced ND from reversible causes did so within 48 h of LSN (37.0%, 10/27), with 14.8% (4/27) occurring within the first 24 h. As demonstrated in Figure 2, Kaplan–Meier analysis was used to assess time to ND between patients with reversible causes of ND and nonreversible causes of ND. The curves appear to differentiate after 1 day with ND of nonreversible cause falling more steeply (log rank $p = 0.007$). The

median time to ND for nonreversible causes was 1.5 days (interquartile range (IQR) 0.9, 2.4 days), while the median time to ND for reversible causes was 2.6 days (IQR 1.4, 5.5 days, $p = 0.011$).

DISCUSSION

To the best of our knowledge, this is the first study to apply parametric models from survival analysis to examine time to ND and factors affecting time to ND in IS patients. In our sample, higher NIHSS on admission and older age was associated with shorter time to ND. In keeping with previous reports, we found that over half of the patients who experienced ND did so within the 48 h of LSN.^{1,17–19} Beyond previous studies, we found the mean time to ND to be 20 days, with 25% occurring by 5.5 days. In addition, we found that despite having similar stroke severity and age, patients with nonreversible causes of ND had significantly shorter median time to ND when compared with patients with reversible causes of ND.

Our study has several limitations. The definition of ND at our center (2 point deterioration over a 24-h period) may be more lenient than others.² However, as discussed above, we have found that even a 2-point increase in the NIHSS is clinically significant and may lead to disability or even in-hospital death and therefore should not be discounted. As our standard is to perform the NIHSS in order to assess for ND each morning prior to attending rounds, our ability to measure the precise time each ND actually occurred is less granular than desired. Certain instances of ND (such as ND due to cardiopulmonary arrest) were likely documented with greater temporal precision due to the acuteness and severity of this type of clinical deterioration. In contrast, other etiologies of ND (such as ND due to stroke progression) may be milder or subclinical and only detectable during neurological examination by a physician. Certainly, because a majority of episodes of ND occurred during the first 24–48 h of hospitalization, more frequent NIHSS examinations may be warranted. We plan to explore this in future investigations. In addition, our sample includes only White and Black Americans raising questions about its generalizability to other ethnic and racial groups. Further, we included only patients with LSN times within 48 h of arrival, limiting the ability to generalize our findings to nonacute patients. Finally, we are constrained by our relatively small number of recorded events.

Table 2. Demographics and clinical presentation of patients who experienced a nonreversible cause of ND compared with patients who experienced ND of reversible cause

	Nonreversible <i>n</i> = 39	Reversible <i>n</i> = 27	<i>p</i>
Age, median y (range); IQR	75 (39–89); 66, 79	66 (42–89); 59, 81	0.177
Gender, No. female (%)	17 (43.6)	12 (44.4)	0.945
Race, No. (%) patients			0.030
Black	23 (59.0)	23 (85.2)	
White	16 (41.0)	4 (14.8)	
Past medical history, No. (%)			
Stroke	9 (23.1)	13 (48.1)	0.034
Carotid artery stenosis > 50%	11 (32.4)	5 (20.8)	0.385
Atrial fibrillation	5 (12.8)	3 (11.5)	1.000
Hypertension	30 (76.9)	24 (92.3)	0.177
Diabetes	12 (30.8)	12 (46.2)	0.208
Hyperlipidemia	10 (25.6)	15 (57.7)	0.009
Coronary artery disease	5 (15.4)	9 (33.3)	0.087
Systolic heart failure	3 (7.7)	1 (3.8)	0.644
Home medications, No. (%)			
Anti-platelet agent	15 (38.5)	15 (55.6)	0.170
Anti-hypertensive agent	26 (68.4)	21 (84.0)	0.239
Oral diabetes medication	7 (18.4)	7 (28.0)	0.371
Lipid-lowering agent	12 (31.6)	13 (52.0)	0.105
Active smoker, No. (%)	9 (23.1)	7 (26.9)	0.724
SBP, median mmHg (range); IQR	175 (122–234); 149, 205	176 (107–207); 146, 195	0.554
DBP, median mmHg (range); IQR	90 (60–139); 82, 117	95 (68–139); 86, 120	0.689
Admission NIHSS, median (range); IQR	11 (0–26) 4, 18	10 (0–29) 5, 20	0.819
Admission glucose, median mg/dL (range); IQR	122 (79–391); 105, 151	108 (78–291); 95, 151	0.208
Treatment, No. (%)			
IV t-PA	18 (46.2)	6 (22.2)	0.047
IAT	5 (12.8)	1 (3.7)	0.388
LDL, median mg/dL (range); IQR	121 (29–210); 73, 142	92 (37–540); 70, 164	0.940
HbA1c, median % (range); IQR	6.1 (5.0–12.0); 5.7, 6.4	6.0 (5.0–13.0); 5.8, 6.8	0.701
24-h NIHSS, median (range); IQR	12 (1–42); 5, 20	14 (2–27); 4, 21	0.504
TOAST, No. (%)			0.211
Cardioembolic	12 (30.8)	7 (25.9)	
Large vessel	13 (33.3)	8 (29.6)	
Small vessel	7 (17.9)	7 (25.9)	
Cryptogenic (> 1 cause)	1 (2.6)	1 (3.7)	
Cryptogenic (no cause)	6 (15.4)	1 (3.7)	
Other	0 (0)	3 (11.1)	

Reversible and nonreversible causes of ND are described in the text. ND, neurological deterioration; IQR, interquartile range; SBP, systolic blood pressure; DBP, diastolic blood pressure; NIHSS, National Institutes of Health Stroke Scale; IV t-PA, intravenous tissue-plasminogen activator; IAT, intra-arterial thrombolysis; LDL, low-density lipoprotein; HbA1c, hemoglobin A1C; TOAST Trial of org 10172 in acute stroke treatment.

In spite of these limitations, our study is unique in that it describes actual time to ND and factors affecting time to ND. Further, we found that patients with nonreversible causes of ND have shorter times to ND than those with reversible causes of ND. Larger prospective studies are needed to confirm our findings. If the average time to ND is 20 days, a time after the

majority of patients have been discharged from the stroke unit, then additional training on the signs of ND may be warranted for rehabilitation specialists and family members. If other studies confirm that nonreversible causes of ND occur significantly earlier than reversible causes, then this information could be used to create stroke unit protocols outlining more frequent

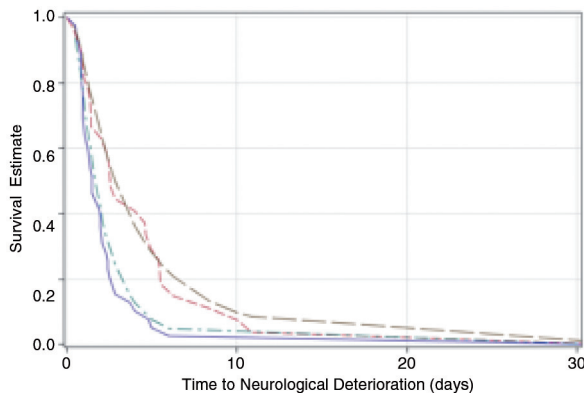


Figure 2. Kaplan–Meier survival curve comparing time to neurological deterioration for patients with nonreversible causes of ND to patients with reversible causes of ND with log-normal curves overlaid. Figure depicts Kaplan–Meier and log-normal curves evaluating differences in time to neurological deterioration according to reversible and nonreversible etiologies. Log Rank $p = 0.007$ for differences.

reassessment of the NIHSS examination and the order in which diagnostic studies should be performed to determine the cause of ND.

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Determining if a Relationship Exists between Tonsillar Ectopia and Symptom Presentation in Chiari Malformation Patients

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Purpose: Chiari malformation type I (CM I) is characterized by cerebellar tonsil ectopia and has varying symptomatology. Previous research has shown a relationship between tonsillar dominance and related conditions, but few have examined association with symptomatology. This study attempts to elucidate a relationship between cerebellar tonsil dominance, age, and symptomatology.

Methods: Data about the CM I patients were extracted from the Conquer Chiari Patient Registry. Tonsillar dominance was determined using a ratio of right-to-left herniation length. Pearson's correlation and one-tailed Student's t-test were used for analysis.

Results: Length of tonsillar descent appears to be negatively correlated with age of onset ($r = -0.266$; $p < 0.001$; $n = 113$) and diagnosis ($r = -0.323$; $p < 0.001$; $n = 113$). No correlation was found between tonsillar dominance and symptom location, or between tonsillar dominance and symptom severity bilaterally ($p > 0.05$). Symptom location and severity ratios appear to be correlated ($r = 0.666$; $p < 0.001$). Tonsillar descent length appears to be strongly correlated bilaterally ($r = 0.972$; $p < 0.001$; $n = 50$).

Conclusion: Inconsistency between tonsillar dominance as related to symptomatology suggests a multifactorial contribution to clinical presentation. The inverse relationship between tonsillar herniation length and age of symptom onset and diagnosis suggests herniation length may be an important predictor for clinical outcomes. Further research is needed to elucidate additional contributing factors and tonsillar dominance and symptomatology association.

Keywords: Chiari malformation type I; tonsillar ectopia; symptom presentation.

INTRODUCTION

Chiari malformation (CM) is a complex disorder of poorly understood etiology, but has a classification scale of type I–type IV.¹ Type I (CM I) is often diagnosed in adulthood and precipitated by head trauma. Type II (CM II) is more commonly diagnosed in childhood and associated with other congenital anomalies such as tethered cord.² Types III and IV of CM exist but will not be discussed in this article. For CM I, tonsillar herniation is defined as herniation of the cerebellar tonsils through the foramen magnum by 5 mm or more. By convention, T1-weighted sagittal MRI scan is used to quantify the degree of ectopia, and tonsillar herniation is measured from the tips of the cerebellar tonsils to a line drawn between the basion and the opisthion.² It should be noted that CM is one of many posterior fossa abnormalities, including Dandy–Walker malformation, and investigation with MRI is necessary for accurate diagnosis and treatment. Multiple anomalies can occur together, such as tonsillar ectopia with concomitant compression of the cerebellar cisterns and empty sella syndrome, though the etiology behind such a relationship has yet to be elucidated.²

Previous research by the authors showed the mean age of symptom onset for a national sample of 768 individuals with CM I to be 20.7 years of age ($SD = 13.7$) with mostly women being affected (80.4%).³ In addition, the preponderance of respondents of 92.7% were Caucasian. Milhorat et al described a similar demographic, with age of onset being 25.2 ($SD = 14.2$) with a female predominance of 94% ($n = 126$).² An exact prevalence of CM I has yet to be established,⁴ but it is estimated that 215,000 Americans suffer from CM I, although this number is believed to be an underrepresentation.⁵ Such underrepresentation exasperates gender, age, and race/ethnicity disparities making prevalence estimates inaccurate.

Much is still unknown about CM I presentation because of the range of symptoms patients experience such as headaches, vestibular abnormalities, and ophthalmological disturbances,² while other patients present with fewer symptoms. For some affected individuals, the descent of the cerebellar tonsils may not be of equal length bilaterally. Little research exists as to the relationship of asymmetric tonsillar descent

and symptom characterization based on severity and location. Previous research by Deng et al⁶ has shown a correlation between tonsillar ectopia dominance and syrinx location, the ratio of tonsillar descent to the ratio of syrinx deviation, and tonsillar ectopia dominance and syrinx location in relation to scoliotic curvature. Research by Tubbs et al⁷ found that asymmetrical tonsillar descent in CM I may suggest an asymmetrical cervicomedullary compression and further clinical implications. With a variety of definitions and symptom presentation, further research is necessary to confirm such suggestions.

Lack of a relationship between tonsillar dominance and symptom presentation may also be due to the complexity of information relay pathways from the body to higher brain centers. Somatosensation of vibration, pressure, and discriminative touch, for example, is relayed through the dorsal column medial lemniscus (DCML) system, such that the right brain perceives somatosensation of the left side of the body.⁸ For this reason, right-sided tonsillar compression at the level of the medulla where the medial lemniscus is present may cause numbness in the left side of the body, whereas compression below the decussation may result in numbness on the right side of the body. For purposes of this research, dominance refers to left- and right-brain tonsillar ectopia and symptom presentation.

In addition to the DCML system, the anterolateral system portion of the nervous system is of importance in relaying information about temperature, pain, and crude touch to higher centers in the brain. Information regarding these sensations is transmitted by the ascending anterior and lateral spinothalamic tracts. Similar to the DCML system, these tracts within the spine ascend ipsilaterally, synapsing with second-order neurons, which then decussate to the contralateral side via the anterior white commissure. The anterolateral system then projects to the thalamus to provide an individual with the sensation of crude touch, pain, and temperature. Due to the decussation of the anterolateral system, damage could potentially cause ipsilateral or contralateral deficit from anesthesia. These deficits would be presented contralaterally if a lesion were rostral to the decussation, and ipsilaterally if a lesion were caudal to the decussation.⁸ Thus, it is possible for a patient to be either unable to sense pain and temperature if the anterolateral system is damaged, or unable to sense vibration and fine touch if the DCML system is damaged.⁸ However, this specific information regarding deficits in those with CM I, which would be tested during a neurological examination, was not

available from this survey. Future studies analyzing the relationship between tonsillar dominance and symptom presentation should consider herniation position along the DCML system and anterolateral system, to more accurately elucidate trends.

METHODS

The US-based Conquer Chiari Research Center and Conquer Chiari Research Foundation established a voluntary, dynamic, online Conquer Chiari Patient Registry (CCPR) for individuals with CM and caretakers. Participants were made aware of the registry by advertisements through the foundation's websites (conquerchiari.org, chiari-research.org) and CM message boards. Information regarding clinical presentation, diagnostic experience, and quality of life was collected. Survey components were completed from the launch date, August 2012, until April 2014 when data were collected for analysis. Survey participants were required to have a diagnosis of CM via a physician or diagnostic MRI consisting of a tonsillar ectopia of greater than 5 mm. They also must be at least 18 years of age, although parents and legal guardians may enter data into the registry for patients under the age of 18 years with CM. Participants were not compensated and their information was de-identified. As of April 2014, 957 individual participants provided responses to survey-style questions. Participants also had the choice to skip over questions as is evident with this research (further defined below). This registry signifies the first time that individuals living with CM can self-report about their experiences.

Instruments

Survey participants were asked if they had access to MRI reports and subsequently prompted to enter information about MRI findings, including length of tonsillar descent (in mm). Patients who did not indicate having access to an MRI report were not included in this study. Patients also provide responses to a vast array of questions regarding type, location, and intensity of CM I symptoms. Zhu's method for calculating the asymmetry of tonsillar descent (hereafter referred to as tonsillar length ratio) was used.⁹ The measure of right tonsillar descent was divided by the measure of left tonsillar descent. Similar to Deng et al,⁶ we considered a tonsillar length ratio greater than 1.10 and less than 0.90 to represent right and left dominance, respectively. Tonsillar length ratio values that fell between 0.90 and 1.10 were considered to be symmetrical.

Cerebellar tonsil descent was compared to the severity of symptoms as reported by the patient (mild, moderate, severe, and very severe) and localized to the right or left side. Symptoms were localized to the arm, hand, leg, and foot bilaterally. Since symptom asymmetry could not be evaluated in a clinical setting, frequencies of right and left symptom presentation were calculated by assigning binary values to 'yes' and 'no' reporting of symptoms along the extremities for each side of the body. For example, an individual who reported numbness and tingling along the right hand, right arm, and right leg with only symptom presentation on the left localized to the hand would receive a score of 3 for the right and 1 for the left (see Fig. 1). A symptom localization ratio was performed as with the tonsils, dividing the summed symptoms for the right side by the summed symptoms for the left. Similar to tonsillar length, we considered a symptom localization ratio greater than 1.10 and less than 0.90 to represent right and left dominance, respectively. Symptom localization ratio values that fell between 0.90 and 1.10 were considered to be symmetrical. For the previous example, the individual would be considered right-dominant concerning symptom presentation.

Statistics

Data were extracted from the dynamic, online CCPR and imported into SPSS version 22 (IBM/SPSS, Inc., Chicago, IL). Pearson's correlation and one-tailed Student's *t*-test were used to analyze the relationship of side dominance between tonsillar herniation and clinical presentations. Pearson's correlation and one-tailed Student's *t*-test were also performed to analyze the correlation between tonsillar herniation distances and symptom severity. An alpha of 0.05 was set with significance of $p < 0.05$.

RESULTS

Tonsillar Asymmetry and Clinical Manifestation

Patient data were included if the following criteria were met: 1) the individual inputting data were a patient or the parent of a patient, 2) the individual inputting data had access to an MRI, and 3) the patient was diagnosed by a physician or MRI to have CM I. The sample size decreased from 786 to 316 individuals (Fig. 2).

Table 1 details patient demographic information. The majority of our sample were identified as female (80.4%) and Caucasian (92.7%) with a mean age of 34.9 (SD = 15.0) years. Average age of symptom onset was

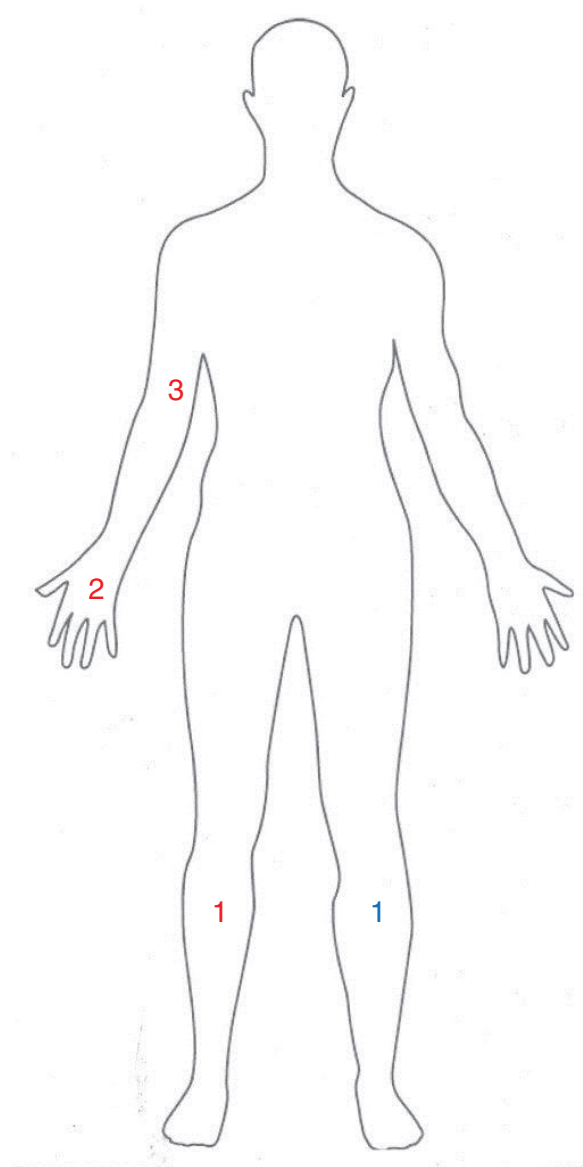


Figure 1. Symptom scoring schematic.

20.6 (SD = 13.9) years with the average age of 32.5 (SD = 15.7) years at diagnosis.

As seen in Table 2, tonsillar descent ranged from 0 to 35 mm on the right side (mean 9.30 mm; SD = 5.90 mm) and from 1 to 35 mm on the left side (mean 9.52 mm; SD = 5.78 mm) with the overall tonsillar herniation range from 2 to 29 mm (mean 9.43 mm; SD = 5.06 mm). Right-sided tonsillar dominance was present in 10 (14.1%) individuals with left-sided dominance present in 13 (18.3%) individuals and overall symmetry present in 48 (67.6%) individuals. Length of tonsillar descent (mm) appeared to be negatively correlated ($r = -0.266$;

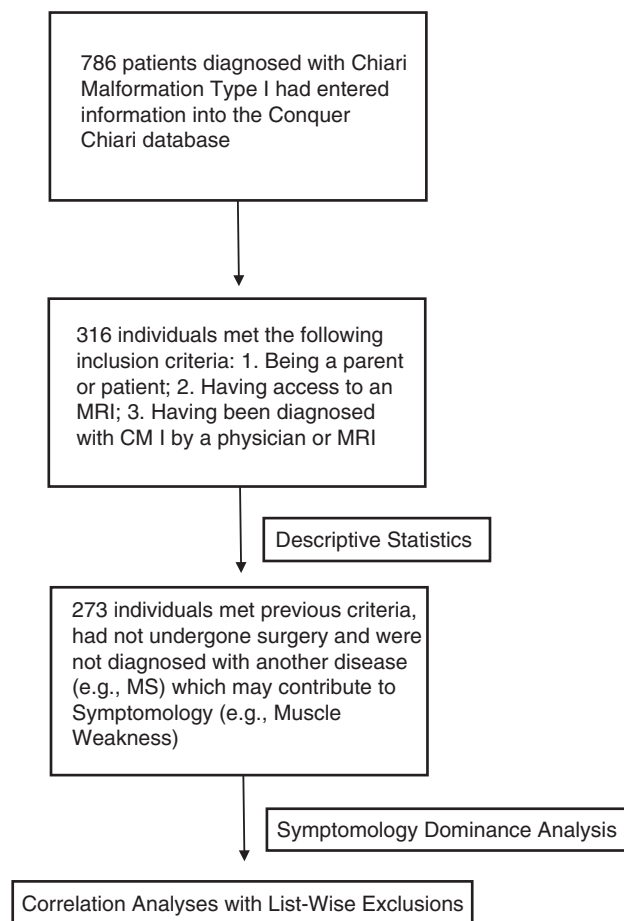


Figure 2. Tonsillar ectopia patient selection.

$p < 0.001$; 95% CI -0.429 to -0.086) with age of onset (years) and age at diagnosis ($r = -0.323$; $p < 0.001$; 95% CI -0.479 to -0.148) for 113 individuals.

Patients were then excluded from further analysis if they had undergone surgery or had been diagnosed with a disease, such as multiple sclerosis, which may account for muscle weakness, numbness, or tingling, so as not to skew statistical results involving symptomatology. The new sample size was further reduced to 273 individuals (Fig. 1).

Clinical manifestations were localized to the right ($n = 117$; 52.2%) or left ($n = 51$; 22.8%) side or were equally represented ($n = 56$; 25.0%) on both sides of the body (missing data: $n = 49$). Symptom severity was also localized to the right ($n = 40$; 22.3%) or left ($n = 46$; 25.7%) side or was symmetrical ($n = 93$; 52%) over the body (missing data: $n = 94$). Symptoms included in the analysis were numbness, tingling, and weakness located in the left or right arm, hand, leg, and foot.

Table 1. Demographic information

	No. CM I	CM I (%) ($n = 316$)
Gender		
Female	254	80.4
Male	49	15.5
Missing	13	4.1
Race ^a		
White or white Hispanic	293	92.7
American Indian	10	3.2
Black, African American, or black Hispanic	7	2.2
Asian	3	0.9
Other	5	1.6
Age (mean (SD)) years	34.9 (15.0)	—
Age at symptom onset (mean (SD)) years	20.6 (13.9)	—
Age at diagnosis (mean (SD)) years	32.5 (15.7)	—

^aIndividuals were able to identify with more than one race but the total number of individuals who answered remained $n = 316$.

Multiple imputations were considered for the missing data; however, due to the structure of the survey, it is difficult to determine if patients did not know the answers or were just electing not to respond.

Table 2. Clinical presentation

	No. CM I	CM I (%)
Tonsil herniation (mean (SD)) mm ($n = 316$)		
Right	9.30 (5.90)	—
Left	9.52 (5.78)	—
Symmetrical	9.43 (5.06)	—
Tonsillar dominance ($n = 71$) ^a		
Right	10	14.1
Left	13	18.3
Symmetrical	48	67.6
Missing	245	—
Symptom dominance ($n = 224$) ^a		
Right	117	52.2
Left	51	22.8
Symmetrical	56	25
Missing	49	—
Symptom severity dominance ($n = 179$) ^a		
Right	40	22.3
Left	46	25.7
Symmetrical	93	52.0
Missing	94	—

^aPercentages and sample size do not include missing data.

Tonsillar Descent and Symptomatology

Pearson's correlation and one-tailed Student's *t*-test ($\alpha = 0.05$) were used to compare dominance of tonsillar descent, symptom severity, symptom location, and symptom presentation. A one-tailed *t*-test was used because our study was only interested in tonsillar descent through the foramen magnum and not tonsillar regression. For this reason, a one-tailed *t*-test allowed for greater statistical power in detecting significant differences along one side of the Gaussian curve. No correlation was found between tonsillar dominance and symptom location ($r = 0.028$; $p = 0.426$), or between tonsillar dominance and symptom severity localized to the right or left side of the body ($r = 0.98$; $p = 0.301$). However, symptom location and severity ratios were correlated ($r = 0.666$; $p < 0.001$), indicating a positive relationship of association between the symptom and patient report of severity of symptom. Cerebellar tonsil descent length was strongly correlated bilaterally ($r = 0.972$; $p < 0.001$; $n = 50$), with the descent length related to symptom location.

Tonsil herniation (mm) and patient self-report of symptom severity produced strong associative relationships. Right tonsillar herniation length appears to be correlated with right symptom presentation ($r = -0.531$; $p = 0.001$; $n = 32$; 95% CI -0.742 to -0.224) and symptom severity localized to the right side of the body ($r = -0.534$; $p = 0.001$; $n = 31$; 95% CI -0.746 to -0.222). Left tonsillar herniation length appears to be negatively correlated with right symptom presentation ($r = -0.489$; $p = 0.002$; $n = 3$; 95% CI -0.709 to -0.181) and symptom severity localized to the right side of the body ($r = -0.504$; $p = 0.001$; $n = 33$; 95% CI -0.722 to -0.195). A similar relationship involving tonsil herniation and symptomatology was not seen involving the left side of the body. Individual localized symptoms (e.g., pain in the right hand) were also compared to tonsillar dominance, but a relationship between these variables was not observed ($p > 0.05$).

DISCUSSION

The results of our study further emphasize that much is left to be understood about CM I, including a better understanding of etiology and the impact of tonsillar compression of the brainstem and spinal cord, especially concerning symptom presentation and correlation. Establishing relationships between tonsillar descent and symptomatology may allow for predictions of symptomatology or patient morbidity. The lack of correlation between tonsillar herniation dominance and

symptom presentation, as would be expected from neuroanatomic relationships, suggests a multifactorial cause for individual symptomatology. Knowing the implications of tonsillar descent length and dominance will further our understanding of CM I as a whole and possibly help tailor treatment options to patients predicted to exhibit certain symptoms or symptom severity. Our study attempted to elucidate relationships involving tonsillar dominance, symptom presentation, and severity. Although previous studies have described tonsillar asymmetry with respect to related conditions, to our knowledge, this is the first time symptom presentation dominance and severities were analyzed in relation to tonsillar dominance.^{6,10}

Our patient sample largely reflects that of previous studies, with higher representation of females (80.4%) than males.^{2,11–13} It is impossible to know if our large proportion of Caucasian (92.7%) patients is representative of those affected with CM due to underrepresentation of minorities in research¹¹ and the lack of inclusion of racial and ethnic information in previous Chiari studies.^{2,11–13} For this study, we were not able to determine why there is such a disparity in our sample.

A majority of individuals showed tonsillar asymmetry in clinical research by Zhu et al⁹ (87%; n individuals = 39) and Deng et al⁶ (91.3%; n individuals = 104); however, our study based on patient reporting indicated symmetry as being more common (67.6%; $n = 71$). Smith et al¹⁴ also showed symmetry in 84% of cases and much larger sample size (n individuals = 2,400).

Disproportionate cranial and cerebral dimensions were thought to be related to Chiari onset and symptomatology, with CM II being diagnosed as a congenital form and CM I being acquired after trauma.¹⁵ However, a relationship was not found with regard to tonsillar descent.¹⁵ Clinical manifestations and severity, therefore, may not be predicted solely by cranial and cerebral architecture. Our study attempted to elucidate a relationship between tonsillar ectopia and symptomatology. Possible negative correlations were observed bilaterally with symptoms localized to the right side of the body. However, a similar relationship was not observed for the left side, highlighting a lack of consistency between variables.

Anomalies concerning association between tonsillar eccentricity and related conditions are not unique to this study.¹⁰ Zhu et al⁹ explains that various imaging techniques may account for alternate findings between studies, a problem which appears to be exacerbated in smaller sample sizes. This survey does not provide

specifics information on the characteristics of the MRI being viewed to determine the length of the patient's cerebellar tonsils. There is also clinical inconsistency as to what criteria necessitate CM I diagnosis.

Symmetrical symptom presentation is more easily explained, especially in individuals showing symmetrical tonsillar ectopia. Symptoms may also present symmetrically in those expressing tonsillar dominance, either by causing bilateral compression of the brainstem as the unaffected side is forced against bony architecture or simply by compressing along the length of nerve projection pathways, involving both the contralateral (more rostral) and ipsilateral (more caudal) portions of the same pathway.

It is interesting that symptom severity was reduced as tonsillar herniation length increased, despite the fact that a larger area of the brainstem and spinal cord would be compressed. Patients suffering from CM I may also present with morphological changes to the tonsils themselves, such as cone-shaped elongation, as the tonsils herniate through the foramen magnum.¹³ Elongation in this way may cause tapering of the tonsils, and this reduction in thickness could possibly result in reduced compression over the length of descent and subsequent reduction in symptom presentation. Further research is warranted to determine if such a phenomenon occurs.

The importance of early intervention has been established in improving clinical outcomes³ and patient quality of life.^{3,16} Intervention delay is associated with increased risk of developing debilitating symptoms such as ataxia, vertigo, and severe headache syndrome.¹¹ The inverse relationship between tonsillar descent length and age of onset and diagnosis suggests severity of herniation may be an important predictor of clinical outcomes.

This study is the first time that symptom localization and severity are compared to tonsillar dominance. The data for this study were collected from the online CCPR. The voluntary, self-reporting nature of the CCPR allows for great insight into the impact of CM I on many individuals. However, the survey did not require that individuals complete every question, resulting in incomplete data entry and missing data. We were unable to access individual MRI reports to determine if imaging was consistent between patients. We were also unable to determine tonsil position in relation to the brainstem and spinal cord to better ascertain which neural structures might be compressed. Further research is needed to examine if a relationship between

tonsillar dominance and symptomatology in a larger sample size exists in order to reveal possible trends.

ETHICAL STANDARDS

The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional guidelines on human experimentation as approved by the Institutional Review Board at The University of Akron and Northeast Ohio Medical University and with the Helsinki Declaration of 1975, as revised in 2008.

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Pain Relief and Intervertebral Disc Rehydration Following Wallis® Interspinous Device Implantation: A Case Report

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Introduction: Degeneration of the lumbar motion segment is the primary cause of low back pain in many individuals. Therefore, new minimally invasive treatments are being sought.

Patient profile: A 47-year-old man presented with severe low back pain and radicular symptoms of several years duration. Lumbar Magnetic Resonance Imaging (MRI) scan revealed severe desiccation, loss of disc height, and an annular tear with right lateral disc protrusion at L4–5.

Interventions/outcomes: After conservative treatment failed, the patient received a Wallis® interspinous spacer at the affected level. A 100% subjective pain relief was obtained at 3 months postoperative. Nucleus pulposus rehydration on MRI was observed.

Discussion: Controversy exists over whether disc dehydration is a reliable indicator of low back pain; however, interspinous spacers seem to alter abnormal motion segment's biomechanics in a way that results in alleviation of low back pain and increased range of motion. With the advent of biologic therapy, this may provide an intriguing minimally invasive treatment modality, although further research is needed.

Keywords: intervertebral disc degeneration; case reports; orthopedics; therapeutics; biologics

INTRODUCTION AND PATIENT PROFILE

Degeneration of the lumbar motion segment is the primary cause of low back pain in many individuals. This not only includes intervertebral disc degeneration, but facet joint abnormalities as well. This is generally understood to be due to increased axial and torsional forces over an extended period of time, similar to the development of arthritis in other joints.^{1–4} Beyond conservative therapies, the standard of care has generally been instrumented fusion. However, fusion surgery has many drawbacks, such as a long recovery period, loss of work productivity, lack of symptom resolution, and adjacent-level degeneration. More recently, disc arthroplasty has been implemented, with clinical results showing better symptom resolution, faster return to work, and less co-morbidity when compared with traditional lumbar fusions.^{5,6}

The Wallis® interspinous implant (Zimmer Spine, Austin, TX) was developed as an alternative to these more invasive procedures. Whereas disc arthroplasty uses an anterior approach through the abdominal cavity, implantation of the Wallis® is done through a small posterior incision with minimal damage and risk to surrounding tissues. The device is a spacer made of polyether ether ketone (PEEK) and is inserted into the interspinous space of the degenerated motion seg-

ment. Two stabilizing bands are subsequently looped around the adjacent spinous processes and secured to the device (Fig. 1). Results of the first-generation Wallis® device, with a titanium spacer and used in Europe during the 1980s, showed favorable outcomes regarding pain relief and increased physical functioning.^{7,8} The newest generation system, which is made of the PEEK material, has been used to a great extent in Europe over the past decade with good results.⁹ This report documents our experience with one patient in particular who received this device.

A 47-year-old male patient presented to our clinic with severe low back and right leg pain that had been ongoing for nearly 8 years. He denied any precipitating trauma, bowel/urinary incontinence, or saddle paresthesia. His Oswestry Disability Index (ODI), a validated tool measuring how low back pain interferes with one's daily activities, was 52, and he had a lumbar Visual Analog Scale (VAS) of 75 mm and a right leg VAS of 60 mm. The VAS is a 100-mm line that a patient places a mark on indicating pain severity, with 0 being none and 100 being the worst. Physical examination demonstrated tenderness to palpation in the lumbar paraspinal region, and full strength and intact sensation in the lower extremities. Straight leg testing was



Figure 1. Wallis[®] device shown in lumbar motion segment model. Lateral view (left) and posterior view (right).

negative. Lumbar MRI revealed severe disc desiccation with minimal loss of disc height and an annular tear and right lateral disc protrusion at the L4–5 level.

INTERVENTIONS AND OUTCOMES

After undergoing several months of conservative treatment with no symptom resolution, it was decided to pursue non-fusion surgical treatment by enrolling the patient into a clinical trial comparing the Charité[™] artificial disc to the Wallis[®] system. The enrollment and entire study process were approved by the Western Institutional Review Board.

The patient was randomized to receive the Wallis[®] device, which was implanted at the L4–5 level without complication in the manner described by Sénégas.⁷ While the patient did have a disc protrusion seen on imaging, no discectomy was performed at the time of surgery. He was seen at 6-week, 3-month, 6-month, and 12-month follow-up visits in accordance with the study protocol. At each of those visits, ODI and VAS questionnaires were administered. The patient's condition had dramatically improved to the point where he was no longer taking narcotic or non-narcotic medications for pain management at 6 weeks post-operative, and by 3 months postoperative his ODI and VAS scores had returned to zero and he reported that he was subjectively pain-free.

In addition, upon review of the patient's protocol-mandated 2-year MRI, we noticed an interesting phenomenon regarding the treatment level. Whereas the preoperative MRI documented rather severe desiccation of the nucleus pulposus of the L4–5 disc (Fig. 2), the 2-year postoperative MRI demonstrated increased T2 signal intensity at the central and posterior portion of the nucleus (Fig. 3), indicating rehydration of the disc space. We also noticed that the previously visualized disc protrusion seemed to have diminished slightly.

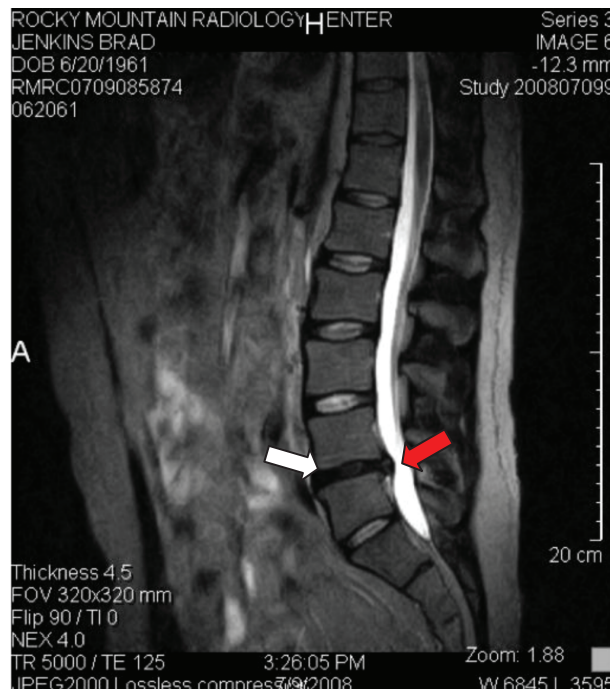


Figure 2. Preoperative MRI. Note the dessication at L4–5, with loss of T2 signal intensity throughout the nucleus pulposus (white arrow). The posterolateral disc protrusion can be seen as well (red arrow).

What makes this case unique is that no other patients at our study site developed disc rehydration, although several had similar clinical improvement, and the trial itself did not include disc rehydration as primary or secondary endpoints.

DISCUSSION

Remarkably, this is not the first documented instance of disc rehydration following insertion of an interspinous stabilization device. Sénégas has published multiple articles on the Wallis[®] system and found that a significant number of patients receiving the device demonstrated increased disc rehydration on MRI.¹⁰ A recently published paper also notes that the MRI scans of several patients showed improvement in Modic grades as well as disc rehydration.¹¹

Currently, there is a controversy over whether disc dehydration is a reliable indicator of discogenic back pain and if rehydration adequately correlates with improvements in a patient's pain and function, and if interspinous spacers should be the preferred treatment option. A recent review article by Gazzeri et al. posits that there is insufficient evidence for or against placement of an interspinous device for the treatment of

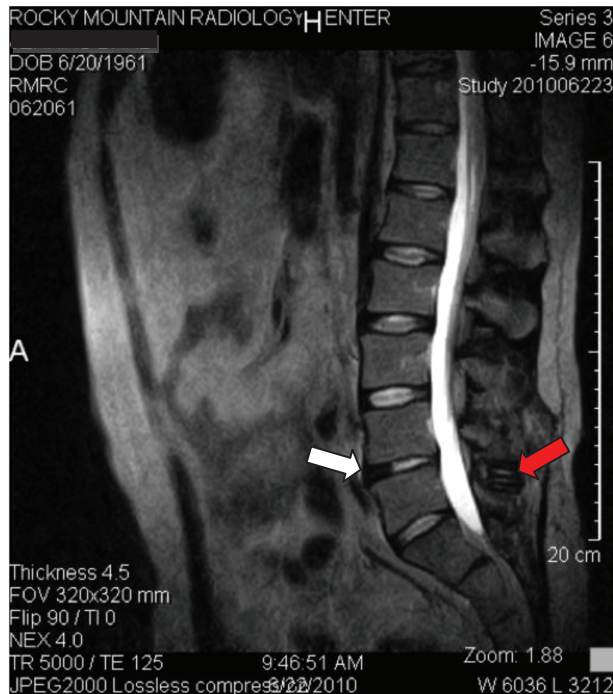


Figure 3. Twenty-four-month MRI. The nucleus pulposus of the L4–5 disc shows distinct rehydration (white arrow). The Wallis® device can be seen in the L4–5 interspinous space (red arrow).

lumbar stenosis, and that laminectomy may be a better treatment option, although its study in patients without stenosis is limited.¹² Nonetheless, it seems that interspinous spacers alter the abnormal motion segment's biomechanics in a way that results in symptom alleviation. Our theory to explain the improvement noted on imaging studies of these patients is based on the idea that these devices reduce load on the intervertebral disc and facet joints, which allows cartilaginous cells in the disc to properly begin the self-healing process. It has been demonstrated that excessive loads on the intervertebral disc can limit the healing properties of intervertebral chondroblasts and can even lead to further degeneration.¹³ Another paper also showed that biomechanical stresses can diminish proteoglycan synthesis in the disc and ultimately play a role in the intervertebral disc self-repair mechanism.¹⁴ In addition, another study showed that interspinous spacers can reduce intradiscal pressures.¹⁵ S  n  gas demonstrated that the Wallis® system also decreases biomechanical stress on the intervertebral disc,⁷ and similar results were replicated.¹⁰

After reviewing the literature and comparing our own experience with the Wallis® device, especially in this single patient, it appears that interspinous spacers may be a viable treatment for certain indications of low

back pain due to degenerative disc disease. Some possible weaknesses to this device exist, however; one rare event in particular, also seen with a similar spacer called the X-Stop®, is the device loosening and backing out of the interspinous spacing, causing severe pain and movement restriction requiring removal.¹⁶

With the recent advent of biologics technology, an intriguing treatment for degenerative disc disease might emerge. For example, the combination of interspinous spacers such as the Wallis® device with an intradiscal injection of the patient's own marrow-derived stem cells with associated growth factors could prove to be a beneficial, minimally invasive treatment. Possible therapies such as these are certainly worth investigating in the near future, particularly as clinical trials on the efficacy of minimally invasive treatments utilizing biologics begin to provide the scientific spine community with reasonable data.^{17,18}

LEARNING POINTS

- (1) Low back pain, while multifactorial, often can be due to degeneration of the lumbar motion segment secondary to repetitive use, trauma, or inflammation.
- (2) Interspinous spacers have shown promise in treating discogenic back pain by altering the abnormal biomechanics of the motion segment and alleviating strain on the intervertebral disc and supporting structures.
- (3) Intervertebral disc rehydration may indicate healing of an injured disc and subsequent pain relief, and may provide an avenue for focused regenerative treatment.
- (4) With the advent of biologic technology, new therapies combining these minimally invasive techniques may provide a better treatment for selected cases of low back pain.

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