VOLUME 9 • ISSUE 3 • Aug. 2016

WHAT'S INSIDE: **ORIGINAL RESEARCH • CASE STUDIES**

KANSAS JOURNAL of MEDICINE

TABLE OF CONTENTS

ORIGINAL RESEARCH

50 Outcomes in Combined Anterior and Posterior Fusion for 3 and 4-Level Degenerative Lumbar Disc Disease
Scott M. Haskins, M.D., Alan Moskowitz, M.D., John J. Lammli, M.D., Eren O. Kuris, M.D., Alexander C.M. Chong, MSAE, MSME

54 Associations between Fall Distance, Age, and Trauma Outcomes in Older Adult Patients
Gina M. Berg, Ph.D., MBA, Ashley M. Hervey, M.Ed., Felecia A. Lee, Ph.D., Sarah Holmes, PA-C, Kayla R. Keuter, PA-C, MPH, M.A., Paul B. Harrison, M.D.

CASE STUDIES

58 Colonic Spirochaetosis: An Unusual Cause of Chronic Diarrhea in the Developed World
Michael Green, M.D., Stephanie Pankow, M.D., Nathan Tofteland, M.D., William Salyers, M.D., MPH

60 Parkinson Disease in a Patient with Multiple Co-morbidities: A Delayed Diagnosis?
Theresa L. King, M.D.

62 Rhombencephalitis Presenting as a Manifestation of Neuropsychiatric Lupus
Muhammad Imran, M.D., Ayesha Irum, M.S., Adam Parker, M.D., Leslie Kimpler, M.D., Phaedra Dowell, M.D., Anand Rajpara, M.D., Julian Magadan III, M.D.

66 Invasive Mucormycosis Causing Rhino-orbital Cellulitis
Padma Poddutoori, M.D. & Da Zhang, M.D., MSc

69 Oral Vitamin C (Ascorbic Acid) Allergy and Avoidance Leading to Severe Hypovitaminosis C
Marissa Love, M.D., Muhammad Imran, M.D., Ayesha Irum, M.S., Garth Fraga, M.D., Selina Gierer, D.O.

71 Savella® (Milnacipran) Causing Elevated Normetanephrines
Ahmed Yehya, M.D., John M. Miles, M.D., FACE, Rajib K. Bhattacharya, M.D., FACE

74 Acute Urticaria Induced by Systemic Corticosteroids in Patient with Preexisting Aspirin Exacerbated Respiratory Disease
Muhammad Imran, M.D., Yuriy Zgherea, M.D., Ayesha Irum, MBBS, Selina Gierer, D.O.

KANSAS JOURNAL of MEDICINE

Outcomes in Combined Anterior and Posterior Fusion for 3- and 4-Level Degenerative Lumbar Disc Disease

Scott M. Haskins, M.D.[1], Alan Moskowitz, M.D.[1,2], John J. Lammli, M.D.[1], Eren O. Kuris, M.D.[1], Alexander C.M. Chong, MSAE, MSME[1,3]

[1]University of Kansas School of Medicine-Wichita, Department of Orthopaedics, Wichita, KS

[2]Kansas Orthopaedic Center, PA, Wichita, KS

[3]Via Christi Health, Department of Graduate Medical Education, Wichita, KS

ABSTRACT

Introduction. This study reported the clinical and functional outcomes in a consecutive series of patients with 3- or 4-level degenerative disc disease (DDD) between vertebral levels L2 to S1, who were treated with combined anterior lumbar interbody fusion (ALIF) and posterior spinal fusion at one-year and two-year follow-ups.

Methods. A retrospective chart review was performed on all patients who underwent long segment fusion for DDD by a single surgeon between August 2002 and January 2012. Fifty-five patients were identified and 32 had complete charts for review (14 had one-year follow-up and 18 two-year follow-up). In addition to demographic data, disability (Oswestry Disability Index, ODI), pain level (Visual Analog Scale, VAS), and flexion-extension range-of-motion were measured pre- and post-operatively. Operative data also were collected, including operative time, blood loss, surgical implants used, surgical approach, operative levels treated, and complications.

Results. Both VAS and ODI improved significantly post-operatively. The average VAS score improved from 6.5 ± 1.5 (range: 4 - 9) to 4.4 ± 1.7 (range: 2 - 7) for one-year follow-up, and 7.0 ± 1.8 (range: 4 - 10) to 4.4 ± 2.6 (range: 1 - 9) for two-year follow-up. For one-year follow-up, the average ODI score improved from 53 ± 19% (range: 18 - 70%) to 37 ± 17% (range: 12 - 64%), and for two-year follow-up, the average improved from 53 ± 18% (range: 18 - 80%) to 31 ± 24% (range: 2 - 92%). The level of improvement in pain and function was similar to previously published data for 1- and 2-level fusions, but overall pain and function scores were worse in this study group.

Conclusions. Arthrodesis for 3- and 4-level DDD is, on average, a successful surgery that shows clinically significant improvements in function and pain similar to fusion for 1- and 2-levels with low rates of re-operation. Patients with involvement of 3- or 4-levels have higher disability and pain both pre- and post-operatively compared to shorter fusion level involvement. ***KS J Med 2016;9(3):50-53.***

INTRODUCTION

Degenerative disc disease (DDD) is a common pathologic process that can cause low back pain. A non-operative approach is preferred initially and is often successful, but some patients progress to lumbar stenosis, facet arthrosis, and/or degenerative spondylolisthesis, all of which may be associated with chronic low back pain and/or sciatica (leg pain, numbness, or tingling) and can lead to significant disability.[1,2] Lumbar spinal fusion improves pain and function in patients with DDD who have failed non-operative treatment, but remains controversial as literature is limited and has focused mainly on 1- and 2-level procedures.[2-5] With improvement of surgical approach, fusion techniques, and patient selection, surgical treatment has shown improvement in pain and disability.[2,6] Despite some clinical success, concern remains over complications, cost, adjacent segment disease, and question of improvement over non-operative treatment.[2,6,7] Fusion for 1- and 2-level disease has become a common practice, but longer fusion has been utilized less due to limited evidence and concern of higher complication rate.

Retrospective studies completed in the last decade have produced mixed results on how length of fusion affects outcomes. Lettice et al.[8] in 2005 showed higher pseudarthrosis and re-operation rates, but equal functional scores comparing long to short fusion over two years of follow-up. This group included posterior and 360° approaches. Suratwala et al.[3] in 2008 showed improvement in post-operative functional scores, including 30% improvement in Oswestry Disability Index (ODI), for patients undergoing 360° fusion with either anterior or transforaminal lumbar interbody fusion. However, there was a 20% pseudarthrosis rate, 11% adjacent segment disease, and no control or comparison group. Most recently, Lee et al.[9] in 2011 found patients undergoing three or more level fusions had lower post-operative functional scores but equal pain and satisfaction outcomes compared to short fusions. Their study used posterior approach with interbody fusion. Overall, this literature indicated improvement in pain, function, and disability but inconsistent results compared with short fusion.

The purpose of this study was to report the clinical and functional outcomes of a consecutive series of patients with 3- or 4-level DDD between vertebral levels L2 to S1 who were treated with combined anterior lumbar interbody fusion (ALIF) and posterior spinal fusion at one-year and two-year follow-ups.

METHODS

After Institutional Review Board approval was obtained, a retrospective chart review was performed on all patients who underwent combined anterior and posterior fusion of 3 or 4 vertebral levels for DDD by one surgeon between August 2002 and January 2012. The inclusion criteria included subjects' age between 18 and 75, diagnosis of 3- or 4-level DDD amenable to treatment with fusion, failure of at least three months of non-operative treatment. Exclusion criteria included previous spine fusion, two or fewer degenerative levels, major deformity, previous infection or tumor, or a diagnosis other than DDD, including any one of the following diagnoses: spinal stenosis

requiring decompression, isthmic spondylolisthesis, or degenerative spondylolisthesis greater than three (3) millimeters.

Subjects who underwent fusion and met the above criteria were identified through surgical log. Data were collected retrospectively by chart review and included pre-operative, surgical, functional, and post-operative information collected as part of the routine clinical visit and standard of care at one-year and two-year follow-up. Patients had their disability and pain level measured at pre-operative (baseline) and on follow-up visits using the Visual Analog Scale (VAS) for back pain and ODI (range 0 to 100%) for function. The VAS scores were recorded as numerical values 0 to 10; "0" indicated no back pain and "10" indicated unbearable back pain. Patients were asked to indicate where their current pain level was on the line. The ODI was measured using a 10-section questionnaire (range: 0, normal to 5, impossible) asking the patient to indicate the intensity of their pain and to what degree pain is affecting daily activities such as sitting, walking, and traveling. Responses were scored and reflected the patient's percentage of disability. The measurement of success improvement criteria was based on VAS with at least one unit scale improvement different compared to the baseline (pre-operatively), and on ODI scores of at least 15% difference compared to the baseline.

Pre- and post-operative data included patient's age, sex, height, weight, race, smoking status, diagnoses, prior surgeries, past medical history, flexion-extension range of motion (forward and backward bending), pain score, and ODI. Operative data included operative time, blood loss, surgical implants used, surgical approach, operative levels treated, and complications. Post-operatively, the same patient demographics were recorded, as well as post-operative complications, pain scores, and ODI.

Statistical analysis. All statistical analyses were conducted using SPSS software (Version 19.0; SPSS Inc, Chicago, IL) and the level of significant difference was defined as $p < 0.05$. The values were recorded as the mean with standard deviation. A one-way analysis of variance (ANOVA) was conducted to determine the difference in pre-operative and post-operative clinical and functional outcomes within each study group. Appropriate Independent Samples t-test was used to compare outcomes between study groups. Demographic and pre-operative data also were compared between study groups.

RESULTS

There were a total of 55 patients who met the inclusion criteria; only 32 (15 female and 17 male) had available medical records for evaluation and were included in this study. Of the 32 patients, 14 (44%) had one-year follow-up and 18 (56%) had two-year follow-up. Both groups had similar ages (average: 46 years, range: 28 - 58 years), body mass index (BMI), race (Caucasians mostly), a high percentage with no previous spine surgery (> 80%), and most had 3-level spinal fusion (Table 1). There were no significant differences between the two groups in gender, age, race, tobacco usage at time of surgery, height, weight, BMI, prior surgical treatment, or number of levels fused ($p > 0.05$).

Intra-operative data. The average operative time for 3-level fusion was 273 ± 31 minutes (range: 225 - 345 minutes), while 4-level fusion was 345 ± 46 minutes (range: 300 - 420 minutes). The 4-level fusion took an average of 72 minutes (26%) more than 3-level fusion. Meanwhile, the average estimated blood loss for 3- and 4-level fusion was 224 ± 152 mL (range: 75 - 600 mL) and 580 ± 297 mL (range: 400 - 1100 mL), respectively. The estimated blood loss for 4-level fusion was about 356 mL (159%) more than 3-level fusion.

Flexion-extension range of motion. For patients with one-year follow-up, 7 (50%) of the 14 patients sustained the same flexion-extension range of motion (ROM) compared to their pre-operative ROM, while six patients (43%) improved their ROM (10° ROM: 2, 20° ROM: 3, 40° ROM: 1), and one patient (7%) reduced 30° of flexion-extension ROM. Of the 18 patients with two-year follow-up, nine (50%) sustained the same flexion-extension ROM, while eight (44%) improved their ROM (10° ROM: 1, 20° ROM: 1, 30° ROM: 3, 50° ROM: 1, 60° ROM: 2). Similar to the one-year follow-up group, there was a patient with reduced 30° ROM compared to the pre-operative ROM.

Table 1. Patient demographics.

		1-year follow-up (N=14)	2-year follow-up (N=18)	p-value
Gender	Female	6 (43%)	9 (50%)	0.699
	Male	8 (57%)	9 (50%)	0.699
Age (years, mean ± SD) (range)		46 ± 8 (28 - 58)	45 ± 9 (28 - 58)	0.656
Race	Caucasians	13 (93%)	16 (89%)	0.713
	African-Americans	1 (7%)	1 (6%)	0.860
	Hispanics	0 (0%)	1 (6%)	0.387
Tobacco Usage at Time of Surgery	Never	4 (29%)	7 (39%)	0.557
	Former	2 (14%)	5 (28%)	0.376
	Current	8 (57%)	6 (33%)	0.189
Height (inches, mean ± SD)		68 ± 4	69 ± 4	0.680
Weight (lbs, mean ± SD)		210 ± 40	211 ± 47	0.947
BMI		31.9 ± 4.9	31.4 ± 5.4	0.771
Prior Surgical Treatment	Yes	3 (21%)	2 (11%)	0.442
	No	11 (79%)	16 (89%)	0.442
Number of Levels Fused	3-level	13 (93%)	14 (78%)	0.258
	4-level	1 (7%)	4 (22%)	0.258

VAS pain scores. The average VAS score improved from 6.5 ± 1.5 (range: 4 - 9) pre-operatively to 4.4 ± 1.7 (range: 2 - 7) post-operatively for one-year follow-up, and 7.0 ± 1.8 (range: 4 - 10) pre-operatively to 4.4 ± 2.6

(range: 1 - 9) post-operatively for two-year follow-up. Both groups showed a statistically significant improvement (Table 2). One patient with two-year follow-up showed a significant increase in pain after surgery (pre-operative: 6, post-operative: 9). There was no significant difference detected between the one-year and two-year follow-up in terms of VAS pain scores.

Table 2. Summary results for VAS pain scores and ODI scores.

		Pre-Op	Post-Op	Difference	p-value (pre vs. post)	p-value (1-yr. vs. 2-yr.)
VAS	1 yr. Follow-up	6.5 ± 1.5	4.4 ± 1.7	2.1 ± 1.6	0.00	0.08
	2 yr. Follow-up	7.0 ± 1.8	4.4 ± 2.6	2.6 ± 2.8	0.00	
ODI	1 yr. Follow-up	52.6 ± 18.5%	37.4 ± 16.6%	15.1 ± 18.5%	0.03	0.26
	2 yr. Follow-up	53.0 ± 18.4%	30.8 ± 24.1%	22.2 ± 24.1%	0.00	

Oswestry Disability Index (ODI) scores. For one-year follow-up, the average ODI score improved significantly from 53 ± 19% (p = 0.03; range: 18 - 70%) pre-operatively to 37 ± 17% (range: 12 - 64%) post-operatively (Table 2). However, four patients (29%) remained unchanged, eight patients (57%) improved but only five patients (36%) improved at least 15% compared to baseline, and two patients (14%) worsened (Table 3). For two-year follow-up, the average improved significantly 53 ± 18% (p = 0.002; range: 18 - 80%) pre-operatively to 31 ± 24% (range: 2 - 92%) post-operatively (Table 2). Four patients (22%) remain unchanged, 12 patients (67%) improved but only 10 out of the 12 patients (56%) improved at least 15% compared to baseline, and two patients (11%) worsened (Table 4). There was no significant difference detected between the one-year and two-year follow-up in terms of ODI scores.

Complications. Seven (22%) of 32 patients experienced some complications and no patient experienced intra-operative or major complications such as death or neurological damage. Post-operatively, one patient was re-hospitalized at five months for severe back pain, and this patient had adjacent-level degenerative disease at one-year post-operatively. One patient had a retroperitoneal hematoma found post-operatively that was resolved by six weeks with a drain and had no further complications. One patient had severe bilateral lower extremity pain that improved with non-operative modalities by six months. Four patients had a superficial surgical site infection that was treated with oral antibiotics and all resolved by the six week post-operative appointment.

Table 3. Clinical Oswestry Disability Index (ODI) scores for one-year follow-up.

	Post-Operative ODI Scores					
Pre-op ODI Scores	Minimal Disability (0 - 20%)	Moderate Disability (21 - 40%)	Severe Disability (41 - 60%)	Crippled (61 - 80%)	Bed-ridden (81 - 100%)	Total (Row Sum)
Minimal Disability (0 - 20%)	2	0	0	0	0	2
Moderate Disability (21 - 40%)	0	0	1	0	0	1
Severe Disability (41 - 60%)	0	2	2	1	0	5
Crippled (61 - 80%)	1	3	2	0	0	6
Bed-ridden (81 - 100%)	0	0	0	0	0	0
Total (Column Sum)	3	5	5	1	0	14

Note: = patient worsens; = no change; = patient improves

Table 4. Clinical Oswestry Disability Index (ODI) scores for two-year follow-up.

	Post-Operative ODI Scores					
Pre-op ODI Scores	Minimal Disability (0 - 20%)	Moderate Disability (21 - 40%)	Severe Disability (41 - 60%)	Crippled (61 - 80%)	Bed-ridden (81 - 100%)	Total (Row Sum)
Minimal Disability (0 - 20%)	2	0	0	0	0	2
Moderate Disability (21 - 40%)	0	0	1	0	0	1
Severe Disability (41 - 60%)	3	4	2	0	0	9
Crippled (61 - 80%)	2	2	1	0	1	6
Bed-ridden (81 - 100%)	0	0	0	0	0	0
Total (Column Sum)	7	6	4	0	1	18

Note: = patient worsens; = no change; = patient improves

DISCUSSION

Degeneration of lumbar intervertebral discs can be a debilitating disease, even without spinal stenosis or dominant lower extremity symptoms.[1] Non-operative modalities are the preferred treatment, but when the symptoms are persistent, surgical intervention can be an option.[10,11] For 1- and 2-level disease, arthrodesis with an anterior-only or 360° fusion has been shown to be safe and successful in improving pain and function.[3,4,12] However, studies on longer fusions for DDD have been scarce and the results less predictable.[3,8,9] This study indicates that patients who undergo combined ALIF and posterior spinal fusion for 3- and 4-level DDD have, on average, significant improvement in both function and pain after one and two years post-operative.

Subjects who underwent long fusion did not have an increased frequency of minor complications, such as persistent severe pain, hematoma, or surgical site infection when compared to subjects who underwent short fusion (1- or 2-level fusion).[4,5] However, the pain level improvement for this study was only 2.1 for one-year follow-up and 2.6 for two-year follow-up, which was significantly less than the improvement seen in 1- and 2-level fusions at two-year follow-up (3.3).[4]

Gains in functional outcomes were similar to those undergoing short fusions and similar percentages of patients undergoing long fusion improved or maintained functionality compared with those who had shorter fusions (current study: one-year follow-up: 15% difference, two-year follow-up: 22% difference, previous study:[4] 17% difference). However, patients undergoing longer fusion had overall higher pre- and post-operative disability compared to those who underwent short fusion (current study: pre 53%, post 1-yr 37% and 2-yr 30%; previous study: pre 44%, post 27%). One subject who underwent 3-level fusion had ODI increase to above 81, bed-ridden classification, which did not occur in any short-fusion subjects. Operative time and blood loss were much higher with longer fusion when compared to the short fusion with only ALIF,[4] but similar to published 360° fusion for two-levels.[5] This was expected, but poses increasing risk of infection and need for transfusion. Finally, the long fusion cohort had a severe complication, acute renal failure eventually leading to death, which was not seen in the short fusion group.

There were limitations to the study. First, radiographic image analysis was not included in this study which did not allow the investigators to evaluate success of bony fusion, adjacent level disease, maintenance of disc height, or loss of fixation. In addition, the sample size was small and only 58% of patients initially identified through surgical logs had available medical records with pre- and post-operative evaluations. The two-year follow-up period was not sufficient for evaluation of full impact of the surgical treatment. In the future, it would be helpful to follow a larger group of patients prospectively for a longer period of time to evaluate function, pain, and risk of adjacent level disease or need for re-operation over time. It also would be useful to compare to a cohort of patients who choose non-operative treatment.

CONCLUSION

Arthrodesis for 3- and 4-level DDD is, on average, a successful surgery that shows clinically significant improvements in function and pain similar to fusion for 1- and 2-levels with low rates of re-operation. Patients with involvement of 3- or 4-levels have higher disability and pain, both pre- and post-operatively, compared to shorter fusion level involvement. Modern surgical approach and arthrodesis technique are improving patient outcomes in DDD, but further research is needed with greater number of patients and longer follow-up with radiographs to strengthen the evidence indicating a safe and effective procedure.

CONFLICT OF INTEREST STATEMENT

The authors of this study did not receive any funds, payments, or other personal benefits. No commitments or agreements were related in any way to the research subject or study investigators.

REFERENCES

[1] Madigan L, Vaccaro AR, Spector LR, Milam RA. Management of symptomatic lumbar degenerative disk disease. J Am Acad Orthop Surg 2009; 17(2):102-111. PMID: 19202123.
[2] Phillips FM, Slosar PJ, Youssef JA, Andersson G, Papatheofanis F. Lumbar spine fusion for lumbar back pain due to degenerative disc disease. Spine (Phila Pa 1976) 2013; 38(7):E409-422. PMID: 23334400.
[3] Suratwala SJ, Pinto MR, Gilbert TJ, Winter RB, Wroblewski JM. Functional and radiologic outcomes of 360 degrees fusion of three or more motion levels in the lumbar spine for degenerative disc disease. Spine (Phila Pa 1976) 2009; 34(10):E351-E358. PMID: 19404164.
[4] Lammli J, Whitaker MC, Moskowitz A, et al. Stand-alone anterior lumbar interbody fusion for lumbar degenerative disc disease of the lumbar spine: Results with a two-year follow-up. Spine (Phila Pa 1976) 2014; 39(15):E894-901. PMID: 24825156.
[5] Delamarter R, Zigler JE, Balderston RA, Cammisa FP, Goldstein JA, Spivak JM. Prospective, randomized, multicenter food and drug administration investigational device exemption study of the prodisc-l total disc replacement compared with circumferential arthrodesis for the treatment of two-level lumbar degenerative disc disease. J Bone Joint Surg Am 2011; 93(8):705-715. PMID: 21398574.
[6] Fritzell P, Hägg O, Wessberg P, Nordwall A. Chronic low back pain and fusion: A comparison of three surgical techniques. Spine (Phila Pa 1976) 2002; 27(11):1131-1141. PMID: 12045508.
[7] Taher F, Essig D, Lebl DR, et al. Lumbar degenerative disc disease: Current and future concepts of diagnosis and management. Adv Orthop 2012; 2012:970752. PMID: 22567411.
[8] Lettice JJ, Kula TA, Derby R, Kim BJ, Lee SH, Seo KS. Does the number of levels affect lumbar fusion outcome? Spine (Phila Pa 1976) 2005; 30(6):675-681. PMID: 15770184.
[9] Lee CS, Chung SS, Shin SK, Park SJ, Lee HI, Kang KC. Differences in post-operative functional disability and patient satisfaction between patients with long (three or more) and short (less than three) lumbar fusions. J Bone Joint Surg Br 2011; 93(10):1400-1404. PMID: 21969442.
[10] Fritzell P, Hägg O, Wessberg P, Nordwall A; Swedish Lumbar Spine Study Group. 2001 Volvo Award Winner in Clinical Studies: Lumbar fusion versus nonsurgical treatment for chronic low back pain: A multicenter randomized controlled trial from the Swedish Lumbar Spine Study Group. Spine (Phila Pa 1976) 2001; 26(23):2521-2532; discussion 2532-2534. PMID: 11725230.
[11] Gibson JN, Waddell G. Surgery for degenerative lumbar spondylosis. Cochrane Database Syst Rev 2005; (4):CD001352. PMID: 16235281.
[12] Gertzbein SD, Hollopeter M, Hall SD. Analysis of circumferential lumbar fusion outcome in the treatment of degenerative disc disease of the lumbar spine. J Spinal Disord 1998; 11(6):472-478. PMID: 9884290.

Keywords: intervertebral disc degeneration, spinal fusion, retrospective studies

KANSAS JOURNAL of MEDICINE

Associations between Fall Distance, Age, and Trauma Outcomes in Older Adult Patients

Gina M. Berg, Ph.D., MBA[1,2], Ashley M. Hervey, M.Ed.[1], Felecia A. Lee, Ph.D.[1], Sarah Holmes, PA-C[3], Kayla R. Keuter, PA-C, MPH, M.A.[3], Paul B. Harrison, M.D.[2]
[1]University of Kansas School of Medicine-Wichita, Department of Family and Community Medicine, Wichita, KS
[2]Wesley Medical Center, Trauma Services, Wichita, KS
[3]Wichita State University, Department of Physician Assistant, Wichita, KS

ABSTRACT

Introduction. Falls are the leading cause of injury death among older adults. This study sought to determine if there are differences between fall distance (ground level vs greater than ground level) and age (old vs very old) in terms of in-hospital mortality, orthopedic consultations, and neurological consultations.

Methods. A retrospective trauma registry review was conducted of older adult patients (aged > 65 years), admitted to a Midwestern Level I trauma facility (2005 - 2010) due to a fall.

Results. Of the 1,064 patients analyzed, the majority fell from ground level compared to greater than ground level (64% and 36%, respectively). Median age was 80 years. Fall distance was not associated significantly with in-hospital mortality (OR 0.88; CI 0.50 - 1.54) or neurological consultations (OR 1.02; CI 0.72 - 1.43), but was associated with orthopedic consultations (OR 1.49; CI 1.09 - 2.04). Age was not associated with in-hospital mortality or neurological or orthopedic consultations.

Conclusions. Fall distance was not associated with in-hospital mortality or receiving a neurological consultation. However, older adults who fell from greater than ground level were more likely to receive orthopedic consultations. There were no differences in in-hospital mortality or receiving a neurological or orthopedic consultation based on age. These findings indicated that as the older adult population increases, burden of care will increase for trauma centers and neurological services. ***KS J Med 2016;9(3):54-57.***

INTRODUCTION

By the year 2040, older adults will comprise approximately 22% of the U.S. population.[1] Falls are the leading cause of fatal injuries among the older adult population, affecting one in three aged 65 years or older and half of those aged 80 years or older.[2] Despite the low-energy mechanism, falls from ground level can result in disproportionate injury and potentially death in older adults.[3] Spaniolas et al.[4] noted a significant increase in incidence of severely injured older adult patients 70 years of age or older after a ground level fall compared with those 69 years and younger (11.5% vs 9%; $p < 0.0001$).

Compared to younger counterparts, older patients sustain severe injury more frequently and die more often following trauma, due to reduced physiological reserve, underlying comorbidities, and ensuing complications.[5,6] In addition to higher mortality rates, older adults who suffer a traumatic event have prolonged hospitalization and consume a disproportionate amount of resources.[7] McKevitt et al.[8] found when using resource requirements as measured by length of stay and number of consults, older adults have greater use per admission than younger patients with similar injury severity. After suffering a fall, 20 - 30% of older adults will experience a moderate to severe injury, including fractures and head traumas, often requiring orthopedic and neurological consultations.[9]

As the population ages and older adults become larger consumers of trauma care, the available resources may not support the growing need of geriatric specific trauma services adequately. Currently, there is a lack of data describing the utilization of trauma resources in the older adult population, specifically neurological and orthopedic consultations in terms of fall-related injuries. Therefore, we sought to determine if, in older adult trauma patients, there were differences between fall distance and age in terms of in-hospital mortality, orthopedic consultations, and neurological consultations.

METHODS

This was a retrospective trauma registry review of older adult patients (aged > 65 years) identified as sustaining an injury due to a fall, admitted to a Midwestern Level I trauma facility in a predominately rural state between January 1, 2005 and December 31, 2010. Patients who were dead on arrival, burn victims, and those transferred to another acute care facility within one week were excluded as their final outcomes are not present in the registry. A total of 635 patients with missing Injury Severity Score (ISS) and hospital Glasgow Coma Scale (GCS) also were excluded from analysis. Approval for this study was obtained from all relevant institutional review boards.

Study variables. Demographic and clinical data extracted from the trauma registry included age, gender, race, ISS, hospital GCS, injury location, fall distance, medical consultations, hospital and intensive care unit (ICU) length of stay (LOS), physiological complications (e.g., pulmonary, cardiovascular), procedures, hospital disposition (excluding deceased), and in-hospital mortality. For comparison, patients were divided into age categories defined as old (aged 65 - 79 years) and very old (aged > 80 years) based on the median age of 80 years. Fall distance was defined as ground level (GL: i.e., standing, slipping, tripping) and greater than ground level (> GL: e.g., stairs, ladder, or one level to another). Outcome variables were defined as in-hospital mortality, orthopedic consultations, and neurological consultations.

Statistical analysis. Descriptive statistics were summarized using frequencies (percentages) and medians (range). Differences in study variables were compared according to fall distance and age

and evaluated by chi-square statistics and Mann-Whitney U tests due to the inability to meet parametric distribution assumptions. Logistic regression analyses were used to analyze outcome differences based on fall distance and age. Medical factors known to be associated with trauma outcomes (age, gender, and ISS)[10,11] were controlled in these analyses in addition to hospital GCS, ICU and hospital LOS, and physiological complications with in-hospital mortality, orthopedic consultations, and neurological consultations as outcome variables. Statistical significance was defined as $p < 0.05$. Adjusted odds ratio (AOR) and 95% confidence intervals (CI) are reported. Statistical analyses were performed using SPSS for Windows, Version 20.0 (IBM, Armonk, NY).

RESULTS

Of the 1,064 patients in the final sample, the median age of the entire population was 80 years (Table 1). GL falls were more common than > GL falls (64% and 36%, respectively).

Fall distance: Univariate analysis. Falls > GL had significantly higher median ISS compared to GL (10 vs 9; $p = 0.019$). No significant differences were observed in hospital GCS ($p = 0.262$) or injury locations between GL and > GL falls (Table 1). There were also no observed differences in the median number of physiological complications ($p = 0.224$). No differences were identified in ICU LOS ($p = 0.394$) or hospital LOS ($p = 0.950$). Differences were found in orthopedic consultations ($p = 0.033$), but not neurological consultations ($p = 0.338$). Falls > GL were more likely to receive an orthopedic consult. There was no significant difference in in-hospital mortality between GL and > GL falls ($p = 0.669$).

Age: Univariate analysis. Neither ISS nor hospital GCS were significantly different between the old and very old (Table 2). The only significantly different injury locations between old and very old were external (7.7% vs 11.4%; $p < 0.05$) and extremities (14.6% vs 17.9%; $p < 0.05$), respectively. There also were no observed differences in the median number of physiological complications ($p = 0.252$). Differences were identified in ICU LOS (0 [0-41] vs 0 [0-18] days; $p = 0.011$), but not hospital LOS ($p = 0.607$). Differences were not found in orthopedic consultations ($p = 0.980$) or neurological consultations ($p = 0.183$). There was no significant difference in in-hospital mortality between the old and very old ($p = 0.764$).

Table 1. Demographics and outcomes based on fall distance.[a]

	Total 1064	Ground Level 681 (64.0)	> Ground Level 383 (36.0)	p
Age (median, range)	80 (65 - 103)	82 (65 - 101)	78 (65 - 103)	**< 0.001**
ISS (median, range)	9 (1 - 42)	9 (1 - 42)	10 (1 - 41)	**0.019**
Hospital GCS (median, range)	15 (3 -15)	15 (3 - 15)	15 (3 - 15)	0.262
ICU LOS (excludes deceased; median, range)	0 (0 - 41)	0 (0-19)	0 (0-41)	0.394
Hospital LOS (excludes deceased; median, range)	3 (1 - 43)	3 (1 - 35)	3 (1 - 43)	0.950
Physiological Complication (median, range)	0 (0 - 7)	0 (0 - 6)	0 (0 - 7)	0.224
Age				**< 0.001**
65 - 79	493 (46.3)	276 (40.5)	217 (56.7)	
> 80	571 (53.7)	405 (59.5)	166 (43.3)	
Gender				**< 0.001**
Female	611 (57.4)	420 (61.7)	191 (49.9)	
Race				0.340
White	1046 (98.4)	671 (98.7)	375 (97.9)	
Injury Location				
Abdominal	27 (2.5)	16 (2.3)	11 (2.9)	0.603
Chest	50 (4.7)	31 (4.6)	19 (5.0)	0.762
External (skin and thermal)	103 (9.7)	67 (9.8)	36 (9.4)	0.849
Extremities (including pelvis)	174 (16.4)	17 (17.2)	57 (14.9)	0.552
Face	43 (4.0)	27 (4.0)	16 (4.2)	0.866
Head or neck	357 (33.6)	234 (34.4)	123 (32.1)	0.456
Neurological Consultation	471 (44.3)	294 (43.2)	177 (46.2)	0.338
Orthopedic Consultation	268 (25.2)	157 (23.1)	111 (29.0)	0.033
Home Disposition[b] (excludes deceased)				0.461
Home	549 (56.5)	349 (55.9)	200 (57.5)	
Continued Care	405 (41.7)	261 (41.8)	144 (35.6)	
Non-Home	18 (1.9)	14 (2.2)	4 (22.2)	
Mortality				0.669
Deceased	92 (8.6)	57 (8.4)	35 (9.1)	
Survived	972 (91.4)	624 (91.6)	348 (90.9)	

Abbreviations: GCS: Glasgow Coma Score; ICU: intensive care unit; ISS: Injury Severity Score; LOS: length of stay.
[a]Percentages may not add to 100 due to incomplete or missing data; data presented as frequency (%) unless otherwise specified. Mann Whitney U test completed for means testing. Chi-square test of association completed for frequency analysis. Bolded numbers denote statistical significance.
[b]Home: home and home with health care; Continued Care: hospice, nursing home, other acute care facility, rehabilitation, skilled nursing, specialty hospital; Non-Home: mental health facility, other.

Table 2. Demographics and outcomes based on age.[a]

	Ages 65 - 79 493 (46.3)	Age ≥ 80 571 (53.7)	p
ISS (median, range)	9 (1 - 42)	9 (1 - 35)	0.550
Hospital GCS (median, range)	15 (3 - 15)	15 (3 - 15)	0.293
ICU LOS (excludes deceased; median, range)	0 (0 - 41)	0 (0 - 18)	**0.011**
Hospital LOS (excludes deceased; median, range)	3 (1-43)	3 (1 - 25)	0.607
Physiological Complication (median, range)	0 (0 - 7)	0 (0 - 5)	0.252
Gender			**0.001**
Female	256 (51.9)	355 (62.2)	
Race			0.127
White	482 (97.8)	564 (53.9)	
Fall Distance			**< 0.001**
Ground Level	276 (56.0)	405 (70.9)	
≥ Ground Level	217 (44.0)	166 (29.1)	
Injury Location			
Abdominal	17 (3.4)	10 (1.8)	0.079
Chest	22 (4.5)	28 (4.9)	0.735
External (skin and thermal)	38 (7.7)	65 (11.4)	**0.012**
Extremities (including pelvis)	72 (14.6)	102 (17.9)	**0.033**
Face	25 (5.1)	18 (3.2)	0.113
Head or neck	160 (32.5)	197 (34.5)	0.481
Neurological Consultation	229 (46.5)	242 (42.4)	0.183
Orthopedic Consultation	124 (25.2)	144 (25.2)	0.980
Home Disposition[b] (excludes deceased)			
Home	290 (64.6)	259 (49.5)	**< 0.001**
Continued Care	154 (34.3)	251 (48.0)	
Non-Home	5 (1.1)	13 (2.5)	
Mortality			0.764
Deceased	44 (8.9)	48 (8.4)	
Survived	449 (91.1)	523 (91.6)	

Abbreviations: GCS: Glasgow coma score; ICU: intensive care unit; ISS: Injury Severity Score; LOS: length of stay.
[a]Percentages may not add to 100 due to incomplete or missing data; data presented as frequency (%) unless otherwise specified. Mann Whitney U test completed for means testing. Chi-square test of association completed for frequency analysis. Bolded numbers denote statistical significance.
[b]Home: home and home with health care; Continued Care: hospice, nursing home, other acute care facility, rehabilitation, skilled nursing, specialty hospital; Non-Home: mental health facility, other.

Multivariable analysis. Logistic regression analyses were completed to determine if fall distance was associated with in-hospital mortality, orthopedic consultations, and neurological consultations (Table 3). Fall distance was not associated significantly with in-hospital mortality (OR 0.88; CI 0.50 - 1.54) or neurological consultations (OR 1.02; CI 0.72 - 1.43), but was associated with orthopedic consultations (OR 1.49; CI 1.09 - 2.04). Age was not associated with in-hospital mortality (OR 1.02; CI 0.98 - 1.06), neurological consultations (OR 0.98; CI 0.96 - 1.00), or orthopedic consultations (OR 1.00; CI 0.98 - 1.02).

Table 3. Logistic regression.[a]

	Mortality	Neurological Consult	Orthopedic Consult
	Adjusted OR 95% CI	Adjusted OR 95% CI	Adjusted OR 95% CI
Age	1.02 (0.98 - 1.06)	0.98 (0.96 - 1.00)	1.00 (0.98 - 1.02)
Fall Distance	0.88 (0.50 - 1.54)	1.02 (0.72 - 1.43)	**1.49 (1.09 - 2.04)**
Gender	1.91 (1.10 - 3.3)	1.03 (0.74 - 1.44)	2.15 (1.56 - 2.96)
Injury Severity Score	3.14 (1.56 - 6.33)	13.65 (8.99 - 20.72)	0.93 (0.63 - 1.38)
Hospital GCS[b]			
Severe	9.22 (4.86 - 17.49)	0.93 (0.46 - 1.88)	3.65 (2.12 - 6.27)
Moderate	3.53 (1.55 - 8.05)	0.36 (0.17 - 0.76)	0.71 (0.32 - 1.55)
Hospital LOS[c]			
1 day or less	21.51 (7.55 - 61.32)	0.66 (0.38 - 1.13)	0.16 (0.09 - 0.26)
2 - 3 days	5.72 (2.37 - 13.80)	2.11 (1.29 - 3.46)	0.33 (0.21 - 0.51)
4 - 6 days	3.08 (1.31 - 7.25)	1.32 (0.80 - 2.18)	0.61 (0.40 - 0.92)
ICU LOS	6.35 (2.73 - 14.79)	3.17 (2.13 - 4.71)	0.61 (0.41 - 0.92)
Physiological Complication Count	5.6 (2.81 - 11.16)	0.89 (0.54 - 1.49)	1.26 (0.82 - 1.94)

Abbreviations: CI: Confidence Interval; OR: odds ratio
[a]Adjusted for gender, injury severity score, hospital GCS, hospital LOS, ICU LOS and physiological complications. Bolded numbers denote statistical significance.
[b]Mild GCS used a reference category
[c]Seven (7) days or more used as reference category

DISCUSSION

This study sought to determine if there were differences in in-hospital mortality, orthopedic consultations, and neurological consultations based on distance fallen and age. Fall distance was not associated with in-hospital mortality or receiving a neurological consultation. Fall distance was associated with receiving an orthopedic consultation. Odds of receiving an orthopedic consultation was 49% higher for those who fell from > GL compared to those who fell from GL. However, there were no differences in injury location between older adults who fell from GL or > GL. Age was not associated with in-hospital mortality, neurological consultations, or orthopedic consultations.

These findings are similar to a study completed by Gelbard et al.[12] who determined there were no significant differences in mortality between non-ground level falls and ground level falls in adults aged 65 years and older. However, when reviewing low velocity falls, Bergeron et al.[13] determined length of stay ($p < 0.001$) and mortality ($p < 0.001$) were significantly higher in the elderly (aged > 65 years) compared to the non-elderly.

Thus, regardless of the distance fallen, age should be an indicator for poorer outcomes due to reduced physiological reserve, comorbidities, and complications.[5,6]

With the growing older adult population, significant strain on resources can affect care. This population shift may result in a higher mortality rate due to an increase in falls as a mechanism of injury.[14] This injured population represents a subset of trauma patients that will place a significant strain on resources and present additional challenges to optimal care.[15] Fallon et al.[15] described the use of a geriatric trauma team which mandates a consult from a group of geriatricians with education and skills in caring for older adults. These specialized care "units" may be necessary in the future to provide appropriate care for older adults. Effective trauma program management of the elderly trauma patient and allocation of resources depend on an understanding of the mechanisms leading to injuries in these cases.

Limitations. The trauma registry is not designed specifically for research purposes. Conclusions drawn from results are specific to a level I trauma center in a predominately rural state and may not generalize to other trauma populations. Additionally, patient characteristics (e.g., comorbidities) which may influence outcomes following falls were not included due to the incomplete nature of the variable.

Future research. Research on falls is limited because of the inability to measure distance fallen directly.[16] Future research should focus on prospective multicenter studies examining factors surrounding falls and explore the interactions between fall distance and age. This is the first step in developing specific protocols in the management of older adult trauma patients, both facility specific and triage guidelines. Further, since the majority of falls are from ground level, fall prevention outreach education coordinated by trauma programs should emphasize strategies to prevent GL falls, with the expectation to reduce fall-related injuries, comorbidities, death, and burden on the health care system. Given the high rate of mortality (8.6%) in this population compared to previous literature utilizing the National Trauma Databank,[4] future research should evaluate mortality trends in older adults who have suffered a fall.

CONCLUSION

Fall distance (GL vs > GL) was not a predictor of in-hospital mortality or likelihood of receiving a neurological consultation in the older adult trauma population. However, older adults who fell from > GL were more likely to receive orthopedic consults. Older adults who fall from GL have similar outcomes compared to those who fall from > GL. Similarly, very old (aged > 80 years) patients have similar outcomes compared to the old (aged 65 - 79 years). There were no differences identified in in-hospital mortality, receiving an orthopedic consultations, or neurological consultation based on age.

As the older adult population increases, patient care burden also will increase for trauma centers and neurological services. A better understanding of the population and the mechanisms leading to injuries will aid in the management of the elderly trauma patient and appropriate allocation of resources.

REFERENCES

[1] Administration on Aging. Aging statistics. http://www.aoa.gov/Aging_Statistics/. Accessed June 14, 2016.
[2] Chisholm KM, Harruff RC. Elderly deaths due to ground-level falls. Am J Forensic Med Pathol 2010; 31(4):350-354. PMID: 20938326.
[3] Sterling DA, O'Connor JA, Bonadies J. Geriatric falls: Injury severity is high and disproportionate to mechanism. J Trauma 2001; 50(1):116-119. PMID: 11231681.
[4] Spaniolas K, Cheng JD, Gestring ML, Sangosanya A, Stassen NA, Bankey PE. Ground level falls are associated with significant mortality in elderly patients. J Trauma 2010; 69(4):821-825. PMID: 20938268.
[5] Blumenthal J, Plummer E, Gambert SR. Trauma in the elderly: Causes and prevention. Clin Geriatr 2010; 18:21-24.
[6] Aschkenasy MT, Rothenhaus TC. Trauma and falls in the elderly. Emerg Med Clin North Am 2006; 24(2):413-432. PMID: 16584964.
[7] MacKenzie EJ, Morris JA Jr, Smith GS, Fahey M. Acute hospital costs of trauma in the United States: Implications for regionalized systems of care. J Trauma 1990; 30(9):1096-1103. PMID: 2213943.
[8] McKevitt EC, Calvert E, Ng A, et al. Geriatric trauma: Resource use and patient outcomes. Can J Surg 2003; 46(3):211-215. PMID: 12812248.
[9] World Health Organization. Falls: Fact Sheet. October 2012. http://www.who.int/mediacentre/factsheets/fs344/en/. Accessed March 15, 2016.
[10] Haider AH, Chang DC, Efron DT, Haut ER, Crandall M, Cornwell EE 3rd. Race and insurance status as risk factors for trauma mortality. Arch Surg 2008; 143(10):945-949. PMID: 18936372.
[11] Heffernan DS, Vera RM, Monaghan SF, et al. Impact of socioethnic factors on outcomes following traumatic brain injury. J Trauma 2011; 70(3):527-534. PMID: 21610339.
[12] Gelbard R, Inaba K, Okoye OT, et al. Falls in the elderly: A modern look at an old problem. Am J Surg 2014; 208(2):249-253. PMID: 24814307.
[13] Bergeron E, Clement J, Lavoie A, et al. A simple fall in the elderly: Not so simple. J Trauma 2006; 60(2):268-273. PMID: 16508481.
[14] Allen CJ, Hannay WM, Murray CR, et al. Causes of death differ between elderly and adult falls. J Trauma Acute Care Surg 2015; 79(4):617-621. PMID: 26402536.
[15] Fallon WF Jr, Rader E, Zyzanski S, et al. Geriatric outcomes are improved by a geriatric trauma consultation service. J Trauma 2006; 61(5):1040-1046. PMID: 17099506.
[16] Sasser SM, Hunt RC, Faul M, et al. Guidelines for field triage of injured patients: Recommendations of the National Expert Panel on Field Triage, 2011. MMWR Recomm Rep 2012; 61(RR-1):1-20. PMID: 22237112.

Keywords: falls, aged, mortality, referral and consultation

CASE REPORT

Colonic Spirochaetosis: An Unusual Cause of Chronic Diarrhea in the Developed World

Michael Green, M.D., Stephanie Pankow, M.D.,
Nathan Tofteland, M.D., William Salyers, M.D., MPH
University of Kansas School of Medicine-Wichita,
Department of Internal Medicine, Wichita, KS

INTRODUCTION

Infection of the intestinal tract with spirochaetosis is not a new phenomenon, but has been a known entity within the gastrointestinal (GI) tract for many centuries.[1] Debate exists as to whether its presence within the GI tract is pathogenic or commensal.[2] The two most common strains of spirochaetes found within the human GI tract are Brachyspira aalborgi and Brachyspira pilosicoli.[3] If the presence of these microbes are pathogenic, the pathway is poorly understood.[4] Spirochaetosis is more common in communities with poor living standards and those who are HIV positive.

Asymptomatic colonization is not uncommon and the prevalence of carriage has a wide distribution. In random rectal biopsies obtained in communities with high living standards, the prevalence was estimated to be 0.4 - 6.9% and there was little association with gastrointestinal symptoms.[5]

We report a case of colonic spirochaetosis associated with chronic diarrhea that improved with treatment.

CASE REPORT

A 50-year-old Caucasian male presented to the gastroenterology clinic by referral from the patient's primary care physician with a complaint of several years' duration of loose bowel movements. The patient had a history of gastroesophageal reflux disease, benign prostatic hyperplasia, and hyperlipidemia. At the time of presentation, the only medications the patient was taking were omeprazole and tamsulosin, both chronic medications.

The patient reported two to three loose bowel movements daily with associated lower abdominal pain and occasional melena. The patient endorsed a diet high in saturated fatty acids and carbohydrates. He increased his fiber intake, believing he suffered from irritable bowel syndrome; however, this intervention had no impact on his pain or loose stools. He denied change in appetite, weight loss, hematochezia, fever, and chills. The patient endorsed a history of extensive handling of chickens and chicken droppings. The patient's examination prior to endoscopy only revealed mild diffuse abdominal tenderness with deep palpation but no guarding or rebound. Given the age-appropriate need for screening colonoscopy and the patient's complaints, a colonoscopy was performed in addition to routine laboratory evaluation with a comprehensive metabolic panel, complete blood cell count, and serology for celiac disease; all were negative. The patient also was tested for HIV and hepatitis C, which were negative.

On endoscopy, he had normal appearing mucosa and random biopsies were obtained throughout the colon to evaluate for possible microscopic colitis. Serum tissue transglutaminase IgA antibody was negative. On pathologic evaluation of the random biopsies, there was a carpeting of spirochaetes on the mucosa throughout the ascending, transverse, and descending colon. The patient was referred to an infectious disease specialist. After evaluation, the patient was started on metronidazole 500 mg four times daily for a duration of ten days. In follow-up after completion of his treatment regimen, the diarrhea and lower abdominal pain had resolved. The patient underwent a repeat colonoscopy with random biopsies three months after he completed treatment, which showed no further spirochaetosis.

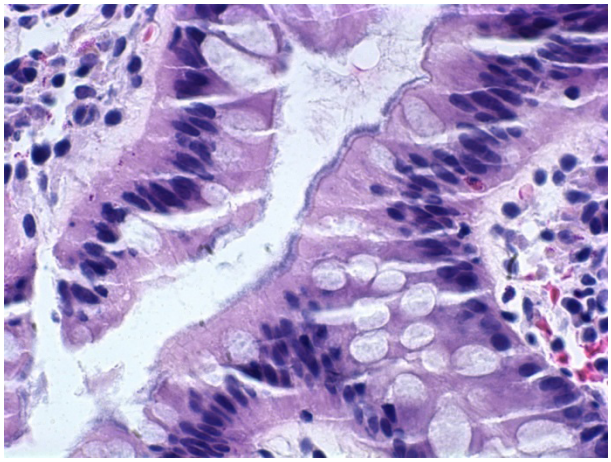

Figure 1. Spirochaete infection noted along the brush border.

DISCUSSION

Chronic watery diarrhea is a common presenting complaint to the primary care physician's clinic with a wide differential diagnosis. Infection by spirochaetes is an uncommon cause of chronic diarrhea, but is a diagnosis which should be considered. The most common presenting complaint of symptomatic infection with spirochaetes is mild to moderate disease symptoms including watery diarrhea, vague abdominal pain, flatulence, constipation, and fecal blood.[6,7]

The prevalence of spirochaete infection within developed countries is believed to be 1.1 - 5% and as high as 11.4 - 63.4% in countries with reduced access to sanitation services.[6,8] The most common pathogens within the human population are gram negative Brachyspira aalboygi and Brachyspira pilosicoli; the aalboygi species is most likely

commensal and the pilosicoli species has greater pathogenicity.[9,10] This theory is supported by the slow-growing nature of the aalboygi species, in contrast to positive blood cultures of the pilosicoli species seen in critically ill patients.[11] Homosexual males and HIV-infected individuals have a higher rate of colonization and findings of spirochaetosis in any patient should be a marker for investigation of HIV status.[7] The diagnosis of spirochaetosis can be obtained either by random biopsies, PCR testing, and/or anaerobic cultures, although culture is limited due to the anaerobic and slow growing nature of the organism.[12]

The pathogenic nature of spirochaetosis is not understood, nor is its clinical significance when found in the GI tract.[13] The enteropathogenicity of this organism has been obtained from zoonotic and observational studies. The leading theory is that the pathogenic nature of this organism is secondary to the depth of invasion into the intestinal wall, with greater penetration leading to a greater symptomatic presentation. With greater penetrance into the intestinal wall, there is increased microvilli destruction leading to decreased resorptive areas of the damaged brush border.[4,14,15] The mode of transmission is not known at this time, but likely is linked to diet, sanitation, and poor living standards.[6] Although the possibility of zoonotic transmission between humans, chickens, and pigs has been established by studies isolating strains of spirochaetes and transferring interspecies.[3]

The need for treatment of this condition is debated. Standard treatment includes metronidazole for a typical 14-day course, with amoxicillin as a second line option, although resistance to penicillin has been noted.[3,16] Eradication of organisms did not lead to improvement of clinical symptoms. In addition, there has been a lack of consistent visualized inflammation on pathologic slides even when carriage is present.[2,9,16] The lack of response has led many experts to take a "wait and see" approach to treatment.[9] At this time, there was no need for follow-up evaluation to detect eradication of the spirochaetes, as there is no correlation between clearance and symptoms.

In the presented case, spirochaetes on biopsy is highly suggestive of spirochaetosis as the source of the diarrhea in combination with his symptom resolution after treatment. Other etiologies of chronic diarrhea were ruled out with thorough endoscopic evaluation, negative biopsies for inflammatory bowel disease, microscopic colitis, and celiac disease. The possibility of irritable bowel syndrome (IBS) as the etiology of the patient's symptoms cannot be excluded, but given the lack of IBS treatments provided to the patient and his quick improvement in symptoms after metronidazole, with no further recurrence, suggest against this diagnosis. No clear medication source was identified as the etiology of the patient's complaints and no medications were withdrawn that would correlate with the patient's improvement.

Although infection with spirochaetosis is uncommon in countries with high living standards, it is important to keep this etiology of diarrhea as a part of the differential diagnosis. A patient diagnosed with spirochaete infection should be evaluated for HIV, with treatment targeted for symptomatic patients.

REFERENCES

[1] Lo TC, Heading RC, Gilmour HM. Intestinal spirochaetosis. Postgrad Med J 1994; 70(820):134-137. PMID: 8170888.
[2] Anthony NE, Blackwell J, Ahrens W, Lovell R, Scobey MW. Intestinal spirochetosis: An enigmatic disease. Dig Dis Sci 2013; 58(1):202-208. PMID: 22851039.
[3] Esteve M, Salas A, Fernandez-Banares F, et al. Intestinal spirochetosis and chronic watery diarrhea: Clinical and histological response to treatment and long-term follow up. J Gastroenterol Hepatol 2006; 21(8):1326-1333. PMID: 16872318.
[4] Tsinganou E, Gebbers JO. Human intestinal spirochetosis: A review. Ger Med Sci 2010; 8:Doc01. PMID: 20200654.
[5] Takeuchi A, Jervis HR, Nakazawa H, Robinson DM. Spiral-shaped organisms on the surface colonic epithelium of the monkey and man. Am J Clin Nutr 1974; 27(11):1287-1296. PMID: 4447095.
[6] Burks ML, Kundrotas L. Unusual colon biopsy. Gastroenterology 2013; 145(2):e10-11. PMID: 23810345.
[7] Korner M, Gebbers JO. Clinical significance of human intestinal spirochetosis: A morphologic approach. Infection 2003; 31(5):341-349. PMID: 14556061.
[8] Tanahashi J, Daa T, Gamachi A, et al. Human intestinal spirochetosis in Japan: Its incidence, clinicopathologic features, and genotype identification. Mod Pathol 2008; 21(2):76-84. PMID: 18084255.
[9] O'Donnell S, Swan N, Crotty P, Sangster D, O'Morain C. Assessment of the clinical significance of intestinal spirochaetosis. J Clin Pathol 2008; 61(9):1029-1033. PMID: 18682422.
[10] Lin RK, Miyai K, Carethers JM. Symptomatic colonic spirochaetosis in an immunocompetent patient. J Clin Pathol 2006; 59(10):1100-1101. PMID: 17021136.
[11] Trott DJ, Jensen NS, Saint Girons I, et al. Identification and characterization of Serpulina pilosicoli isolates recovered from the blood of critically ill patients. J Clin Microbiol 1997; 35(2):482-485. PMID: 9003622.
[12] Jensen TK, Boye M, Ahrens P, et al. Diagnostic examination of human intestinal spirochetosis by fluorescent in situ hybridization for Brachyspira aalborgi, Brachyspira pilosicoli, and other species of the genus Brachyspira (Serpulina). J Clin Microbiol 2001; 39(11):4111-4118. PMID: 11682538.
[13] Walia R, Shuja C, Hong D, et al. An unusual cause of abdominal pain. J Pediatr Gastroenterol Nutr 2012; 55(6):e141. PMID: 22258290.
[14] Rodgers FG, Rodgers C, Shelton AP, Hawkey CJ. Proposed pathogenic mechanism for the diarrhea associated with human intestinal spirochetes. Am J Clin Pathol 1986; 86(5):679-682. PMID: 3776923.
[15] Gebbers JO, Ferguson DJ, Mason C, Crucioli V, Jewell DP. Local immune reaction in human intestinal spirochetosis. Schweiz Med Wochenschr 1987; 117(29):1087-1091. PMID: 3672059.
[16] Umeno J, Matsumoto T, Nakamura S, et al. Intestinal spirochetosis due to Brachyspira pilosicoli: Endoscopic and radiographic features. J Gastroenterol 2007; 42(3):253-256. PMID: 17380285.

Keywords: colitis, spirochete infections, diarrhea

KANSAS JOURNAL of MEDICINE

Parkinson Disease in a Patient with Multiple Co-morbidities: A Delayed Diagnosis?

Theresa L. King, M.D.
University of Kansas Medical Center, Kansas City, KS
Department of Internal Medicine, Division of General and Geriatric Medicine

INTRODUCTION

Parkinson disease (PD) is a progressive neurodegenerative disorder with an estimated prevalence of 0.3% in the United States, while in those individuals 85 years and older, the prevalence increases to 4 - 5%.[1] It is a condition that can be difficult to identify, especially in patients with multiple comorbidities, where signs and symptoms may overlap significantly.

CASE REPORT

A 64-year-old male with previous diagnoses of chronic inflammatory demyelinating polyneuropathy (CIDP), ulcerative colitis resulting in a remote partial small bowel resection, rheumatoid arthritis, and monoclonal gammopathy of unknown significance presented to the hospital with complaints of intractable abdominal pain, primarily post-prandial, and significant weight loss. His body mass index was 16 and vital signs were within normal limits. Review of symptoms revealed difficulty walking, frequent falls, tremor, and problems with memory. His physical exam revealed an abdomen mildly tender to deep palpation. He exhibited a stooped, lordotic posture and an unsteady, relatively wide-based gait. Routine labs indicated a stable anemia with hemoglobin of 11.9 g/dl. Esophagogastroduodenoscopy, colonoscopy, and gastric emptying study were unremarkable. An abdominal computer tomography (CT) scan showed possible bowel ischemia and vascular surgery was consulted. An abdominal CT angiogram (CTA) showed marked focal stenosis of the celiac artery origin, inferior mesenteric artery origin, and proximal to mid superior mesenteric artery. He was taken to the operating room for angioplasty and stent placement of affected vessels. His abdominal pain improved and his caloric intake increased sufficiently for discharge. At follow-up with neurology, the possibility of Parkinson disease (PD) was raised and he underwent a DaTScan, which uses single photon emission computed tomography (SPECT) brain imaging to assist in the evaluation of patients with suspected Parkinsonian syndromes. The DaTScan showed no activity in the bilateral putamen and only faint activity in the bilateral caudate nuclei, with slightly more activity seen on the left. These findings were consistent with PD. The patient recalled that symptoms initially began in 2006 with tremors in his right hand. It was thought to be an essential tremor, as several individuals in his family had the same. Although he had several features not typical of PD, including having a long history of tremors, severe CIDP, and the lack of a typical resting tremor, he was started on carbidopa/levodopa and his tremors and gait improved. While diagnosis and treatment of PD did not resolve every symptom, it improved the patient's function and safety, making this an important finding.

DISCUSSION

Parkinson disease is a progressive degeneration of the central nervous system, mainly affecting the motor system.[2] Characteristic neuropathologic features of the disease are dopaminergic neuron degeneration in the substantia nigra and the presence of eosinophilic intracytoplasmic inclusions (Lewy bodies) in the residual dopaminergic neurons. The etiology is likely multifactorial, with hereditary predisposition, environmental factors, and physiologic changes of aging all contributing. The disease encompasses a range of severity, from "parkinsonism", manifested by minimal, non-life-altering symptoms, to full-blown disease that greatly affects activities of daily living. PD generally presents with gait instability, changes in memory and cognition, slowed movement (bradykinesia), postural instability often resulting in falls, increased muscle rigidity or the development of masked facies. Lesser manifestations of these signs and symptoms can be subtle and difficult to recognize. Onset is often unilateral and may include other abnormal movements, such as postural or action tremors.

Patients may complain of insomnia, depression, anxiety, fatigue, constipation, dysautonomia, and anosmia.[2] Later in the disease, psychosis, involving visual hallucinations and delusions, and dementia occur in up to 25% of patients. A differential diagnosis must include Lewy body dementia, progressive supranuclear palsy (PSP), corticobasal degeneration (CBD), essential tremor, post-encephalitic conditions, and Alzheimer disease, as all can mimic PD.[2] Parkinson disease is the second most common neurodegenerative disorder, following Alzheimer disease, and is more common among Hispanics and non-Hispanic whites than Asians and African Americans.

The American Academy of Neurology (AAN) recommends initial treatment with levodopa or a dopamine agonist, depending on whether the need is to improve motor disability (levodopa is better) or decrease motor complications (dopamine agonists cause fewer motor complications), replacing endogenous dopamine in the form of levodopa, which is converted to dopamine in the brain.[3] Levodopa is effective at controlling bradykinesia and rigidity.

Levodopa is combined with carbidopa, which prevents peripheral conversion to dopamine by blocking dopa decarboxylase. Other effective agents which directly stimulate dopamine receptors include bromocriptine (Parlodel), pergolide (Permax), pramipexole (Mirapex), and ropinirole (Requip). Inhibitors of catechol-O-methyltransferase (COMT), including entacapone (Comtan) and tolcapone (Tasmar), decrease the breakdown of levodopa and extend its half-life, lessening the end-of-dose wearing-off effect. Amantadine, an antiviral, provides benefits lasting for less than eight months, with its withdrawal resulting in a 10% to 20% rebound increase in dyskinesia.[4] Anticholinergics can be used to treat the depression, dementia, and psychoses that develop in 20% to 40% of patients.[5]

The Unified Parkinson Disease Rating Scale (UPDRS; available at http://www.mdvu.org/pdf/updrs.pdf) is a standard assessment tool that provides a measure of disease progression and treatment response.[6] The four-part scale measures mental effects, limitations in activities of daily living (ADLs), motor impairment, and treatment or disease complications.

Treatment of advanced or disabling symptoms can include deep brain stimulation of the subthalamic nucleus or globus pallidus.[2] Deep brain stimulation of the subthalamic nucleus effectively improves motor function and reduces motor fluctuations, dyskinesia, and antiparkinsonian medication use.[7] Parkinsonism-directed physical therapy is often effective in reducing falls.

CONCLUSION

This case report illuminates that diagnoses often are delayed, especially when signs and symptoms overlap with other diseases. In a patient with multiple medical comorbidities, it can be challenging to diagnose this insidious disease.

REFERENCES

[1] de Lau LM, Giesbergen PC, de Rijk MC, Hofman A, Koudstaal PJ, Breteler MM. Incidence of parkinsonism and Parkinson disease in a general population: The Rotterdam Study. Neurology 2004; 63(7):1240-1244. PMID: 15477545.
[2] Farlow J, Pankratz ND, Wojcieszek J, Foroud T. Parkinson Disease Overview. In: Pagon RA, Adam MP, Ardinger HH, et al. (Eds). GeneReviews. Seattle: University of Washington, Seattle, 2004. Available from: http://www.ncbi.nlm.nih.gov/books/NBK1223/.
[3] Miyasaki JM, Martin W, Suchowersky O, Weiner WJ, Lang AE. Practice parameter: Initiation of treatment for Parkinson's disease: An evidence-based review: Report of the Quality Standards Subcommittee of the American Academy of Neurology. Neurology 2002;58(1):11-17. PMID:11781398.
[4] Thomas A, Iacono D, Luciano AL, Armellino K, Di Iorio A, Onofrj M. Duration of amantadine benefit on dyskinesia of severe Parkinson's disease. J Neurol Neurosurg Psychiatry 2004;75(1):141-143. PMID: 14707325.
[5] Aarsland D, Andersen K, Larsen JP, Lolk A, Kragh-Sorensen P. Prevalence and characteristics of dementia in Parkinson disease: An 8-year prospective study. Arch Neurol 2003; 60(3):387-392. PMID: 12633150.
[6] Movement Disorder Society Task Force on Rating Scales for Parkinson's disease. The Unified Parkinson's Disease Rating Scale (UPDRS): Status and recommendations. Mov Disord 2003; 18(7):738-750. PMID: 12815652.
[7] Pahwa R, Factor SA, Lyons KE, et al. Practice parameter: Treatment of Parkinson disease with motor fluctuations and dyskinesia (an evidence-based review): A report of the Quality Standards Subcommittee of the American Academy of Neurology. Neurology 2006; 66(7):983-995. PMID: 16606909.

Keywords: Parkinson Disease, tremor, gait

KANSAS JOURNAL of MEDICINE

Rhombencephalitis Presenting as a Manifestation of Neuropyschiatric Lupus

Muhammad Imran, M.D.[1], Ayesha Irum, M.S.[2],
Adam Parker, M.D.[1], Leslie Kimpler, M.D.[3],
Phaedra Dowell, M.D.[3], Anand Rajpara, M.D.[4],
Julian Magadan III, M.D.[1]
[1]University of Kansas Medical Center, Kansas City, KS
Department of Internal Medicine, Division of Allergy, Clincial Immunology & Rheumatology
[2]Army Medical College, Pawalpindi, Pakistan
University of Kansas Medicial Center, Kansas City, KS
[3]Department of Neurology
[4]Department of Internal Medicine, Division of Dermatology

INTRODUCTION

Systemic lupus erythematosus (SLE) is a chronic, relapsing-remitting autoimmune disease which primarily affects the skin, joints, and kidneys but may involve any organ system, including peripheral, autonomic, or central nervous system (CNS).[1] The CNS involvement may be considered primary if directly related to SLE activity or secondary when related to treatment complications, infections, or metabolic abnormalities such as uremia.[2] The neuropsychiatric involvement in SLE (NPSLE), first mentioned by Kaposi more than 100 years ago, remains one of the main challenges facing the rheumatologist and other physicians.[2]

NPSLE can precede the onset of lupus or occur at any time during its course, most frequently within the first three years.[3-6] The prevalence of CNS involvement in SLE ranges from 14% to 80%, depending on the diagnostic criteria.[7] SLE commonly involves the meninges, cranial nerves, cerebrum, spinal cord, and rarely involves the hindbrain, causing rhombencephalitis (RE), which is a syndrome of multiple causes and variable outcomes. The term "rhombencephalitis" refers to an inflammatory disease of the rhombencephalon or the hindbrain, which is composed of the pons, cerebellum, and the medulla oblongata. The term is derived from the Greek word, "rhombos" meaning a lozenge-shaped figure, plus "enkephalos", meaning the brain.[8-10] No cases of SLE and rhombencephalitis were identified in a search of the medical literature.

CASE REPORT

The patient was a 43-year-old, right-handed, Caucasian female who presented to a local hospital several days after returning from a trip to Mexico. Her complaints included nausea, vomiting, urinary retention, headaches, and neck stiffness. The symptoms began suddenly while she was in Mexico, though she was not seen by a healthcare provider until she returned home. Her past medical history revealed she takes cetirizine as needed for seasonal allergies. She lived on a farm with her husband and two children. She denied any tobacco, alcohol, or illicit drug use. She had a family history of colon cancer; otherwise, family history was noncontributory.

She was admitted to the hospital at time of presentation and diagnosed with bacterial meningitis. She was treated empirically with vancomycin, ceftriaxone, and dexamethasone. She showed complete improvement clinically and was discharged home with a steroid taper and a total of 21 days of ceftriaxone.

The patient responded well until six months later when she again developed nausea, vomiting, diarrhea, and urinary retention. She was admitted to the same hospital for work-up. Magnetic resonance imaging (MRI) of the brain revealed a T2 hyperintensity at C2 - C3. A lumbar puncture revealed a red blood count of 2 UL, a white blood count of 63 UL with 31% neutrophils and 30% lymphocytes, glucose of 42 mg/dl, and protein of 41 mg/dl. Gram stain and culture on cerebrospinal fluid were negative. Other infectious studies also were negative, including West Nile, varicella zoster, and human immunodeficiency virus.

Rheumatologic serologic evaluation consisted of a positive antinuclear antibody test with titer 1:160 and positive anti-ds DNA. All other studies were negative, including rheumatoid factor, anti-Smith, anti-RNP, anti SSA/SSB, c-ANCA, and p-ANCA. The antiphospholipid antibodies were negative. Neuroinflammatory work-up revealed a negative neuromyelitis optica antibody, no oligoclonal bands on cerebrospinal fluid, and normal methylmalonic acid and serum protein electrophoresis.

The patient was diagnosed with transverse myelitis at the outside facility without having clear findings on MRI to support that diagnosis, which was based solely on symptoms of urinary retention. She was started on methylprednisolone, 1 gram for three days. Urinary retention resolved, but the patient remained fatigued. Steroids were discontinued and the patient was discharged home.

No acute events occurred until eight weeks later when she again presented to her local hospital with nausea, vomiting, diarrhea, urinary retention, and fevers. Her temperature prior to presentation was 39.5°C. Transverse myelitis was suspected again and the patient was transferred to our facility for further evaluation.

Upon presentation to our facility, the patient's exam was non-focal and unremarkable except erythematous rash on chest and back. She was alert and oriented to person, place, and time. Speech was intact for fluency, comprehension, articulation, repetition, and naming. Cranial nerves II-XII were intact.

Strength was 5/5 throughout; deep tendon reflexes were 2/4 throughout, and plantar response was down-going. Coordination was intact to finger-to-nose, heel-to-shin, and rapid alternating movements. Sensation was intact to light touch and pin prick; vibratory sensation was felt for more than 10 seconds at the bilateral great toes. Muscle tone and bulk were normal with no fasciculation, tremor, or pronator drift. Gait was normal and the patient was able to perform heel, toe, and tandem walk.

MRIs of the head and cervical spine revealed a fluid-attenuated inversion recovery (FLAIR) signal abnormality in the dorsal medulla and left lateral upper cervical spinal cord. This finding was not present on films performed at the outside facility. There was no MRI or clinical finding suggestive of transverse myelitis. Lumbar puncture revealed an opening pressure of 20 cm H_2O, red blood cell count of 30/UL, white blood cell count of 80/UL with 6% neutrophils and 56% lymphocytes, glucose of 35 mg/dl, and protein of 48 mg/dl.

Clinically, the patient did not have signs of infection. Her fever had resolved. An infectious disease specialist was consulted and agreed with holding antibiotics at that time. Fever returned with nightly spikes to greater than 103°F. She was treated with acetaminophen and fever resolved with one dose. The patient required frequent catheterization to empty her bladder. All other symptoms persisted.

Lumbar puncture was repeated two days after admission and revealed opening pressure of 8 cm H_2O, red blood cell count of 0, white blood cell count of 380 with 63% neutrophils and 20% lymphocytes, glucose of 32 mg/dl, and protein of 69 mg/dl. Oligoclonal bands were negative. In light of this increase in white blood cell count, MRI findings in the brainstem, and return of fever, the patient was started empirically on ampicillin for Listeria coverage as it was suspected as the most likely organism contributing to her rhombencephalitis.

Her fevers continued cyclically with spikes of greater than 102°F overnight every night. Rheumatologic workup revealed antinuclear antibodies of 380 with nucleolar pattern, complement C3 of 19.6 mg/dl, complement C4 of greater than 5.0 mg/dl, complement CH50 of 3 AU, anti-Smith positive, anti-RNP positive, anti-SSA and SSB negative, and ds-DNA positive. IgM, IgA, and IgG were within normal limits. Histoplasma antigen also was negative.

The patient had an erythematous rash on her back and chest throughout admission. The patient reported a similar rash had accompanied her two prior episodes as well, which would improve once steroids were initiated. The rash was described as a v-shaped, photo-distributed erythematous area with scaly papules on the anterior chest (Figure 1). A punch biopsy was consistent with cutaneous lupus erythematosus (Figure 2). The v-shape rash and interface dermatitis can be seen in dermatomyositis, but the patient had no muscle weakness, Gottron's papules, and heliotrope rash on physical examination and her CPK, aldolase and anti Jo were negative.

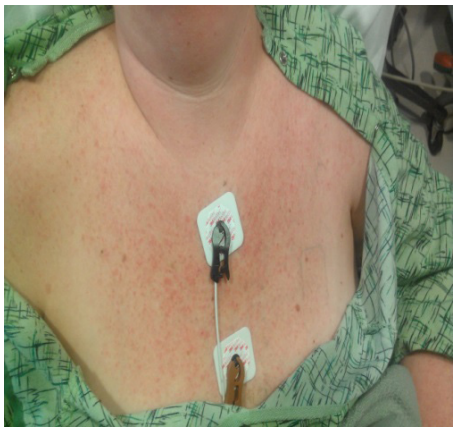

Figure 1. A v-shaped, photo-distributed erythematous area with scaly papules on the anterior chest.

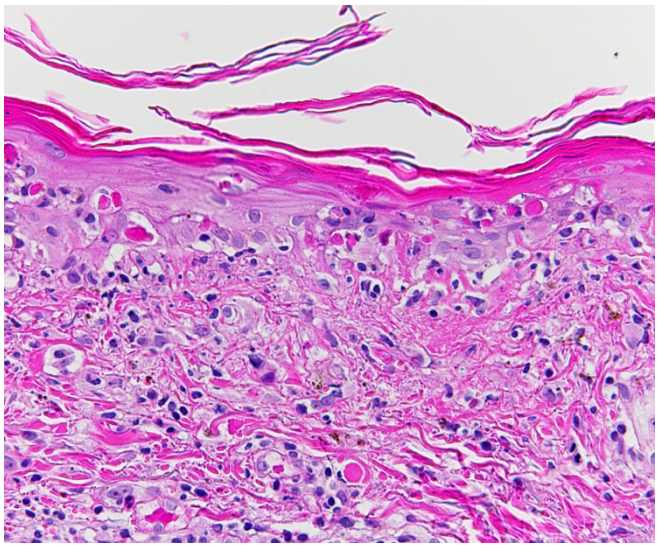

Figure 2. Vacuolar interface dermatitis with scale, epidermal thinning and scattered necrotic keratinocytes in the epidermal spinous layer; basal layer vacuolization and a dermal infiltrate of lymphocytes, histiocytes and melanophages (hematoxylin-eosin, X200).

Lumbar puncture was repeated and revealed an opening pressure of 12.5 cm H_2O, red blood cell count of 53/UL, white blood cell count of 100/UL with 19% neutrophils and 57% lymphocytes, glucose of 55 mg/dl, and protein of 176 mg/dl. Ampicillin was discontinued in light of these results as well as no appreciable improvement in cerebrospinal fluid white blood cell count after one week of treatment. The patient was started on prednisone for systemic lupus erythematosus and discharged home.

Since discharge, the patient has been followed closely as an outpatient. Disease modifying anti-rheumatic drug therapy (DMARD) was initiated with mycophenolate mofetil 1,000 mg twice a day and hydroxychloroquine 200 mg twice a day. She improved clinically and has been tapered off prednisone.

DISCUSSION

Rhombencephalitis (RE) has a wide variety of etiologies, some potentially severe and life threatening without proper early diagnosis and treatment. The etiologies

include infections, autoimmune diseases, and paraneoplastic syndromes.[2] The most common infectious etiologies include Listeria, enterovirus 71, and herpes viruses, while the most common autoimmune etiology is Behçet's disease. RE is seen in SLE and relapsing polychondritis.[11-13] The exact pathogenesis is not known, but large numbers of pathophysiologic processes are hypothesized to be involved, including anti-neuronal antibodies, antibodies against ribosomal P-protein, cytokines, vascular injury induced by circulating immune complex, occlusive vasculopathy as a result of endothelial cell activation induced by cytokines and complement activation, or macro- and microvascular thrombosis induced by antiphospholipid antibodies. In the later stages of disease, cerebrovascular manifestations often are related to accelerated atherosclerosis.[1,14,15] However, direct and unequivocal evidence for the implication of any of the above-mentioned mechanisms is lacking.

The clinical features of RE include altered mental status, hallucination, headache, unilateral cranial nerve paresis (mainly V, VII, VI, IX, and X), cerebellar deficits (hemiataxia, vertigo, or dysarthria), respiratory failure, dysphagia, quadriplegia, ocular movement dysfunction, meningitis, and encephalopathy.[16-18] Our patient had headache followed by the development of encephalopathy. There is no single test laboratory or imaging finding which is diagnostic for NPSLE. The diagnosis is established based on the constellation of clinical presentation, serologic tests, and neuroimaging techniques which are used to exclude other potential etiologies prior to the diagnosis of SLE related RE.

Our patient did not have another possible explanation for RE and her serologic testing was supportive of a new diagnosis of SLE (SLICC classification criteria: cutaneous lupus, positive ANA, positive anti-ds DNA, and hypocomplementemia). The serologic studies revealed elevated anti-double stranded DNA and hypocomplementemia, suggestive of active disease. The cerebrospinal fluid analysis in CNS lupus usually presents with lymphocytic pleocytosis and elevated protein.[19] MRI of the brain is the imaging modality of choice in case of CNS lupus, especially rhombencephalitis. The usual MRI findings in rhombencephalitis are increased signal intensity in the pons, medulla, upper cervical cord, and cerebellum more frequently than the midbrain on T2-weighted images.[20]

Therapy usually consists of high-dose intravenous corticosteroids followed by slow oral tapering doses.[21,22] The most commonly used steroid sparing agents in these cases are azathioprine or cyclophosphamide. Less frequently used immunosuppressive agents include cyclosporine, methotrexate, and anti–tumor necrosis factor alpha (TNF-α) agents.[20-23] The most commonly used steroid sparing agents are azathioprine, mycophenolate mofetil, or cyclophosphamide. Mycophenolate mofetil was chosen given its more favorable side effect profile compared to cyclophosphamide and case reports of aseptic meningitis in association with azathioprine.[23-26]

Some poor prognostic factors include repeated attacks, incomplete recovery, progression of disease, and a high level of CSF pleocytosis during the acute attack.[24,26] About 25% of patients have complete recovery, while 75% have residual motor, sensory, visual, and cognitive impairments.

CONCLUSION

SLE may have variable CNS manifestations. SLE should be considered as a potential cause of rhombencephalitis. MRI is useful in demonstrating brain lesions and in evaluating treatment efficacy.

REFERENCES

[1] Scolding NJ, Joseph FG. The neuropathology and pathogenesis of systemic lupus erythematosus. Neuropathol Appl Neurobiol 2002; 28(3):173-189. PMID: 12060342.
[2] Johnson RT, Richardson EP. The neurological manifestations of systemic lupus erythematosus. Medicine (Baltimore)1968; 47(4):337-369. PMID: 5212395.
[3] Bluestein HG. Neuropsychiatric disorders in systemic lupus erythematosus. In: RG Lahita (Ed). Systemic Lupus Erythematosus. New York: John Wiley and Sons, 1986.
[4] Borchers AT, Aoki CA, Naguwa SM, Keen CL, Shoenfeld Y, Gershwin ME. Neuropsychiatric features of systemic lupus erythematosus. Autoimmun Rev 2005; 4(6):329-344. PMID: 16081024.
[5] Unterman A, Nolte JE, Boaz M, Abady M, Shoenfeld Y, Zandman-Goddard G. Neuropsychiatric syndromes in systemic lupus erythematosus: A meta-analysis. Semin Arthritis Rheum 2011; 41(1):1-11. PMID: 20965549.
[6] Hanly JG, McCurdy G, Fougere L, Douglas JA, Thompson K. Neuropsychiatric events in systemic lupus erythematosus: Attribution and clinical significance. J Rheumatol 2004; 31(11):2156-2162. PMID: 15517627.
[7] Sanna G, Bertolaccini ML, Khamashta MA. Neuropsychiatric involvement in systemic lupus erythematosus: Current therapeutic approach. Curr Pharm Des 2008; 14(13):1261-1269. PMID: 18537650.
[8] Armstrong RW, Fung PC. Brainstem encephalitis (rhombencephalitis) due to Listeria monocytogenes: Case report and literature review. Clin Infect Dis 1993; 16(5):689-702. PMID: 8507761.
[9] Smiatacz T, Kowalik MM, Hlebowicz M. Prolonged dysphagia due to Listeria-rhombencephalitis with brainstem abscess and, acute polyradiculoneuritis. J Infect 2006; 52(6):e165-e167. PMID: 16260041.
[10] Crawford JR, Kadom N, Santi MR, Mariani B, Lavenstein BL. Human herpesvirus 6 rhombencephalitis in immunocompetent children. J Child Neurol 2007; 22(11):1260-1268. PMID: 18006954.
[11] Antal EA, Dietrichs E, Løberg EM, Melby KK, Maehlen J. Brain stem encephalitis in listeriosis. Scand J Infect Dis 2005; 37(3):190-194. PMID: 15849051.
[12] Wadia N, Williams E. Behcet's syndrome with neurological complications. Brain 1957; 80(1):59-71. PMID: 13412995.
[13] Wasserfallen JB, Schaller MD. Unusual rhombencephalitis in relapsing polychondritis. Ann Rheum Dis 1992; 51(10):1184. PMID: 1444642.
[14] Hanly JG, Walsh NM, Sangalang V. Brain pathology in systemic lupus erythematosus. J Rheumatol 1992; 19(5):732-741. PMID: 1613703.
[15] Hahn BH, Grossman J, Chen W, McMahon M. The pathogenesis of atherosclerosis in autoimmune rheumatic diseases: Roles of inflammation and dyslipidemia. J Autoimmun 2007; 28(2-3):69-75. PMID: 17433865.
[16] Moragas M, Martínez-Yélamos S, Majós C, Fernández-Viladrich P, Rubio F, Arbizu T. Rhombencephalitis: A series of 97 patients. Medicine (Baltimore) 2011; 90(4):256-261. PMID: 21694648.
[17] Jubelt B, Mihai C, Li TM, Veerapaneni P. Rhombencephalitis/brainstem encephalitis. Curr Neurol Neurosci Rep 2011; 11(6):543-552. PMID: 21956758.
[18] Kamm C, Zettl UK. Autoimmune disorders affecting both the central and peripheral nervous system. Autoimmun Rev 2012; 11(3):196-202. PMID: 21619947.
[19] Graham JW, Jan W. MRI and the brain in systemic lupus erythematosus. Lupus 2003; 12(12):891-896. PMID: 14714907.
[20] Trevisani VF, Castro AA, Neves Neto JF, Atallah AN. Cyclophosphamide versus methylprednisolone for treating neuropsychiatric involvement in systemic lupus erythematosus. Cochrane Database Syst Rev 2006; (2):CD002265. PMID: 16625558.

[21] Barile-Fabris L, Ariza-Andraca R, Olguín-Ortega L, et al. Controlled clinical trial of IV cyclophosphamide versus IV methylprednisolone in severe neurological manifestations in systemic lupus erythematosus. Ann Rheum Dis 2005; 64(4):620-625. PMID: 15769918.
[22] Fortin PR, Abrahamowicz M, Ferland D, et al. Steroid-sparing effects of methotrexate in systemic lupus erythematosus: A double-blind, randomized, placebo-controlled trial. Arthritis Rheum 2008; 59(12):1796-1804. PMID: 19035431.
[23] Blank M, Shoenfeld Y. B cell targeted therapy in autoimmunity. J Autoimmun 2007; 28(2-3):62-68. PMID: 17391915.
[24] Castellino G, Govoni M, Giacuzzo S, Trotta F. Optimizing clinical monitoring of central nervous system involvement in SLE. Autoimmun Rev 2008; 7(4):297-304. PMID: 18295733.
[25] Gonzales-Crespo MR, Blanco FJ, Ramos A, et al. Magnetic resonance imaging of the brain in systemic lupus erythematosus. Br J Rheumatology 1995; 34(11):1055-1060. PMID: 8542207.
[26] Metreau-Vastel J, Mikaeloff Y, Tardieu M, Koné-Paut I, Tran TA. Neurological involvement in paediatric Behçet's disease. Neuropediatrics 2010; 41(5):228-234. PMID: 21210339.

Keywords: neuropsychiatric systemic lupus erythematosus, rhombencephalon, inflammation

KANSAS JOURNAL of MEDICINE

CASE REPORT

Invasive Mucormycosis Causing Rhino-orbital Cellulitis

Padma Poddutoori, M.D.[1] & Da Zhang, M.D., MSc[2]
University of Kansas Medical Center, Kansas City, KS
[1]Department of Internal Medicine
[2]Department of Pathology and Laboratory Medicine

INTRODUCTION

Mucormycosis manifests in a variety of different clinical presentations in humans, particularly in immunocompromised patients and those with diabetes mellitus.[1] The agents of mucormycosis are common in the environment and can be found on decaying vegetation and in the soil.[2] All humans have ample exposure to these fungi during day-to-day activities. The fact that mucormycosis is a rare human infection reflects the effectiveness of the intact human immune system. This is supported by the finding that almost all human infections, due to the agents of mucormycosis, occur in the presence of some underlying compromising condition.

We report a case of devastating rhino-orbital mucormycosis in a patient with uncontrolled diabetes resulting in exenteration of the left eye. Prognosis is poor for patients with brain, cavernous sinus, or carotid involvement.[3-5] Hence, it is important to make an early diagnosis and initiate appropriate treatment, along with strict glycemic control in diabetics, to decrease morbidity and mortality.

CASE REPORT

A 67-year-old male with stage IV chronic kidney disease, sleep apnea, coronary artery disease status post coronary artery bypass graft, and uncontrolled diabetes mellitus presented to an outside hospital with headache, nasal congestion, diplopia, and photophobia. The patient had invasive fungal sinusitis and underwent endoscopic sinus surgery and debridement. Cultures grew Rhizopus. The patient was transferred to our hospital after he became blind in the left eye (reportedly the night prior to transfer) for further aggressive management with endoscopic sinus surgery for debridement of invasive fungal sinusitis.

On exam, the patient had proptosis of the left eye. He had left afferent pupillary defect, severely restricted gaze, and decreased sensation in all branches of the trigeminal nerve. Labs were significant for hemoglobin of 9.2 g/dl, a white blood count of 13.5 K/µl, BUN of 62 mg/dl, creatinine of 2.05 mg/dl, and glucose of 323 mg/dl.

Maxillofacial computed tomography (CT) showed interval left maxillary antrectomy with improvement in maxillary sinusitis, progression in left ethmoid, frontal and bilateral sphenoid sinusitis, and development of post-septal fat stranding with asymmetric prominence of optic nerve consistent with orbital (post-septal) cellulitis.

Ophthalmology was consulted and the patient underwent left medial orbital exploration and radical orbital exenteration. Pathology showed involvement of middle turbinate, inferior orbital nerve, orbital floor bone, and orbital contents with fungal organisms with vascular invasion consistent with Mucor (Figure 1).

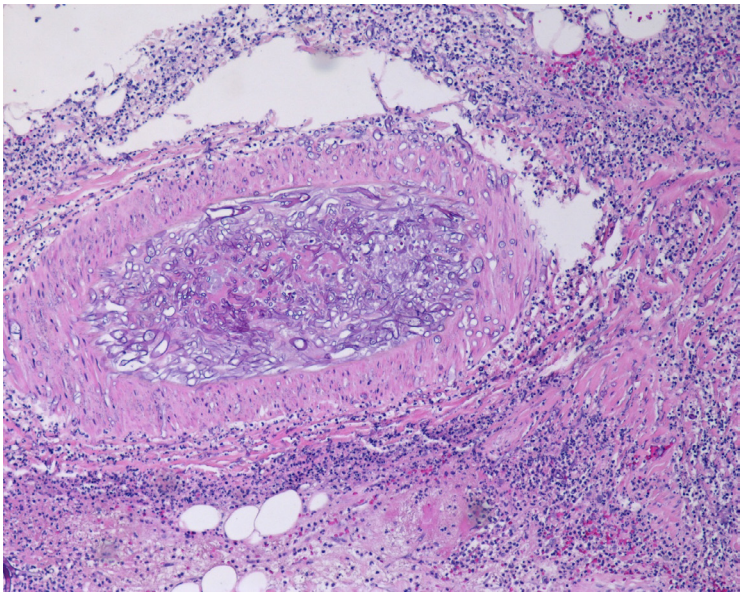

Figure 1. Left orbit enucleation specimen showing fungal organisms with vascular invasion consistent with Mucor.

The patient was started on piperacillin and tazobactam, micafungin sodium, and amphotericin B; oral posaconazole was added later. Strict glycemic control was targeted and achieved throughout the hospital course. Piperacillin and tazobactam was discontinued on discharge. The patient was discharged to a skilled nursing facility [SNF] and advised to continue IV amphotericin and micafungin sodium, to complete a total of four weeks, and oral posaconazole indefinitely. He did well while he was on IV antifungals; once the duration of IV antifungals ended, he rapidly deteriorated and eventually passed away at the SNF.

DISCUSSION

Mucormycosis can manifest as devastating rhino-orbital-cerebral (ROC) and pulmonary infections in immunocompromised patients and in diabetics.[1] The genera common in humans are Rhizopus, Mucor, and Rhizomucor. The hyphae are broad, irregularly branched, and have rare septations. Rhizopus organisms have an enzyme, ketone reductase, which allows them to thrive in high glucose, acidic conditions. ROC and pulmonary mucormycosis are acquired by inhalation of spores. Infection usually begins in the nasal turbinates or alveoli.[6]

The agents of mucormycosis are angioinvasive; infarction of infected tissues is a hallmark of invasive disease.[7] Predisposing conditions are diabetes mellitus, particularly with diabetic ketoacidosis, glucocorticoid use, hematologic malignancies, hematopoietic stem cell/solid organ transplantation, deferoxamine, iron overload, AIDS, IV drug use, trauma/burns and malnutrition. ROC mucormycosis presents with fever, nasal ulceration/necrosis, periorbital/facial swelling, decreased vision, ophthalmoplegia, sinusitis, and headache. Signs of orbital involvement are periorbital edema, proptosis, and blindness. Facial numbness results from infarction of sensory branches of trigeminal nerve. The spread of infection from the ethmoid sinus to the frontal lobe results in obtundation. Spread from the sphenoid sinuses to cavernous sinus can result in cranial nerve palsies, thrombosis of the sinus, and involvement of carotid artery.

ROC mucormycosis should be suspected in patients with diabetes mellitus and metabolic acidosis who present with sinusitis, altered mentation, and infarcted tissue in the nose/palate.[2] The diagnosis of mucormycosis relies upon the identification of organisms in tissue by histopathology with culture confirmation. However, culture often yields no growth and histopathologic identification of an organism with a structure typical of Mucorales may provide the only evidence of infection. A clinician must think of this entity in the appropriate clinical setting and pursue invasive testing to establish a diagnosis as early as possible. The presence of the characteristic hyphae in a clinical specimen provides a presumptive diagnosis that should prompt further evaluation.

Further evaluation includes imaging of the head with either CT or magnetic resonance imaging (MRI) to look for sinus involvement and evaluate contiguous structures, such as the eyes and brain.[8] Treatment of mucormycosis includes surgical debridement and antifungal therapy.[9] IV amphotericin B is the drug of choice for initial therapy.[10] Lipid formulation of amphotericin B is preferred over amphotericin B deoxycholate to deliver a high dose with less nephrotoxicity. The usual duration of treatment with IV amphotericin B is several weeks, until a favorable clinical response is achieved and at that point can be switched to posaconazole.

Posaconazole is used as step-down therapy for patients who have responded to amphotericin B. Posaconazole also can be used as salvage therapy for patients who do not respond or cannot tolerate amphotericin B. For salvage therapy, the decision to use oral or intravenous posaconazole depends on how ill the patient is, whether an initial course of amphotericin B was administered, and whether the patient had a functioning gastrointestinal tract. When switching to oral posaconazole, delayed-release formulation (300 mg every 12 hours on the first day, then 300 mg once daily) is favored.[11] Therapy with posaconazole should continue until there is clinical resolution of the signs and symptoms of infection, as well as resolution of radiographic signs of active disease which often takes months. Isavuconazole, available in both an IV and an oral formulation, can be used if the patient cannot tolerate posaconazole.

Echinocandins [Micafungin] have no in vitro activity against the agents of mucormycosis,[12-14] but Rhizopus oryzae, the most common cause of mucormycosis, expresses the target enzyme for echinocandins, suggesting that these agents may have clinical utility.[15]

Mortality from ROC mucormycosis ranges from 25% to 62%.[16] Factors associated with death are delayed diagnosis, presence of hemiparesis/hemiplegia, bilateral sinus involvement, leukemia, renal disease, and deferoxamine use.[17] Prognosis is poor for patients with brain, cavernous sinus, or carotid involvement.

CONCLUSION

ROC mucormycosis is an invasive disease with high mortality. Despite early diagnosis and aggressive combined surgical and medical therapy, the prognosis for recovery from mucormycosis is poor. Bilateral sinus involvement is one of the poor prognostic indicators. Our patient had bilateral sphenoid sinus involvement. Hence, being cognizant of the clinical manifestations and presentation is important for an early diagnosis and initiating appropriate treatment at the earliest is crucial to decrease morbidity and mortality.

REFERENCES

[1] Kauffman CA, Malani AN. Zygomycosis: An emerging fungal infection with new options for management. Curr Infect Dis Rep 2007; 9(6):435-440. PMID: 17999877.
[2] Cox GM. Mucormycosis (zygomycosis). http://www.uptodate.com/contents/mucormycosis-zygomycosis?source=machineLearning&search=mucormycosis&selectedTitle=1~69&sectionRank=1&anchor=H18#H18. Accessed March 3, 2016.
[3] Strasser MD, Kennedy RJ, Adam RD. Rhino cerebral mucormycosis. Therapy with amphotericin B lipid complex. Arch Intern Med 1996; 156(3):337-339. PMID: 8572846.
[4] Weprin BE, Hall WA, Goodman J, Adams GL. Long-term survival in rhinocerebral mucormycosis. Case report. J Neurosurg 1998; 88(3):570-575. PMID: 9488314.
[5] Shah PD, Peters KR, Reuman PD. Recovery from rhinocerebral mucormycosis with carotid artery occlusion: A pediatric case and review of the literature. Pediatr Infect Dis J 1997; 16(1):68-71. PMID: 9002105.
[6] Ferguson BJ. Mucormycosis of the nose and paranasal sinuses. Otolaryngol Clin North Am 2000; 33(2):349-365. PMID: 10736409.
[7] Greenberg RN, Scott LJ, Vaughn HH, Ribes JA. Zygomycosis (mucormycosis): Emerging clinical importance and new treatments. Curr Opin Infect Dis 2004; 17(6):517-525. PMID: 15640705.
[8] Saltoğlu N, Tasova Y, Zorludemir S, Dűndar IH. Rhinocerebral zygomycosis treated with liposomal amphotericin B and surgery. Mycoses 1998; 41(1-2):45-49. PMID: 9610133.
[9] Spellberg B, Walsh TJ, Kontoyiannis DP, Edwards Jr J, Ibrahim AS. Recent advances in the management of mucormycosis: From bench to bedside. Clin Infect Dis 2009; 48(12):1743-1751. PMID: 19435437.
[10] McCarthy M, Rosengart A, Schuetz AN, Kontoyiannis DP, Walsh TJ. Mold infections of the central nervous system. N Engl J Med 2014; 371(2):150-160. PMID: 25006721.
[11] Noxafil (posaconazole). Highlights of prescribing information. https://www.merck.com/product/usa/pi_circulars/n/noxafil/noxafil_pi.pdf. Accessed on March 18, 2014.

[12] Espinel-Ingroff A. Comparison of in vitro activities of the new triazole SCH56592 and the echinocandins MK-0991 (L-743,872) and LY303366 against opportunistic filamentous and dimorphic fungi and yeasts. J Clin Microbiol 1998; 36(10):2950-2956. PMID: 9738049.
[13] Pfaller MA, Marco F, Messer SA, Jones RN. In vitro activity of two echinocandin derivatives, LY303366 and MK-0991 (L-743,792), against clinical isolates of Aspergillus, Fusarium, Rhizopus, and other filamentous fungi. Diagn Microbiol Infect Dis 1998; 30(4):251-254. PMID: 9582584.
[14] Del Poeta M, Schell WA, Perfect JR. In vitro antifungal activity of pneumocandin L-743,872 against a variety of clinically important molds. Antimicrob Agents Chemother 1997; 41(8):1835-1836. PMID: 9257774.
[15] Ibrahim AS, Bowman JC, Avanessian V, et al. Caspofungin inhibits Rhizopus oryzae 1,3-beta-D-glucan synthase, lowers burden in brain measured by quantitative PCR, and improves survival at a low but not a high dose during murine disseminated zygomycosis. Antimicrob Agents Chemother 2005; 49(2):721-727. PMID: 15673756.
[16] Roden MM, Zaoutis TE, Buchanan WL, et al. Epidemiology and outcome of zygomycosis: A review of 929 reported cases. Clin Infect Dis 2005; 41(5):634-653. PMID: 16080086.
[17] Yohai RA, Bullock JD, Aziz AA, Markert RJ. Survival factors in rhino-orbital-cerebral mucormycosis. Surv Opththalmol 1994; 39(1):3-22. PMID: 7974189.

Keywords: invasive, mucormycosis, nose, orbital diseases, orbital cellulitis

KANSAS JOURNAL of MEDICINE

CASE REPORT

Oral Vitamin C (Ascorbic Acid) Allergy and Avoidance Leading to Severe Hypovitaminosis C

Marissa Love, M.D.[1], Muhammad Imran, M.D.[2], Ayesha Irum, M.S. [3], Garth Fraga, M.D.[4], Selina Gierer, D.O.[2]
University of Kansas Medical Center, Kansas City, KS
[1]Department of Pediatrics
[2]Department of Internal Medicine, Division of Allergy, Clinical Immunology & Rheumatology
[3]Army Medical College, Rawalpindi, Pakistan
University of Kansas Medical Center, Kansas City, KS
[4]Department of Pathology & Laboratory Medicine

INTRODUCTION

Scurvy, or vitamin C deficiency, is rare in industrialized countries.[1] Vitamin C is an essential nutrient that is derived from the diet and patients with poor nutritional intake are primarily those affected. In industrialized nations, scurvy is observed mostly with severely malnourished patients, such as those living in poverty, drug or alcohol abusers, and neglected children or the elderly.[2]

Patients can present with vague constitutional symptoms including fatigue, irritability, myalgia and vasomotor instability.[3] The classic manifestations, which occur later, include perifollicular petechiae, bleeding gums, purpura, hemarthroses, coiled or corkscrew hairs, hyperkeratosis, and poor skin healing. Treatment is oral vitamin C replacement. Because vitamin C is nearly ubiquitous in the modern diet, it is rare to find a person with a vitamin C allergy.[2] There are no reports of allergy to oral vitamin C and only a few reported hypersensitivities to the vitamin C derivatives used in cosmetics.[4] We report the first case, to our knowledge, of severe hypovitaminosis C due to vitamin C allergy and avoidance.

CASE REPORT

A 51-year-old male presented with acute onset of bilateral lower extremity rash and dermal pruritus after ingesting a multivitamin tablet the night prior. He had a history of chronic generalized nonpruritic rash aside from the present dermal eruption. He also had a history of poor dentition, limited diet consisting mostly of fast food, and vitamin C deficiency for which he tried oral replacement therapy on three occasions. He reported not visiting a physician for 10 years. He denied a history of recent trauma, travel, tick bites, or medication changes.

Pertinent medical history included a 30 pack-year history of tobacco exposure. On physical examination, he had normal vitals, poor dentition, and three skin findings: 1) a chronic large ecchymoses over his lower abdomen, groin, and right thigh, 2) pitting edema in the lower extremities, and 3) acute palpable petechiae on his anterior shins with excoriations. Cutaneous punch biopsy demonstrated noninflammatory purpura with many extravasated erythrocytes. The biopsy was negative for neutrophilia, leukocyte karyorrhexis, endothelial cell alteration, or perivascular fibrin deposits (Figure 1). Infectious, autoimmune, and tick born etiologies were ruled out.

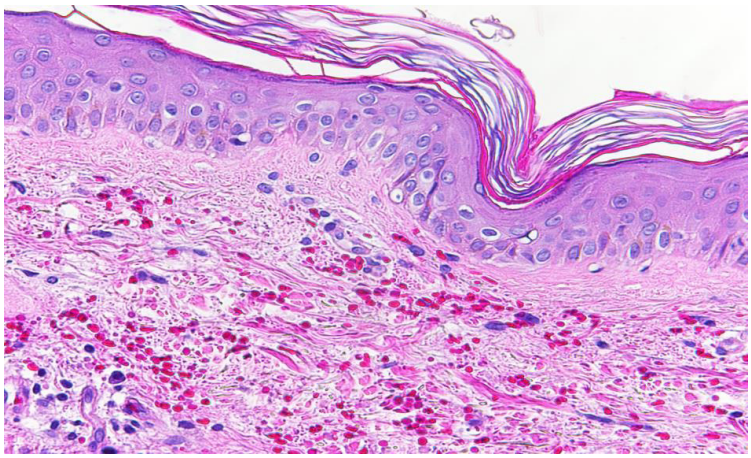

Figure 1. Cutaneous punch biopsy with non-inflammatory purpura and many extravasated erythrocytes. Notably, there is absence of neutrophilia, leukocyte karyorrhexis, endothelial cell alteration, or perivascular fibrin deposits.

The patient was severely vitamin C deficient with a vitamin C level less than 0.1 mg/dl (reference range 0.6 - 2.0 mg/dl), consistent with his history of avoiding ascorbic acid due to previous presumed allergic reactions. The vitamin C deficiency was believed to have caused his current mucocutaneous symptoms. He previously had taken ascorbic acid on three different occasions during his early adulthood. During all three episodes, he developed generalized hives within one hour of taking the medication. He denied associated angioedema, anaphylaxis symptoms, difficulty breathing, wheezing, cough, rhinorrhea, nasal congestion, sneezing, post-nasal drip, or gastrointestinal symptoms with these episodes. He recalled developing hives after eating oranges or drinking orange soda; skin testing as a child was positive to orange. Since then, he has avoided ascorbic acid supplements and foods high in ascorbic acid. He had not seen an allergist for follow-up during his adult life.

During his inpatient hospitalization, an allergist was consulted to address the possibility of ascorbic acid allergy and vitamin C desensitization. It was difficult to orchestrate inpatient vitamin C skin testing and there are no validated skin testing protocols for this nutritional supplement described in the medical literature. A protocol for desensitization using liquid ascorbic acid was created as no protocols existed in the literature.

The desensitization started with 1/10,000th of the final dose (100 mg) and slowly titrated up by 100% increments at each step to the full dose of 100 mg three times a day (Table 1). After each step, the patient was observed for 15 - 30 minutes. If he did not exhibit symptoms of allergic reaction, he was advanced to the next step. The patient then received full doses every eight hours thereafter. The patient tolerated the entire regimen without adverse events and was discharged with the oral supplement.

Table 1. Drug desensitization protocol of ascorbic acid with goal dose of 100 mg PO TID.

Dose #	Concentration	Dose
1	1:10,000	0.01 mg
2	1:5,000	0.02 mg
3	1:2,500	0.04 mg
4	1:1,250	0.08 mg
5	1:625	0.16 mg
6	1:300	0.33 mg
7	1:150	0.67 mg
8	1:75	1.3 mg
9	1:40	2.5 mg
10	1:20	5 mg
11	1:10	10 mg
12	1:5	20 mg
13	1:2.5	40 mg
14	Full strength dose	100 mg
	Total tolerated dose	180.11 mg

DISCUSSION

Vitamin C is an essential nutrient obtained from our diet.[1] Vitamin C and its derivatives are used safely in food, cosmetic, and pharmacology industries.[2] Although scurvy is rare in industrialized nations, it is seen in cases of poor nutrition and can lead to severe and fatal conditions.

A few reports of allergic reactions to vitamin C derivatives were found in topical cosmetics, resulting in contact dermatitis.[1-3] One abstract reported an allergic reaction after IV administration.[4] Another case reported a delayed type hypersensitivity reaction to oral ingestion of vitamin C, but there have not been any reports regarding desensitization to oral vitamin C.[5] This is the first case that described a desensitization protocol for oral vitamin C and one of the few cases of oral hypersensitivity with strict avoidance leading to scurvy.

In hindsight, this patient would have benefited from a prior proper allergic evaluation and education. His scurvy may have been avoided if he had received appropriate desensitization during young adulthood. Since vitamin C is ubiquitous in several foods, it raises the question if the patient was truly allergic to vitamin C. He actually may have been allergic to an excipient in oral vitamin C products.

In spite of repeated attempts to get the patient to keep a follow-up appointment and to contact the patient electronically and by mail, he was lost to follow-up. We are unaware if his clinical symptoms from scurvy improved or if he was able to eat any other foods containing vitamin C. He certainly tolerated oral vitamin C for more than seven days while hospitalized.

CONCLUSIONS

Patients with allergies to foods, particularly those that affect intake of essential nutrients such as vitamin C, need proper allergic evaluation, follow-up, and education to receive therapy to prevent serious consequences of nutritional deficiencies. In this case, an apparently successful desensitization was performed and long-term vitamin C replacement hopefully would alleviate the clinical symptoms of scurvy due to vitamin C hypersensitivity and avoidance.

REFERENCES

[1] Yagami A, Suzuki K, Morita Y, Iwata Y, Sano A, Matsunaga K. Allergic contact dermatitis caused by 3-o-ethyl-L-ascorbic acid (vitamin C ethyl). Contact Dermatitis 2014; 70(6):376-377. PMID: 24846587.
[2] Belhadjali H, Giordano-Labadie F, Bazex J. Contact dermatitis from vitamin C in a cosmetic anti-aging cream. Contact Dermatitis 2001; 45(5):317. PMID: 11722505.
[3] Swinnen I, Goossens A. Allergic contact dermatitis caused by ascorbyl tetraisopalmitate. Contact Dermatitis 2011; 64(4):241-242. PMID: 21392035.
[4] Bilyk M, Dudchik G. [Allergic reaction to intravenous administration of ascorbic acid.] [Russian] Vrach Delo 1980; (5):81-82. PMID: 6446806.
[5] Metz J, Hundertmark U, Pevny I. Vitamin C allergy of the delayed type. Contact Dermatitis 1980; 6(3):172-174. PMID: 7389324.

Keywords: allergic reaction, ascorbic acid deficiency, scurvy

KANSAS JOURNAL of MEDICINE

Savella® (Milnacipran) Causing Elevated Normetanephrines

Ahmad Yehya, M.D.[1], John M. Miles, M.D., FACE[1,2], Rajib K. Bhattacharya, M.D., FACE[1,2]
University of Kansas Medical Center, Kansas City, KS
[1]Department of Internal Medicine
[2]Division of Endocrinology

INTRODUCTION

Pheochromocytoma and paraganglioma are neuroendocrine tumors that can cause hypertension, anxiety, and palpitations, and are considerations in the evaluation of secondary causes of hypertension.[1] Medications used to control mood disorders, especially selective serotonin and norepinephrine reuptake inhibitors (SNRIs), specifically venlafaxine, can mimic such neuroendocrine tumors both biochemically, through elevations in normetanephrine levels, and clinically, through elevations in blood pressure and heart rate.

SNRIs increase the activity of serotonin and norepinephrine in the brain. Milnacipran HCl (Savella®) is an SNRI that is indicated for the management of fibromyalgia in adults; it is not indicated for management of depression, although the drug is chemically similar to other SNRIs used in treating depression.[2] Recent studies, however, have demonstrated the efficacy of milnacipran in the treatment of major depression.[3-5] In contrast with venlafaxine and duloxetine, which have a higher affinity for serotonin than for norepinephrine receptors, milnacipran has a balanced ratio of potency in the inhibition of norepinephrine and serotonin uptake.[6] Adverse effects of milnacipran most commonly include nausea (37%), headache (18%), constipation (16%), hot flush (12%), and insomnia (12%).[7,8] Other side effects of serotonin syndrome and increased suicidal behavior, especially in the young age group, are similar to antidepressants of the same class.

We describe a patient with resistant hypertension on milnacipran. This case revealed the relationship between milnacipran use and hypertension through elevation of catecholamines.

CASE REPORT

A 64-year-old female with uncontrolled hypertension, type 2 diabetes, and hyperlipidemia was seen in the endocrinology clinic after her primary care physician raised a question of a possible pheochromocytoma. Her symptoms had gotten worse over a period of five years and included palpitations, hyperhidrosis, headaches, anxiety, and dizziness with standing. The patient had been taking milnacipran for several years for the treatment of severe fibromyalgia.

Prior to this presentation, she had a five-year work-up for secondary causes of hypertension after holding milnacipran for a few weeks, including aldosterone to renin ratio and thyroid function tests; all results were normal (Table 1). She had a modestly elevated 24-hour urine for normetanephrines at 1381 with normal urinary metanephrines (Table 1). A clonidine suppression test was normal, with a suppression rate greater than 50%. CT of the abdomen and pelvis was unremarkable.

Repeat studies in the endocrinology clinic, while she was on milnacipran, revealed elevated plasma normetanephrine as well as elevated 24-hour urine norepinephrine and normetanephrines with the other labs unremarkable (Table 1). After these lab results, a metaiodobenzylguanidine (MIBG) scan and CT scan of the abdomen and pelvis showed no evidence of pheochromocytoma. Therefore, a PET scan was obtained as a localization study for a pheochromocytoma or a paraganglioma; the scan came back negative. It was concluded that, in the setting of normal PET, CT, and MIBG scans, the likely source of elevated normetanephrines, and probable cause of worsening hypertension, dizziness, palpitations, and sweating was milnacipran.

DISCUSSION

Serotonin norepinephrine reuptake inhibitors commonly are prescribed as therapy for depression and for fibromyalgia.[9,10] The three SNRIs approved in the United States are venlafaxine, duloxetine, and milnacipran. Although venlafaxine and duloxetine have a 30- and 10-fold selectivity, respectively, for serotonin, milnacipran is nonselective in blocking the uptakes of norepinephrine and serotonin.[11] In our case, a neuroendocrine tumor (e.g., a pheochromocytoma or a paraganglioma) was ruled out through serology and imaging. Specifically, CT scanning has a sensitivity of greater than 93% in the detection of pheochromocytomas and a specificity of 95% in the diagnosis of these tumors.[12] Whereas for MIBG, sensitivity is 86 - 90% for pheochromocytomas (especially in extra-abdominal tumors); specificity is as high as 99% with I-MIBG and is higher with I-MIBG (90% sensitivity, 100% specificity).[12,13] CT of the abdomen and MIBG showed no evidence of pheochromocytoma in our case. In addition, PET scan has 78% sensitivity for nonmetastatic pheochromocytomas and 76% sensitivity for metastatic pheochromocytomas, and is considered the best means of localizing primary pheochromocytomas and ruling out metastases.[12] The PET scan was negative in our case.

Table 1. Labs obtained by primary care and endocrinology.

Labs	First Set	Second Set
Plasma Norepinephrine	590 (ref 0-874)	
Plasma Epinephrine	29 (ref 0-62)	
Plasma Dopamine	< 30 (ref 0-48)	
Urine Normetanephrine	502	
24-hour Urine Normetanephrine	**1381 (ref 82-500)**	**2251 (ref 82-500)**
Urine Metanephrine	33	
24-hour Urine Metanephrine	91 (ref 45-290)	81 (ref 45-290)
Urine Epinephrine	1	
24-hour Urine Epinephrine	3 (ref 0-20)	6 (ref 0-20)
Urine Norepinephrine	60	
24-hour Urine Norepinephrine	78 (ref 0-135)	**165 (ref 0-135)**
Urine Dopamine	131	
24-hour Urine Dopamine	360 (ref 0-510)	74 (ref 0-510)
24-hour Urine Free Cortisol	11 (ref 0-50)	
Free T4	1.22 (ref 0.7-1.71)	
Total T3	156 (ref 80-181)	
TSH	1.263 (ref 0.4-4)	1.418 (ref 0.35-5)
Plasma Metanephrine		< 0.2 (ref < 0.5)
Plasma Normetanephrine		**1.2 (ref < 0.9)**
24-hour Urine VMA		4 (ref 0-7.5)
24-hour Urine Creatinine	1189 (ref 500-2000)	1340 (ref 500-2000)

Patients generally tolerate SNRIs well and milnacipran has an excellent cardiovascular safety profile with little effect on electrophysiologic values.[13,14] Clinical investigators have documented very modest increases in heart rate (3 - 5 beats/min) and systolic pressure (1 - 3 mmHg) in study subjects who took 100 to 200 mg of oral milnacipran daily. In rare instances, however, oral milnacipran has caused significant and sustained hypertension and tachycardia,[9,10] which appeared to occur in our patient. Intravenous milnacipran has increased heart rate significantly (by approximately 19% in the first 50 minutes) and systolic blood pressure (by approximately 21% in the first 10 minutes).[14] For instance, one patient with manic-depressive psychosis who took 100 mg/d of oral milnacipran developed a hypertensive response (blood pressure, 160/100 mmHg)[1]; another patient who took 150 mg/d of milnacipran developed severe hypertension, but his blood pressure fell to acceptable levels when the dose was reduced to 100 mg/d.[15]

One randomized study revealed that fibromyalgia patients receiving milnacipran had mean increases in blood pressure, both systolic and diastolic, by 4 - 5 mmHg, and heart rate by 13 - 14 bpm.[16] On the other hand, in a three year study of milnacipran for the treatment of fibromyalgia which included 1227 patients, clinically significant increases in blood pressure or heart rate occurred in ≤ 1.1% of patients, whereas nausea (25.9%) and headache (13.4%) were the most common events.[17] There also were increases in supine blood pressure (+4/3 mmHg) and heart rate (+5 bpm).[17]

The proposed mechanism of hypertension from SNRIs is increased vascular resistance, mediated by increased noradrenergic neurotransmission secondary to greater availability of norepinephrine at the postjunctional receptor.[1] This increase in noradrenergic neurotransmitters associated with SNRIs is supported further in a case of Tako Tsubo cardiomyopathy which was reported in a patient after an overdose of the SNRI, venlafaxine.[18] In that case, the urinary collection showed an elevated norepinephrine of 122 µg/24 h (normal level < 100 µg/24 h), comparable to our case, indicating that milnacipran can be associated with this noradrenergic response manifested by worsening hypertension, tachycardia, palpitations, and dizziness.

In another prospective study, plasma normetanephrine levels were increased in four patients receiving either venlafaxine or desvenlefaxine, including one patient with a level of 8800 pmol/L,[19] which further reinforces the correlation between the SNRI, specifically milnacipran in our case, and elevated catecholamines, namely normetanephrines. In one study comparing milnacipran to selective serotonin reuptake inhibitors (SSRIs) for major depression management, milnacipran was associated with a higher incidence of headache, dry mouth, and dysuria,[3] with our patient presenting with complaints of headaches and dry mouth. The tolerability of milnacipran was comparable to that of the SSRIs, with a higher incidence of dysuria with milnacipran, and a higher frequency of nausea and anxiety with the SSRIs.[4] Milnacipran may offer clinical advantages over tricyclic antidepressants (TCAs) in terms of tolerability, and over SSRIs in terms of efficacy. In particular, the lack of cardiovascular adverse events appears to offer advantages in cases of deliberate overdose.[5]

Our case confirmed that elevated normetanephrine levels do not always indicate the presence of pheochromocytoma/paraganglioma and illustrated that milnacipran use, in particular, can mimic the symptoms of these neuroendocrine tumors. A similar finding was mentioned in a study by Neary et al.[20] which concluded that before blood is drawn to measure catecholamine levels, patients should discontinue all medications that could interfere with the results. SNRIs, such as venlafaxine (Effexor®), historically, and milnacipran (Savella®), as described in our case, could interfere with elevations in neuroendocrine hormones and may contribute to worsening blood pressure, dizziness, sweating, and palpitations. Therefore, the patient was switched to another antidepressant that did not affect these hormones and, more recently, the patient reported significant improvement in her headaches, palpitations, and dizziness and her blood pressure has been within normal limits.

Keywords: milnacipran, serotonin and noradrenaline reuptake inhibitors, catecholamines, hypertension, pheochromocytoma

REFERENCES

[1] de Toledo Ferraz Alves T, Guerra de Andrade A. Hypertension induced by regular doses of milnacipran: A case report. Pharmacopsychiatry 2007; 40(1):41-42. PMID: 17327962.
[2] Forest Pharmaceuticals, Inc. Savella relieves symptoms of fibromyalgia. February 2015. Available at: http://www.savella.com. Accessed February 10, 2016.
[3] Lopez-Ibor J, Guelfi JD, Pletan Y, Tournoux A, Prost JF. Milnacipran and selective serotonin reuptake inhibitors in major depression. Int Clin Psychopharmacol 1996; 11 (Suppl 4):41-46. PMID: 8923126.
[4] Puech A, Montgomery SA, Prost JF, Solles A, Briley M. Milnacipran, a new serotonin and noradrenaline reuptake inhibitor: An overview of its antidepressant activity and clinical tolerability. Int Clin Psychopharmacol 1997; 12(2):99-108. PMID: 9219045.
[5] Montgomery SA, Prost JF, Solles A, Briley M. Efficacy and tolerability of milnacipran: An overview. Int Clin Psychopharmacol 1996; 11(Suppl 4):47-51. PMID: 8923127.
[6] Forman MB, Sutej PG, Jackson EK. Hypertension, tachycardia, and reversible cardiomyopathy temporally associated with milnacipran use. Tex Heart Inst J 2011; 38(6):714-718. PMID: 22199446.
[7] Truven Health Analytics. Micromedex Consumer Medication Information. December 1, 2015. Available at: http://www.ncbi.nlm.nih.gov/pubmedhealth/PMHT0011227/?report=details#side_effects. Accessed February 10, 2016.
[8] First Databank, Inc. October 2015. Available at: http://www.reference.medscape.com/drug/savella-milnacipran-345054#4. Accessed February 10, 2016.
[9] Mease PJ, Clauw DJ, Gendreau RM, et al. The efficacy and safety of milnacipran for treatment of fibromyalgia. A randomized, double-blind, placebo-controlled trial. J Rheumatol 2009; 36(2):398-409. PMID: 19132781.
[10] Clauw DJ, Mease P, Palmer RH, Gendreau RM, Wang Y. Milnacipran for the treatment of fibromyalgia in adults: A 15-week, multicenter, randomized, double-blind, placebo-controlled, multiple-dose clinical trial. Clin Ther 2008; 30(11):1988-2004. PMID: 19108787.
[11] Montgomery SA. Tolerability of serotonin norepinephrine reuptake inhibitor antidepressants. CNS Spectr 2008; 13(7 Suppl 11):27-33. PMID: 18622372.
[12] Timmers HJ, Chen CC, Carrasquillo JA, et al. Comparison of 18F-Fluoro-L-DOPA, 18F-fluoro-deoxyglucose, and 18F-fluorodopamine PET and 123I-MIBG scintigraphy in the localization of pheochromocytoma and paraganglioma. J Clin Endocrinol Metab 2009; 94(12):4757-4767. PMID: 19864450.
[13] Periclou A, Palmer RH, Zheng H, Lindamood C 3rd. Effects of milnacipran on cardiac repolarization in healthy participants. J Clin Pharmacol 2010; 50(4):422-433. PMID: 20103694.
[14] Caron J, Libersa C, Hazard JR, et al. Acute electrophysiological effects of intravenous milnacipran, a new antidepressant agent. Eur Neuropsychopharmacol 1993; 3(4):493-500. PMID: 8111222.
[15] Yoshida K, Higuchi H, Takahashi H, Shimizu T. Elevation of blood pressure induced by high-dose milnacipran. Hum Psychopharmacol 2002; 17(8):431. PMID: 12457380.
[16] Trugman JM, Palmer RH, Ma Y. Milnacipran effects on 24-hour ambulatory blood pressure and heart rate in fibromyalgia patients: A randomized, placebo-controlled, dose-escalation study. Curr Med Res Opin 2014; 30(4):589-597. PMID: 24188161.
[17] Arnold L, Palmer R, Ma Y. A 3-year, open-label, flexible-dosing study of milnacipran for the treatment of fibromyalgia. Clin J Pain 2013; 29(12):1021-1028. PMID: 23446068.
[18] Christoph M, Ebner B, Stolte D, et al. Broken heart syndrome: Tako Tsubo cardiomyopathy associated with an overdose of the serotonin-norepinephrine reuptake inhibitor Venlafaxine. Eur Neuropsychopharmacol 2010; 20(8):594-597. PMID: 20451358.
[19] Neil CJ, Chong CR, Nguyen TH, Horowitz JD. Occurrence of Tako-Tsubo cardiomyopathy in association with ingestion of serotonin/noradrenaline reuptake inhibitors. Heart Lung Circ 2012; 21(4):203-205. PMID: 22285074.
[20] Neary NM, King KS, Pacak K. Drugs and Pheochromocytoma - Don't be fooled by every elevated metanephrine. N Engl J Med 2011; 364(23):2268-2270. PMID: 21651412.

KANSAS JOURNAL of MEDICINE

CASE REPORT

Acute Urticaria Induced by Systemic Corticosteroids in Patient with Pre-existing Aspirin Exacerbated Respiratory Disease

Muhammad Imran, M.D.[1,2], Yuriy Zgherea, M.D.[1,2],
Ayesha Irum, MBBS[1], Selina Gierer, D.O.[1,2]
University of Kansas Medical Center, Kansas City, KS
[1]Department of Internal Medicine
[2]Division of Allergy, Clinical Immunology, & Rheumatology

INTRODUCTION

Despite the allergic, inflammatory, and immunologic modulating properties of corticosteroids, acute and delayed hypersensitivity reactions have been reported.[1-9] There is increasing data regarding hypersensitivity reactions to systemic corticosteroids from these reports. The prevalence of hypersensitivity reactions with topical corticosteroids is 2.9 - 6%[10-12] and less than 1% with inhaled and systemic corticosteroids.[1,2,13]

Delayed hypersensitivity reactions after topical corticosteroid use have been reported for decades and they were recognized as the allergen of the year in 2005 by the American Contact Dermatitis Society.[14] Acute IgE-mediated hypersensitivity reactions occurring within one hour are characterized by urticaria and anaphylaxis; while delayed T-cell mediated reactions are characterized by urticaria and maculopapular exanthems.[14,15] Reactions may occur to the corticosteroid or to its allergens, making it difficult to identify the true culprit.[15]

We identified a patient without pre-existing urticaria who exhibited hypersensitivity reactions to oral steroids (prednisone and methylprednisolone), inhaled corticosteroids/long-acting beta agonists (fluticasone/salmeterol and budesonide/formoterol), and aspirin which caused acute urticaria, angioedema, and bronchospasm. Clinicians, particularly emergency room staff, must be aware of the potential for hypersensitivity to corticosteroids and consider it in the differential diagnosis of a patient who has received corticosteroids with subsequent sequelae of a hypersensitivity reaction.

CASE REPORT

The patient was a 58-year-old female with a history of allergic rhinitis, classic aspirin exacerbated respiratory disease (AERD), and drug-induced urticaria for almost three decades. Her first prednisone exposure was thirty years prior for an asthma exacerbation. Within 12 hours, she developed urticaria and has not used oral steroids since. In 2012, she was given methylprednisolone for asthma and developed urticaria within 12 hours after the initial dose (Figure 1). She was challenged with prednisone 60 mg, and a similar reaction was observed. Additionally, she had developed urticaria within several hours of using fluticasone/salmeterol and budesonide/formoterol. Interestingly, she has tolerated inhaled fluticasone, intranasal fluticasone, and inhaled beta agonists alone, making the etiology of this reaction difficult to determine.

As the patient had AERD, we attempted aspirin desensitization, but she developed mild urticaria prior to desensitization with a pretreatment protocol of prednisone. The patient was brought back for aspirin desensitization without prednisone, and over the next six hours had progressive urticaria associated with difficulty breathing. Thus, the desensitization was discontinued. Her tryptase level was normal. Given her recurrent immediate and delayed hypersensitivity reactions to systemic and inhaled corticosteroids, further diagnostic testing was pursued.

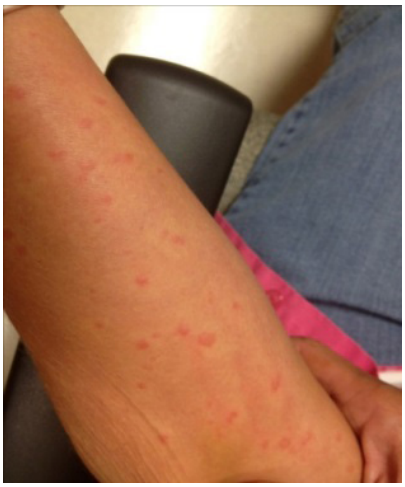

Figure 1. Acute urticaria appeared within 12 hours after taking oral prednisone.

Skin testing. We used the following medications for testing: prednisolone sodium phosphate oral solution 3 mg/1 ml (Morton Grove Pharmaceuticals, IL), dexamethasone sodium phosphate injection suspension 4 mg/1 ml (APP Pharmaceuticals, LLC, Schaumburg), methylprednisolone acetate injection suspension 40 mg/1 ml (Novaplus, USA), and saline negative control and histamine positive control.

Skin puncture tests (SPT; Table 1) were performed with each of the corticosteroids in 10-fold increasing concentrations (1:100, 1:10, to undiluted). A wheal ≥ 3 mm larger than the negative control (saline) was considered positive. Tests were read at 20 minutes. Intradermal tests (Table 2) with the same corticosteroids were performed in 10-fold increasing concentrations (1:100 to 1:10) only if the SPTs were negative. Skin puncture tests (SPT; Table 1) were performed with each of the corticosteroids in 10-fold increasing concentrations (1:100, 1:10, to undiluted). A wheal ≥ 3 mm larger than the negative control (saline) was considered positive. Tests were read at 20 minutes.

Intradermal tests (Table 2) with the same corticosteroids were performed in 10-fold increasing concentrations (1:100 to 1:10) only if the SPTs were negative. One volunteer who was known to tolerate corticosteroids was used as a control. His skin testing was negative with adequate positive and negative controls, verifying these were non-irritating concentrations of steroid.

By traditional skin testing, she was positive to all steroids and should avoid systemic steroids. It was also determined that she would not be able to tolerate aspirin desensitization with corticosteroid premedication.

Table 1. Skin puncture test results.

REAGENT	WHEAL/FLARE (mm)	RESULTS
Percutaneous testing		
Saline	0/0	Negative
Histamine	5/5	**Positive**
Prednisolone 3 mg/ml (1:100)	0/0	Negative
Methylprednisolone 40 mg/ml (1:100)	2/2	Negative
Dexamethasone 4 mg/ml (1:100)	0/0	Negative
Prednisolone 3 mg/ml (1:10)	0/0	Negative
Methylprednisolone 40 mg/ml (1:10)	0/0	Negative
Dexamethasone 4 mg/ml (1:10)	2/2	Negative
Prednisolone 3 mg/ml	0/0	Negative
Methylprednisolone 40 mg/ml	4/4	**Positive**
Dexamethasone 4 mg/ml	4/6	**Positive**

Table 2. Intradermal test results.

REAGENT	WHEAL/FLARE (mm)	RESULTS
	Zero time	20 minutes after
Saline	7/0	Negative
Prednisolone 0.03 mg/1 ml (1:100)	5/0	4/0 Negative
Methylprednisolone 0.4 mg/1 ml (1:100)	5/0	6/9 Negative
Dexamethasone 0.04 mg/1 ml (1:100)	5/0	7/0 Negative
Orapred 0.03 mg/1 ml (1:10)	6/0	10/0 **Positive**

DISCUSSION

Corticosteroids often are referred to as "steroids" and are produced synthetically. They are related closely to cortisol, a hormone naturally produced from cholesterol within the adrenal cortex (Figure 2). Corticosteroids have been used since the late 1940s for their anti-inflammatory and immunomodulatory effects to treat a wide variety of diseases.[16] Despite their clinical efficacy, steroids can induce multiple severe adverse effects, including hypersensitivity reactions, weight gain, agitation, and skin thinning, limiting their long-term use.[17]

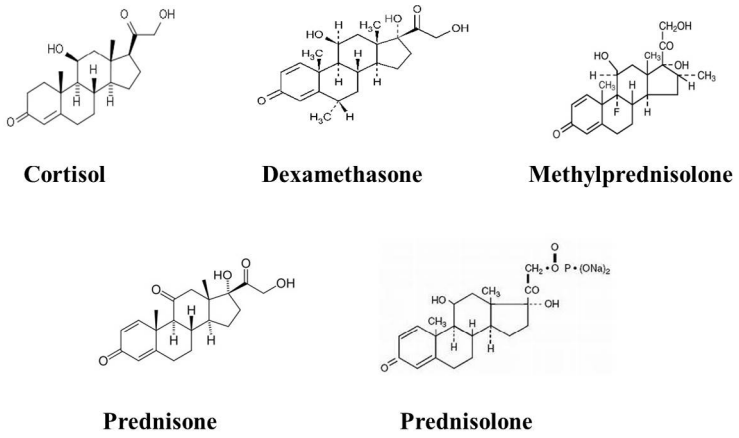

Figure 2. Structural formulas of different steroids.[4,7,18]

The overall rate of hypersensitivity reactions to corticosteroids appears to be low in comparison with their high utilization.[17] However, these reactions may be under-diagnosed; especially in cases where corticosteroids are being used to treat an ongoing allergic reaction and the reaction to the corticosteroid may confound the clinical picture. Risk factors that have been described for hypersensitivity reactions to corticosteroids include atopy, contact dermatitis, drug allergy, asthma or renal transplant. However, it is not clear if these are truly risk factors or represent conditions in which corticosteroid use is prevalent and therefore, a higher number of patients have hypersensitivity reactions.[17] The corticosteroids most frequently implicated in hypersensitivity reactions are non-fluorinated, such as topical hydrocortisone and budesonide and systemic methylprednisolone and hydrocortisone.[1,18] In a few cases, the reactions can be induced by salts, such as succinate, or rarely by diluents such as carboxymethylcellulose or metabisulfite.[3-5,19] With topical corticosteroids, the reaction can be due to other ingredients, such as neomycin or cetyl stearyl alcohol.[19]

Some authors only found skin test positivity with the topical corticosteroid,[3,4,19] while others[20] showed that the corticosteroid was responsible for the reaction in a patient who developed bronchospasm after intravenous methylprednisolone. The majority of hypersensitivity reactions to corticosteroids appear to be due to Gell and Coombs Type I and Type IV immunologically mediated mechanisms.[1-3,6-8,20] Type I (acute) reactions classically occur less than one hour after drug administration, are mediated by drug-specific IgE antibodies, and typically present with urticaria and anaphylaxis. Type IV (delayed) reactions are induced by T cells, occur within an interval of twenty-four to forty-eight hours, and commonly present with urticaria and maculopapular exanthems.[2,9,19,20] Our patient had evidence of an IgE mediated reaction based on the results of the skin testing, utilized for acute hypersensitivity reactions.

Assessment of cross-reactivity to corticosteroids may be difficult as most individuals have received corticosteroids either topically or systemically at some point in the past.

In many cases, patients do not remember receiving the corticosteroid, nor do they recall the type of corticosteroid they received. In those cases, it is difficult to confirm whether the clinical presentation is due to cross-reactivity or prior sensitization.

CONCLUSION

Hypersensitivity to corticosteroids is recognized more in the literature.[1,2,19,20] Corticosteroid reactions have important therapeutic consequences, given the frequency they are used in the treatment of a myriad of disease processes.[1,2,19-21] Although rare, allergic reactions to corticosteroids exist and an immunological mechanism, IgE or T cell dependent, have been established.[20,21] Skin testing, in-vitro testing, patch testing, and drug provocation tests are useful diagnostic tools to determine sensitivity. Patients who notice a new rash or worsening of their skin disease after using corticosteroids should alert their physicians, who should be aware to the possibility of a hypersensitivity reaction. Emergency room staff, in particular, must be aware of corticosteroid hypersensitivity reactions and take this into consideration in a patient who has received corticosteroids.

REFERENCES

[1] Venturini M, Lobera T, del Pozo MD, Gonzalez I, Blasco A. Immediate hypersensitivity to corticosteroids. J Investig Allergol Clin Immunol 2006; 16(1):51-56. PMID: 16599249.
[2] Padial A, Posadas S, Alvarez J, et al. Nonimmediate reactions to systemic corticosteroids suggest an immunological mechanism. Allergy 2005; 60(5):665-670. PMID: 15813813.
[3] Mansfield LE, Ting S, Haverly RW. Anaphylaxis caused by the sodium succinate ester of hydrocortisone and methylprednisolone. J Asthma 1986; 23(2):81-83. PMID: 3528118.
[4] Borja JM, Galindo PA, Feo F, Gomez E. Urticaria to methylprednisolone sodium hemisuccinate. Allergy 2001; 56(8):791. PMID: 11488681.
[5] García-Ortega P, Corominas M, Badia M. Carboxymethylcellulose allergy as a cause of suspected corticosteroid anaphylaxis. Ann Allergy Asthma Immunol 2003; 91(4):421. PMID: 14582827.
[6] Burgdorff T, Venemalm L, Vogt T, Landthaler M, Stolz W. IgE-mediated anaphylactic reaction induced by succinate ester of methylprednisolone. Ann Allergy Asthma Immunol 2002; 89(4):425-428. PMID: 12392389.
[7] Compalati E, Guerra L, Rogkakou A, Zanella C, Scordamaglia A, Passalacqua G. Angioedema after administration of methylprednisolone to treat drug allergy. Allergy 2007; 62(11):1346-1348. PMID: 17919150.
[8] Nakamura H, Matsuse H, Obase Y, et al. Clinical evaluation of anaphylactic reactions to intravenous corticosteroids in adult asthmatics. Respiration 2002; 69(4):309-313. PMID: 12169742.
[9] Nucera E, Buonomo A, Pollastrini E, et al. A case of cutaneous delayed-type allergy to oral dexamethasone and to betamethasone. Dermatology 2002; 204(3):248-250. PMID: 12037457.
[10] Lauerma AI. Screening for corticosteroids contact sensitivity. Comparison of toxicortol pivalate, hydrocortisone 17-butyrate and hydrocortisone. Contact Dermatitis 1991; 24(2):123-130. PMID: 1828209.
[11] Dooms-Goossens A, Morren M. Results of routine patch testing with corticosteroid series in 2073 patients. Contact Dermatitis 1992; 26(3):182-191. PMID: 1505184.
[12] Thomson KF, Wilkinson SM, Powell S, Beck MH. The prevalence of corticosteroid allergy in two U.K. centres: Prescribing implications. Br J Dermatol 1999; 141(5):863-866. PMID: 10583168.
[13] Klein-Gitelman MS, Pachman LM. Intravenous corticosteroids: Adverse reactions are more variable than expected in children. J Rheumatol 1998; 25(10):1995-2002. PMID: 9779857.
[14] Levine B. Immunological mechanisms of penicillin allergy. A haptenic model system for the study of allergic diseases in man. N Engl J Med 1966; 275(20):1115-1125. PMID: 5923027.
[15] Torres MJ, Canto G. Hypersensitivity reactions to corticosteroids. Curr Opin Allergy Clin Immunol 2010; 10(4):273-279. PMID: 20502322.
[16] Sulzberger MB, Witten VH. The effect of topically applied compound F in selected dermatoses. J Invest Dermatol 1952; 19(2):101-102. PMID: 14955641.
[17] Elliot F, Ellis MD. Adverse effects of corticosteroid therapy. J Allergy Clin Immunol 1987; 80:515-517.
[18] Butani L. Corticosteroid-induced hypersensitivity reactions. Ann Allergy Asthma Immunol 2002; 89(5):439-445. PMID: 12452199.
[19] Reitamo S, Lauerma AI, Stubb S, Kayhko K, Visa K, Forstrom L. Delayed hypersensitivity to topical corticosteroids. J Am Acad Dermatol 1986; 14(4):582-589. PMID: 3958273.
[20] Mendelson LM, Meltzer EO, Hamburger RN. Anaphylaxis-like reactions to corticosteroid therapy. J Allergy Clin Immunol 1974; 54(3):125-131. PMID: 4850575.
[21] Isaksson M, Bruze M. Corticosteroids. Dermatitis 2005; 16(1):3-5. PMID: 15996344.

Keywords: hypersensitivity, corticosteroids, steroids, aspirin

KANSAS JOURNAL of MEDICINE

KANSAS JOURNAL OF MEDICINE

AUGUST 2016

kjm.kumc.edu

PUBLICATION STAFF

Jon P. Schrage, M.D.
Editor

K. James Kallail, Ph.D.
Managing Editor/Collection Administrator

Christina M. Frank
Editorial Assistant

EDITORIAL BOARD MEMBERS

Stephen D. Helmer, Ph.D.
Mark E. Harrison, M.D.
Kamran Ali, M.D.
Ruth Weber, M.D.
Laura Mayans, M.D.
Rami Mortada, M.D.

Have a manuscript ready to publish? Visit our website for instructions on submitting a manuscript.

Office of Research
1010 N. Kansas, Wichita, KS 67214
316-293-2617 • Email: kjm@kumc.edu

The University of Kansas Medical Center prohibits discrimination on the basis of race, color, ethnicity, religion, sex, national origin, age, ancestry, disability, status as a veteran, sexual orientation, marital status, parental status, gender identity, gender expression, and genetic information in the University's programs and activities. The following office has been designated to handle inquiries regarding the non-discrimination policies: The University of Kansas Medical Center Department of Equal Employment Opportunity, 1054 Wescoe, 3901 Rainbow Blvd., Kansas City, KS, 66160, 913-588-5088.