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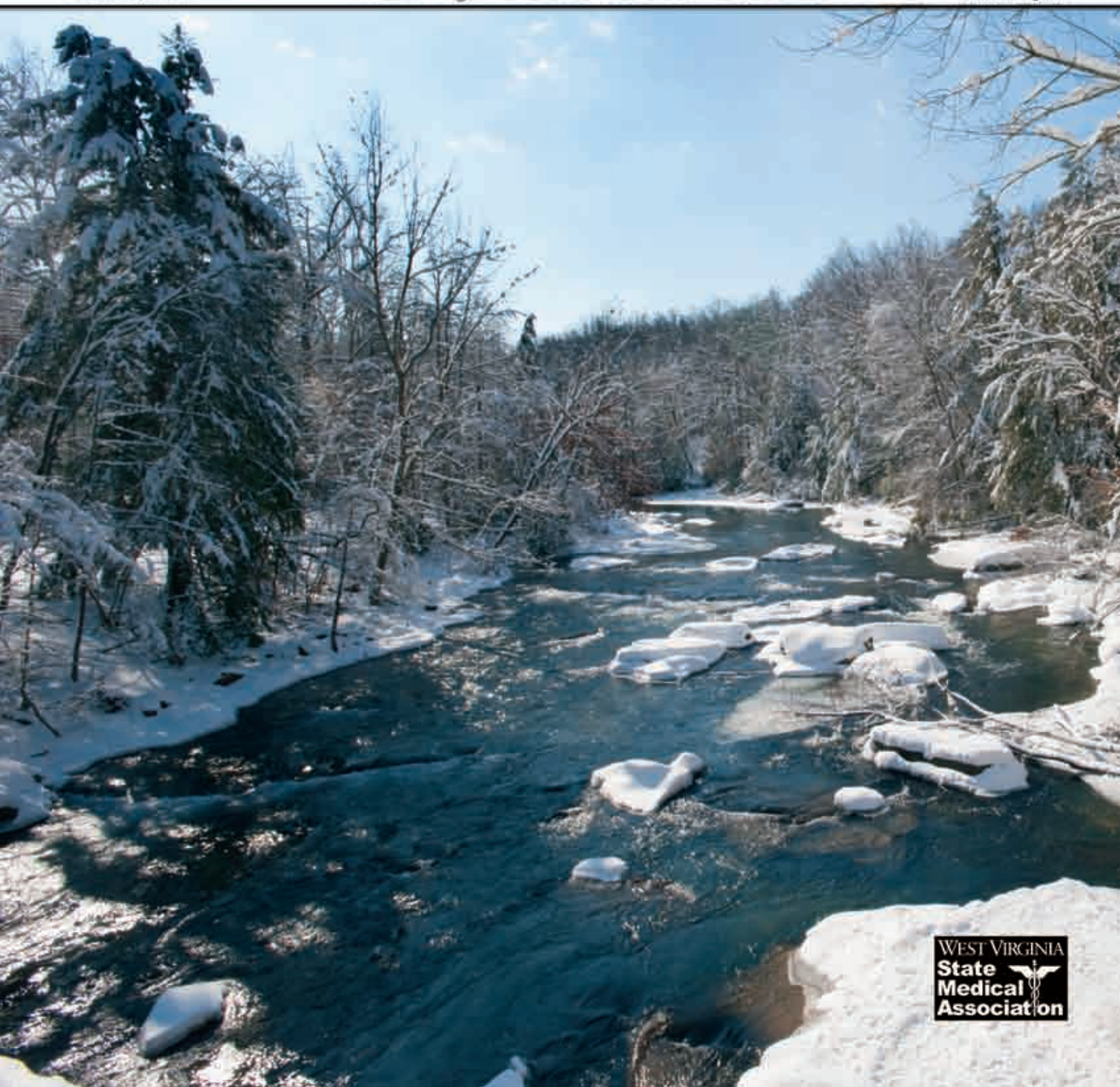
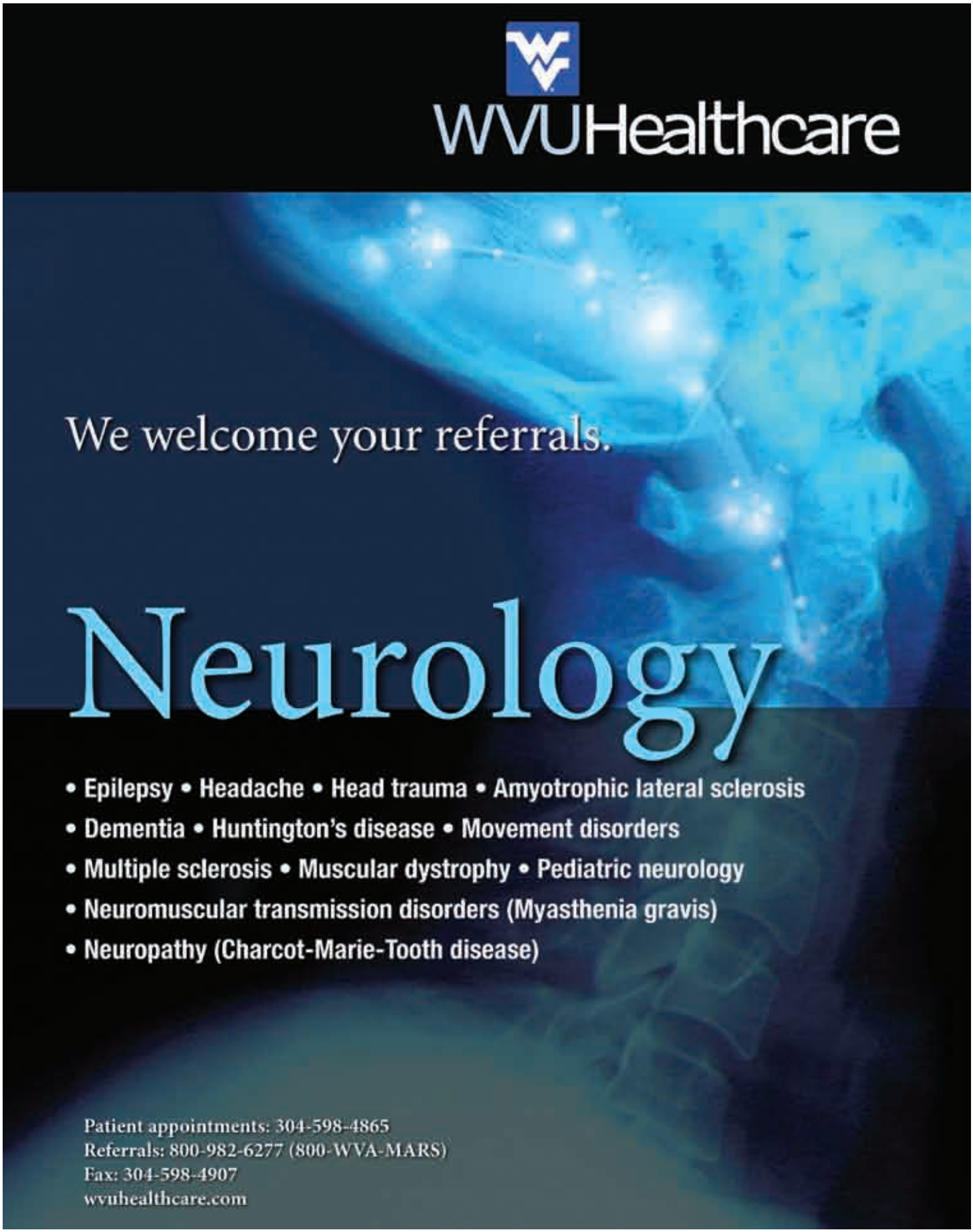
West Virginia State Medical Association

The Voice of Medicine in West Virginia

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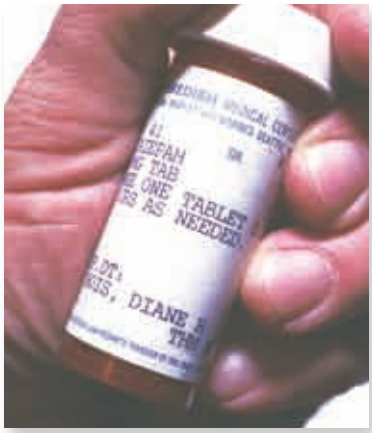

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features

CORRECTION

In the article, "The Integration of Clerkships," published in the *West Virginia Medical Journal* November/December 2011 on page 20, Table 1, the Charleston OB/GYN mean score was published incorrectly.The score should have been 73.7 as published by the NBME over the same time period.—Submitted by R. Todd DePond, MD, FACOG, Assistant Professor OB/GYN Department, Medical Student Clerkship Director, West Virginia University-Charleston.

In this issue...

Scientific Articles

UPCOMING EVENTS

2012 **CODING AND MEDICARE UPDATE**
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Register Today! See page 51

✦ **WVSMA Annual Midwinter Business Meeting**
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(see highlights on the opposite page)

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The ***West Virginia Medical Journal*** is published bimonthly by the West Virginia State Medical Association, 4307 MacCorkle Ave., SE, Charleston, WV 25304, under the direction of the Publication Committee. The views expressed in the *Journal* are those of the individual authors and do not necessarily reflect the policies or opinions of the *Journal's* editor, associate editors, the WVSMA and affiliate organizations and their staff.

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President's Message

Look in the Mirror

We call it the art and science of medicine. This is true for those of us who realize the practice of medicine is not merely writing prescriptions and ordering tests. The analysis of all the facts, gleaned from a carefully done history and physical examination and appropriately ordered tests are used by a physician, utilizing his/her vast knowledge of medicine and scientifically based medical evidence, to appropriately treat a disease process. The art is knowing when to treat and when to observe, when to hold the hand of a frightened patient, and how to present sometimes bad news in a comforting way. This kind of knowledge is learned in medical school! Years and years of studying and training are needed in order to be a physician.

Medical conditions are not always "right out of the textbook." Things happen during procedures and surgery that require the ability to quickly analyze the situation and often act immediately. If these kinds of decisions can be made by an allied health professional, then why send our young men and women to medical school followed by years of postgraduate training? Why require documented continuing medical education?

My fellow colleagues, health care delivery is changing before our eyes. We are losing control of the practice of medicine. This is not a turf war! Health care extenders are demanding and gaining privileges to practice medicine—often with little or no physician supervision. More and more, patients are calling extenders who have no Allopathic or Osteopathic degree …"Doctor". *We have no one to blame for this but ourselves.*

For many years we have used physician assistants, nurse practitioners and nurse anesthetists to ASSIST the physician. Now these extenders want to practice medicine independently. Extending the scope of practice has been the battle cry. Who is granting these privileges? Did all of this start from greed? Do health care payment models encourage seeing more patients per day, so physician can make more?

Teaching a technique to an extender can work well until that one time when things do not go smoothly. Without extensive training, deep knowledge of physiology and pharmacology, this is a disaster waiting to happen!

Do not go away from this article blaming nurse practitioners, physician assistants, nurse anesthetists and the like. We physicians need to look in the mirror. *We as physicians are the ones who need to wake up!* Get involved in organized medicine and its efforts to limit any scope of practice expansion that jeopardizes patient safety. This is not a fight for the dollar; this is a fight for the welfare of our patients.

There is no more noble profession than that of a physician. We need to encourage those who want to truly practice the art and science of medicine to go to medical school.

MaryAnn N. Cater, DO
WVSMA President

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Our Editor Speaks

It's Just a Business Decision

A few months ago we received notice from one of the insurance companies that we deal with that they would no longer allow us to use our in office CT scanner for their patients. They based their decision on the fact that we did not do five different types of scans and that we did not have a radiologist on our staff with advance cardiac life support. We only do sinus scans and do not use contrast of any kind so these restrictions seemed a bit unreasonable.

Before we purchased our scanner about six years ago we did an audit of the number of sinus scans we were sending out. In every year since, we have done roughly the same number of scans as we did prior to having our own scanner.

Prior to having our own CT a patient with sinus complaints often had to make three visits: a new patient visit with us, a CT on another day somewhere else and a return visit with us to review CT and establish a treatment plan. That often meant three days away from work for many of our patients.

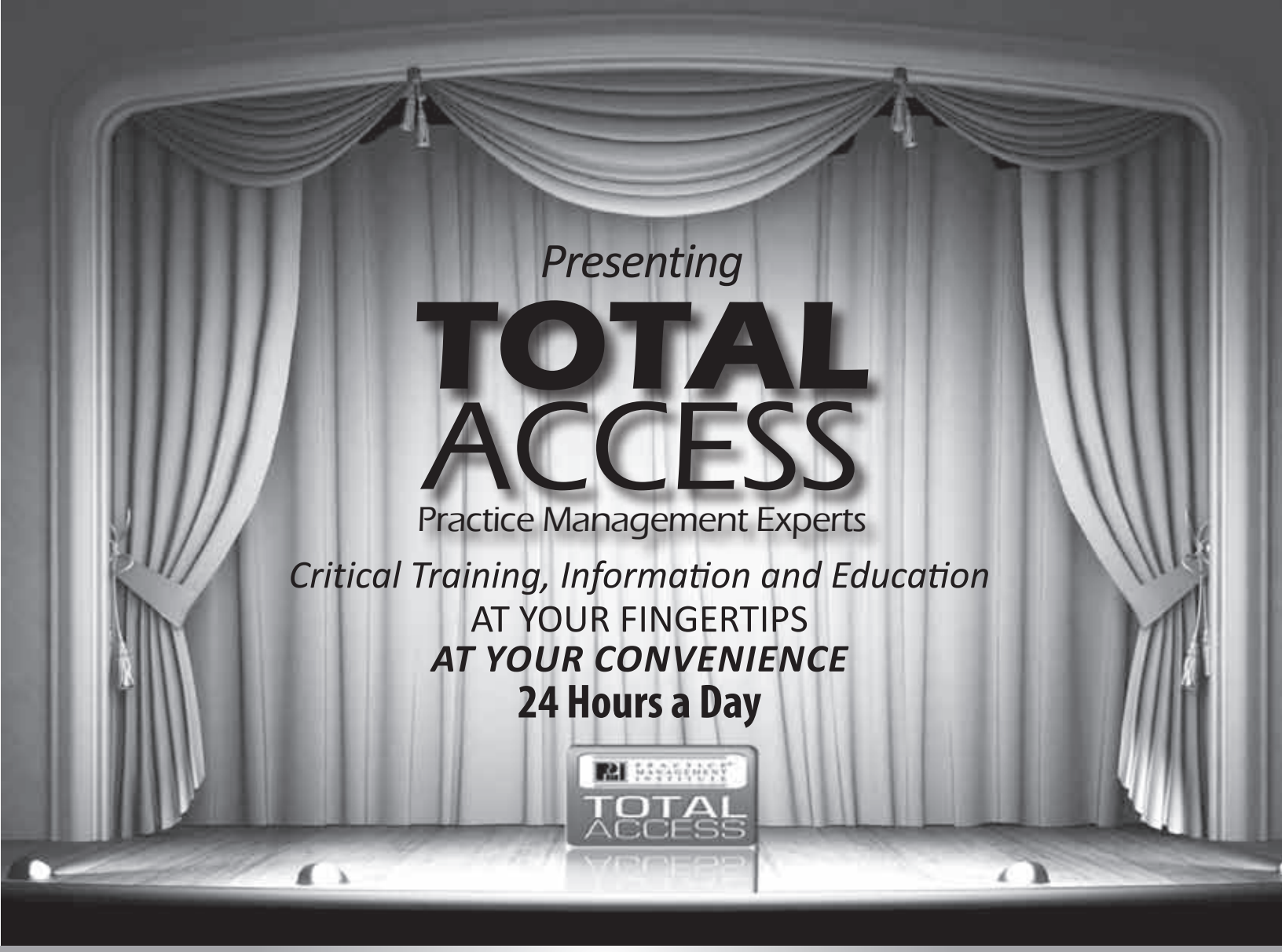
Using our scanner, a typical visit for sinusitis including CT if indicated, can be accomplished in about a half hour. The scan itself takes 45 seconds. This is a huge savings for both patient and employer. The scanner uses an extremely small radiation exposure.

We are accredited by a national accreditation organization and have regular inspections.

Several other ENT offices in the state have also been affected by this decision. A few weeks ago we were given the opportunity to have a conference call with the company's Medical Director. On the call with us were three other offices, a representative of our national academy and the CEO of our accrediting organization. The call lasted about an hour and we presented our case. The medical director kept repeating that this was simply a business decision.

It certainly is not a wise choice for our patients and their employers.

F. Thomas Sporck, MD, FACS
Editor



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The Relationship Between Gamma-Glutamyl Transferase Levels and Chronic Kidney Disease Among Appalachian Adults

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Anoop Shankar, MD, MPH, PhD

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Abstract

Background: Serum gamma-glutamyl transferase (GGT), a marker of oxidative stress has been associated with diabetes and hypertension, which are risk factors for chronic kidney disease (CKD). However, it is unclear whether serum GGT is independently associated with CKD.

Methods: We analyzed data from a population-based study of Appalachian adults residing in six communities in Ohio and West Virginia, who were aged ≥18 years (n=55,187, 52% women). Serum GGT was examined as gender-specific quintiles (quintiles 1-5 in women: 0-11 U/L, 12-14 U/L, 15-19 U/L, 20-29 U/L and >29 U/L; quintiles 1-5 in men: 0-17 U/L, 18-23 U/L, 24-30 U/L, 31-45 U/L, and >45 U/L). The main outcome of interest was CKD (n=4482), defined as an estimated glomerular filtration rate of <60 mL/min/1.73 m^2 from serum creatinine.

Results: Higher serum GGT levels were not found to be associated with CKD after adjusting for age, education, smoking, alcohol intake, body mass index (BMI), diabetes, hypertension and total cholesterol. In women, compared to quintile 1 of GGT, the odds ratio (OR) (95% confidence interval[CI]) of CKD associated with quintile 5 was 0.93 (0.82-1.06); p-trend=0.3102. Similarly, in men, compared to quintile 1 of GGT, the odds ratio (OR) (95% confidence interval[CI]) of CKD associated with quintile 5 was 0.94 (0.80-1.10); p-trend=0.4372. Subgroup analyses that examined the relation between GGT and CKD by alcohol intake and BMI categories also showed a consistent null association.

Conclusion: In a community-based sample of Appalachian adults, higher serum GGT was not found to be independently associated with CKD.

Introduction

Serum gamma-glutamyl transferase (GGT), an enzyme responsible for extracellular catabolism of glutathione and a marker of oxidative stress[1] has been shown to be associated with diabetes mellitus[2] and hypertension,[3] which are considered to be independent risk factors for chronic kidney disease (CKD). However, few epidemiological studies have explored the independent relationship between CKD and GGT.[4,5] In this context, we examined the association between gamma-glutamyl transferase and chronic kidney disease in a population-based study of Appalachian adults after controlling for the effect of major confounding factors such as body mass index (BMI), diabetes mellitus, and hypertension.

Subjects and Methods

Study Population

The C8 Health Study is a population-based study of Appalachian individuals residing in six communities in West Virginia and Ohio. The study was primarily aimed at examining the health effects of environmental exposures among community residents. The study subjects were examined and blood samples collected between August 2005 and August 2006. Written informed consent was obtained from each subject at the examination and the study was approved by the Institutional Review Board of the West Virginia University Medical School, Morgantown.

We estimated the participation rate among adults aged ≥20 years using the 2005 census data. The overall study participation rate among adults aged ≥20 years was 81% and this ranged from 70.2% to 94.8% in these six communities. In the current paper, out of 69,030 subjects who were examined for the C8 Health Study, we excluded subjects who were <18 years of age (n=10,543), those with missing data for variables included in the multivariable analysis, including missing serum gamma-glutamyl transferase(n=2430), missing serum creatinine (n=2429), smoking status (n=148), years of school completed (n=1346), BMI (n=13,069) and alcohol intake (n= 2860), that could confound the association between serum GGT and CKD, resulting in 55,187 eligible subjects. In subsequent analyses, those who had cardiovascular disease (n=5,814) were also excluded to further eliminate possible confounding, resulting in 49,373 eligible subjects.

Exposure measurement

The study examination included administering a standardized questionnaire that collected information regarding participants' demographic characteristics, details regarding cigarette smoking, alcohol intake, medical histories and medications taken, including diagnosis of diabetes, hypertension or CVD by a physician. Blood specimens were obtained for measurement of plasma glucose, serum total cholesterol, high density lipoprotein

(HDL) cholesterol and triglycerides. A detailed medical chart review was also performed to verify the accuracy of self-reported diagnoses.

Age was defined as the participants' age at the time of examination. Education was categorized as below high school, high school, or above high school. BMI was defined as the participants' weight in kilograms divided by the height in meter squared. Hypertension was defined as self-reported hypertension diagnosis by a physician and use of antihypertensive medications. Persons were defined as having diabetes mellitus if they had a history of diabetes diagnosis by a physician and were treated with insulin, oral hypoglycemic agents or diet, or were newly classified as having diabetes based on the presence of a casual blood sugar value ≥200 mg/dL (11.1 mmol/L) or fasting glucose ≥126 mg/dL (7.0 mmol/L); fasting blood samples were available only on a subset of subjects (30.1% of the whole sample).

Outcome of Interest: Chronic Kidney Disease

Serum creatinine was measured using a kinetic rate Jaffe method consistent with the current National Kidney Disease Education Program (NKEDP) recommendations for serum creatinine measurement.[6] Glomerular filtration rate (GFR) was estimated from serum creatinine using the re-expressed 4-variable Modification of Diet in Renal Disease (MDRD) equation defined as follows: eGFR = 175 X (serum creatinine in mg/ dL)$^{-1.154}$ X age$^{-0.203}$ X 0.742 (if the individual is female) or X 1.212 (if the individual is black.[7] CKD was defined as an eGFR of <60 mL/min/1.73 m^2, based on the US National Kidney Foundation Kidney Disease Outcome Quality Initiative working group definition[8] and the Kidney Disease Improving Global Outcomes (KDIGO).[9]

Statistical Analysis

We examined serum GGT as gender-specific quintiles (quintiles 1-5 in women: 0-11 U/L, 12-14 U/L, 15-19 U/L, 20-29 U/L and >29 U/L; quintiles 1-5 in men: 0-17 U/L, 18-23 U/L, 24-30 U/L, 31-45 U/L, and > 45 U/L). We also analyzed GGT as a continuous variable after logarithmic transformation due to its skewed distribution. The prevalence ratio (PR) [95% confidence interval (CI)] of CKD was calculated for each serum gamma-glutamyl tranferase quintile, with the lowest quartile as the reference, employing a log-linear model using PROC GENMOD in SAS, as in cross-sectional studies,

the PR is a more unbiased estimate of the magnitude of association than the odds ratio when the outcome is not rare. We used two models: the unadjusted model and the multivariable model adjusted for age (years), race-ethnicity (non-Hispanic whites, non-Hispanic blacks, all others), education categories (<high school, high school, >high school), smoking (never, former, current), alcohol intake (never, former, current), body mass index (normal, overweight, obese), diabetes mellitus (absent, present), hypertension (absent, present) and serum cholesterol (mg/dL). Trends in the PR of CKD across increasing GGT quintiles were determined by modeling GGT quintile as an ordinal variable. To examine the consistency of the association between GGT and CKD, we performed subgroup analyses by gender (women, men), BMI categories (<25 kg/m^2, ≥25 kg/m^2), alcohol intake categories (never drinker, current/former drinker). The observed association between GGT and CKD may be confounded by the presence of cardiovascular disease, as both high GGT levels and CKD may occur secondary to cardiovascular disease. Therefore, we repeated the analysis among study subjects who were free of cardiovascular disease (n=49,373). All analyses were performed in SAS version 9.2 (SAS Institute, Cary).

Table 1. Characteristics of the study population by categories of serum gamma-glutamyltransferace (GGT) levels

WOMEN*

Characteristics	Quintile 1 (0-11 U/L)	Quintile 2 (12-14 U/L)	Quintile 3 (15-19 U/L)	Quintile 4 (20-29 U/L)	Quintile 5 (> 29 U/L)	p-value
Number at risk	6087	4831	6194	5996	5707	
Age, years	38.3 ± 0.2	43.0 ± 0.2	45.8 ± 0.2	47.8 ± 0.2	50.0 ± 0.2	< 0.0001
Race-ethnicity, %						
Non-Hispanic whites	97.5%	97.3%	96.8%	96.1%	97.1%	0.0002
Non-Hispanic blacks	0.7%	0.8%	0.9%	1.5%	0.9%	
All others combined	1.8%	1.9%	2.3%	2.4%	2.0%	
Education categories, %						
Below high school	8.6%	11.1%	10.9%	13.0%	14.4%	< 0.0001
High school	36.6%	38.4%	41.8%	41.3%	41.8%	
Above high school	54.8%	50.5%	47.3%	45.7%	43.8%	
Smoking, %						
Never smoker	58.3%	54.1%	51.3%	49.8%	50.2%	< 0.0001
Former smoker	21.2%	20.7%	20.3%	22.3%	21.5%	
Current smoker	20.5%	25.2%	28.4%	27.9%	28.3%	
Alcohol intake, %						
Never drinker	27.0%	28.3%	29.4%	30.1%	31.0%	< 0.0001
Former drinker	26.6%	27.2%	27.1%	28.2%	31.5%	
Current drinker	46.4%	44.5%	43.5%	41.7%	37.5%	
Body mass index, kg/m^2	25.5 ± 0.1	26.8 ± 0.1	28.7 ± 0.1	30.3 ± 0.1	31.4 ± 0.1	< 0.0001
Diabetes mellitus, %*	4.6%	5.2%	7.9%	10.7%	16.5%	< 0.0001
Hypertension, %	11.4%	17.0%	24.6%	31.5%	39.9%	< 0.0001
Total cholesterol, mg/dL	188.3 ± 0.5	193.6 ± 0.6	201.2 ± 0.5	205.6 ± 0.5	213.0 ± 0.6	< 0.0001

**Data presented are row percentages or mean values*
† P-value for difference in characteristics by GGT quintile based on analysis of variance or chi-square test as appropriate

Results

Among 55,187, Appalachian adults ≥18 years of age, there were 28815 women and 26372 men. Overall, there were 4482 subjects with CKD (8.1%), including 2793 women and 1729 men.

Table 1 presents the characteristics of the study population by GGT quintiles for women. Female individuals with higher levels of GGT were more likely to be below high school educated, older and current smokers and more likely to have higher BMI and hypertension and diabetes and higher total cholesterol levels.

Table 2 presents the characteristics of the study population by GGT quintiles for men. Male individuals with higher levels of GGT were more likely to be non-Hispanic black, current/former smokers and current/former drinkers and more likely to have higher BMI and hypertension and higher total cholesterol levels.

Table 3 presents the PR of CKD by increasing GGT quintiles separately in women and men. Among women, there was an initial positive association between GGT quintiles and CKD in the unadjusted model. However, after multivariable adjustment for confounders, such as BMI, diabetes mellitus, and hypertension, the association disappeared and PRs revealed a null association. Among men, there was an initial negative association between GGT quintiles and CKD in the unadjusted model. However, here also, after multivariable adjustment for confounders, the PRs revealed a null association

Table 4 presents the prevalence ratios of CKD by increasing GGT separately by alcohol intake. Both among current/former drinkers and never drinkers, we observed a null association between increasing quintiles of GGT and CKD.

Table 5 presents the prevalence ratios of CKD by increasing GGT quintiles separately by BMI

Table 2. Characteristics of the study population by categories of serum gamma-glutamyltransferace (GGT) levels

MEN*

Characteristics	Quintile 1 (0-17 U/L)	Quintile 2 (18-23 U/L)	Quintile 3 (24-30 U/L)	Quintile 4 (31-45 U/L)	Quintile 5 (> 45 U/L)	p-value
Number at risk	5413	5329	4788	5421	5241	
Age, years	43.5 ± 0.2	46.4 ± 0.2	46.5 ± 0.2	45.9 ± 0.2	45.9 ± 0.2	< 0.0001
Race-ethnicity, %						
Non-Hispanic whites	96.7%	97.2%	96.7%	96.8%	96.1%	0.0017
Non-Hispanic blacks	1.0%	0.9%	1.6%	1.2%	1.6%	
All others combined	2.3%	1.9%	1.6%	2.0%	2.3%	
Education categories, %						
Below high school	13.8%	12.6%	11.5%	11.4%	13.2%	0.0008
High school	43.6%	45.0%	44.9%	45.4%	45.9%	
Above high school	42.6%	42.4%	43.6%	43.2%	40.9%	
Smoking, %						
Never smoker	46.3%	42.8%	42.9%	40.7%	38.5%	< 0.0001
Former smoker	28.7%	32.7%	32.8%	32.4%	30.4%	
Current smoker	25.0%	24.6%	24.3%	26.9%	31.0%	
Alcohol intake, %						
Never drinker	22.2%	19.6%	16.9%	15.0%	13.0%	< 0.0001
Former drinker	29.3%	30.2%	29.5%	27.7%	26.1%	
Current drinker	48.6%	50.3%	53.6%	57.4%	60.9%	
Body mass index, kg/m^2	25.9 ± 0.1	27.8 ± 0.1	29.1 ± 0.1	30.1 ± 0.1	30.3 ± 0.1	< 0.0001
Diabetes mellitus, %*	9.6%	9.4%	9.5%	10.0%	10.4%	0.3622
Hypertension, %	19.5%	25.5%	27.2%	29.8%	34.2%	< 0.0001
Total cholesterol, mg/dL	175.1 ± 0.6	188.3 ± 0.6	195.6 ± 0.6	201.2 ± 0.6	210.7 ± 0.6	< 0.0001

**Data presented are row percentages or mean values*
† P-value for difference in characteristics by GGT quintile based on analysis of variance or chi-square test as appropriate

category. Both normal weight and overweight/obese subjects, we observed a null association between increasing quintiles of GGT and CKD.

We conducted a supplementary analysis excluding those with cardiovascular disease to examine the robustness of our findings. Overall consistent with the main results, we observed a null association between GGT and CKD among either gender among subjects without cardiovascular disease. For women, compared to serum GGT quintile 1 (referent), the HR (95% CI) of CKD was 0.86 (0.73 - 1.02) in quintile 2, 0.98 (0.85- 1.14) in quintile 3, 0.88 (0.75 - 1.02) in quintile 4 and 0.90 (0.78 - 1.05) in quintile 5; p-trend=<0.0001. For men, compared to serum GGT quintile 1 (referent), the HR (95% CI) of CKD was 1.00 (0.83, 1.21) in quintile 2, 1.06 (0.87, 1.28) in quintile 3, 0.99 (0.81, 1.20) in quintile 4 and 0.89 (0.72, 1.11) in quintile 5; p-trend=<0.0001.

Discussion

In a population-based study of Appalachian adults, serum gamma-glutamyl transferase levels were not found to be associated with CKD, independent of age, gender, smoking status, alcohol intake, education, diabetes mellitus, hypertension, body mass index and total cholesterol. The observed null association between serum gamma-glutamyl transferase levels and CKD remained consistent in subgroup analyses by gender, alcohol intake, BMI and in a supplementary analysis excluding subjects with cardiovascular disease.

Our finding of no association between higher gamma-glutamyl transferase levels and CKD shows high internal validity, as shown by the magnitude of the association, independence from confounding factors such as age, smoking, alcohol intake, and the consistency of this association in subgroup analyses by gender, drinking status and BMI. When we examined the association between gamma-glutamyl transferase levels and CKD among study subjects free of cardiovascular disease, the results were found to be consistent with the main multivariable findings, suggesting the findings to be independent of cardiovascular disease.

Our results of a null association between gamma-glutamyl transferase levels and CKD are inconsistent with previous studies conducted in an occupational cohort of Korean men.[4,5] The reason for the difference in our findings— from a US Appalachian general population sample—to that from the Korean occupational study is not fully clear. Reasons may include the fact that 1) we studied both men and women, as opposed to the Korean study that studied only men, 2) our study was a general community-based sample, as opposed to the Korean study which was an occupational cohort of workers from a semiconductor manufacturing plant, and 3) as GGT levels are influenced by alcohol and diet, findings from Asian populations may not be directly applicable to Western populations with different alcohol intake and dietary patterns. Furthermore, our findings are consistent with a recent study based on the US National Health and Nutritional Examination Survey that reported a similar null finding as ours.[10]

Table 3. Association between serum gamma-glutamyltransferace (GGT) levels and chronic kidney disease (CKD), by gender

Serum GGT quintiles	No. at risk	No. of cases	Unadjusted prevalence ratio (95% confidence interval)	Multivariable-adjusted prevalence ratio (95% confidence interval)
Women (n=29390)				
Quintile 1(0-11 U/L)	6087	360	1 (referent)	1 (referent)
Quintile 2 (12-14 U/L)	4831	387	1.35 (1.1y, 1.56)	0.92 (0.80, 1.06)
Quintile 3 (15-19 U/L)	6194	647	1.77 (1.55, 2.01)	0.99 (0.87, 1.12)
Quintile 4 (20-29 U/L)	5996	654	1.84 (1.62, 2.10)	0.91 (0.80, 1.04)
Quintile 5 (>29 U/L)	5707	705	2.09 (1.84, 2.37)	0.93 (0.82, 1.06)
p-trend			< 0.0001	0.3102
Log-transformed serum GGT, U/L			1.40 (1.33, 1.48)	1.00 (0.94, 1.06)
Men (n=23383)				
Quintile 1(0-17 U/L)	5413	400	1 (referent)	1 (referent)
Quintile 2 (18-23 U/L)	5329	388	0.99 (0.86, 1.13)	0.94 (0.82, 1.09)
Quintile 3 (24-30 U/L)	4788	324	0.92 (0.79, 1.06)	0.98 (0.84, 1.13)
Quintile 4 (31-45 U/L)	5421	323	0.81 (0.70, 0.93)	0.94 (0.81, 1.09)
Quintile 5 (>45 U/L)	5241	294	0.76 (0.65, 0.88)	0.94 (0.80, 1.10)
p-trend			< 0.0001	0.4372
Log-transformed serum GGT, U/L			0.86 (0.79l 0.92)	0.97 (0.89. 1.05)

**Adjusted for age (years), race-ethnicity (non-Hispanic whites, non-Hispanic blacks, others), education categories (<high school, high school, >high school), smoking (never, former, current), alcohol intake (never, former, current), body mass index (normal, overweight, obese), diabetes (absent, present), hypertension (absent, present) and serum cholesterol (mg/dL)*

Table 4. Association between serum gamma-glutamyltransferace (GGT) levels and chronic kidney disease (CKD), by alcohol intake status

	Never drinker (n=12959)		Current/former drinker (n=42043)	
Serum GGT quintiles	No. at risk (CKD cases)	Multivariable Prevalence Ratio (95% confidence interval)*	No. at risk (CKD cases)	Multivariable Prevalence Ratio (95% confidence interval)*
Women				
Quintile 1(0-11 U/L)	1645 (176)	1 (referent)	4442 (184)	1 (referent)
Quintile 2 (11-14 U/L)	1366 (191)	0.90 (0.73, 1.10)	3465 (196)	0.95 (0.78 01.16)
Quintile 3 (14-19 U/L)	1825 (346)	1.04 (0.86, 1.25)	4369 (301)	0.94 0(.78, 1.13)
Quintile 4 (19-29 U/L)	1805 (346)	0.96 (0.80, 1.15)	4191 (308)	0.86 (0.71, 1.04)
Quintile 5 (>29 U/L)	1770 (322)	0.89 (0.74, 1.07)	3937 (383)	0.96 (0.79, 01.15)
p-trend		0.3461		0.5215
Men				
Quintile 1(0-17 U/L)	1200 (120)	1 (referent)	4213 (280)	1 (referent)
Quintile 2 (17-23 U/L)	1044 (119)	1.11 (0.86, 1.44)	4285 (269)	0.87 (0.74, 1.03)
Quintile 3 (23-30 U/L)	809 (88)	1.14 (0.86, 1.51)	3979 (236)	0.92 (0.77, 1.09)
Quintile 4 (30-45 U/L)	812 (73)	0.97 (0.72, 1.31)	4609 (250)	0.91 (0.77, 1.09)
Quintile 5 (> 45 U/L)	683 (68)	1.09 (0.80, 1.48)	4558 (226)	0.88 (0.73, 1.06)
p-trend		0.8715		0.3102

**Adjusted for age (years), sex (men, women), race-ethnicity (non-Hispanic whites, non-Hispanic blacks, others), education categories (<high school, high school, >high school), smoking (never, former, current), body mass index (normal, overweight, obese), diabetes (absent, present), hypertension (absent, present) and serum cholesterol (mg/dL*

The major strengths of our study are its large sample size, standardized methods of data collection, detailed measurement of biomarkers that represent potential confounding pathways such as serum cholesterol, and the validation of medical diagnoses by chart review. Internal validity of our results are high as we stratified by gender, alcohol intake, BMI, and cardiovascular disease and performed multivariable adjustment of confounders. The first major limitation of this study is its cross-sectional design. Therefore, we are unable to draw any conclusions about the temporal association between serum gamma-glutamyl transferase and chronic kidney disease. Second, the large representative sample is primarily comprised of whites, reflecting the typical Appalachian community. Therefore, our results may not be generalized to other populations.

In conclusion, in a population-based sample of Appalachian adults, we found that increasing gamma-glutamyl transferase levels were not associated with CKD. Future prospective studies should be conducted to explore the temporal association between gamma-glutamyl transferase and CKD and to confirm the null association.

Acknowledgments

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Author Disclosure Statement

"No competing financial interests exist."

Table 5. Association between serum gamma-glutamyltransferace (GGT) levels and chronic kidney disease (CKD), by body mass index

	Normal weight (n=16886)		Overweight/ obese (n=38121)	
Serum GGT quintiles	**No. at risk (CKD cases)**	**Multivariable Prevalence Ratio (95% confidence interval)**	**No. at risk (CKD cases)**	**Multivariable Prevalence Ratio (95% confidence interval)**
Women				
Quintile 1(0-11 U/L)	3433(156)	1 (referent)	2654(204)	1 (referent)
Quintile 2 (11-14 U/L)	2219(149)	0.97 (0.77, 1.22)	2612(238)	0.89 (0.74, 1.07)
Quintile 3 (14-19 U/L)	2127(188)	1.03 (0.83, 1.28)	4067(459)	0.97 (0.82, 1.14)
Quintile 4 (19-29 U/L)	1549(154)	0.93 (0.74, 1.17)	4447(500)	0.90 (0.76, 1.06)
Quintile 5 (>29 U/L)	1127(144)	0.97 (0.77, 1.23)	4580(561)	0.92 (0.78, 1.08)
p-trend		0.7049		0.3934
Men				
Quintile 1(0-17 U/L)	2455(111)	1 (referent)	2958(289)	1 (referent)
Quintile 2 (17-23 U/L)	1530(78)	1.03 (0.77, 1.38)	3799(310)	0.91 (0.78, 1.07)
Quintile 3 (23-30 U/L)	929(52)	1.13 (0.81, 1.58)	3859(272)	0.93 (0.79, 1.10)
Quintile 4 (30-45 U/L)	813(42)	1.02 (0.71, 1.47)	4608 (281)	0.90 (0.76, 1.07)
Quintile 5 (> 45 U/L)	704(42)	1.04 (0.72, 1.51)	4537(252)	0.90 (0.75, 1.07)
p-trend		0.7666		0.2664

**Adjusted for age (years), sex (men, women), race-ethnicity (non-Hispanic whites, non-Hispanic blacks, others), education categories (<high school, high school, >high school), smoking (never, former, current), body mass index (normal, overweight, obese), diabetes (absent, present), hypertension (absent, present) and serum cholesterol (mg/dL).*

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Ectopic Production of HCG by a Benign Ovarian Mature Cystic Teratoma Simulating an Extra-uterine Pregnancy: a Case Report

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Abstract

Physicians should consider a benign mature cystic teratoma in their differential diagnosis of a patient with an elevated serum human chorionic gonadotropin concentration.

BACKGROUND: Following tubal ligation, a woman with amenorrhea and elevated serum human chorionic gonadotropin (HCG) concentrations may be experiencing either an ectopic or an intrauterine pregnancy. Other sources of HCG production can include ovarian germ cell tumors or gestational trophoblastic disease such as a complete or partial molar pregnancy. A rare source of HCG production is a benign mature ovarian teratoma.

CASE: A 31-year old Gravida 2 para 2 presented with a positive home pregnancy test three years after she had experienced a Pomeroy tubal ligation. Her serum HCG was 57,914 mIU/mL but a transvaginal ultrasound did not find an intrauterine pregnancy. Laparoscopy was performed due to a suspicion of an ectopic pregnancy and an 11-cm benign mature cystic teratoma (dermoid cyst) within the right ovary was removed. An ectopic pregnancy was not visualized. Post-operatively, her serum HCG levels decreased and were negative within four weeks.

CONCLUSION: Mature ovarian cystic teratomas have rarely been reported to secrete HCG. They can be an infrequent source of HCG production and may lead to emergency surgery to treat a suspected extra-uterine pregnancy.

Introduction

The incidence of an ectopic pregnancy is one in fifty pregnancies in the United States; however, pregnancy in a woman post tubal ligation is more likely to be an ectopic pregnancy compared to the general population. One third of post-sterilization failures are ectopic pregnancies due to the disruption of normal tubal anatomy.[1] Pregnancy following a tubal ligation by the Pomeroy method is as high as 16%; pregnancy can occur because of spontaneous re-anastomosis of the Fallopian tubes or fistula formation.

An ectopic pregnancy mimics a normal intrauterine pregnancy until significant hemorrhage occurs. Breast tenderness, nausea, frequent urination, and amenorrhea are common symptoms of both intra- and extra-uterine pregnancies. Fifty percent of women with an ectopic pregnancy are asymptomatic until a fallopian tube ruptures.[2] They may present with vaginal bleeding, abdominal cramping and pain. A tubal rupture may result in severe internal bleeding which can lead to shock and death. Ectopic pregnancies may resolve by spontaneous tubal abortion expelling the pregnancy without complications, but frequently, pain, bleeding, and hemorrhagic shock are associated. Ectopic pregnancies must be identified and removed early to avoid these life-threatening complications.

Transvaginal ultrasound can detect an intrauterine pregnancy with a Beta-hCG level of 1500 mIU/ml and detect an extra-uterine pregnancy in up to 80 percent of women. An ectopic pregnancy is treated with either medical management such as Methotrexate or surgical management such as laparoscopy. Afterwards, HCG concentrations are monitored weekly until levels drop below 5 mIU/mL.

Trophoblastic tissue secretes beta-hCG and the differential diagnosis for an elevated serum HCG concentration includes intra-uterine and extra-uterine pregnancy, gestational trophoblastic neoplasia, and ovarian germ cell tumors. Forty percent of complete moles are associated with an HCG concentration greater than 100,000 mIU/mL.[3] Sequellae of a molar pregnancy can be persistent gestational trophoblastic neoplasia (GTN) or choriocarcinoma. An abnormally large uterus, advanced maternal age, and abnormally elevated HCG levels raise suspicions for malignant GTN. Metastasis to the lung, liver, bone, etc. most often occurs from a choriocarcinoma within the ovary. Choriocarinomas develop from extra-embryonic differentiation of malignant germ cells of the placenta as opposed to molar pregnancies which are benign trophoblastic cells generated from abnormal fertilization. Ultrasound may reveal the abnormality, but histological examination is necessary to confirm the diagnosis.

Serum pregnancy markers such as alpha-fetoprotein (AFP) and HCG are useful when diagnosing a particular ovarian germ cell tumor. Granulosa cell tumors elevate inhibin levels while embryonal carcinomas increase AFP and HCG. The most common ovarian tumor is the mature cystic teratoma (dermoid cyst) which is usually

hormonally inactive. Ultrasound is used to make a diagnosis and ovarian cystectomy is used to confirm the diagnosis, preserve ovarian tissue, and allow for removal.

Case Report

A 31-year old gravida 2 para 0-2-0-2 complained of amenorrhea, abdominal discomfort, nausea, and breast tenderness and had a positive home pregnancy test. She had a Pomeroy tubal ligation three years ago and a known right dermoid cyst. An office quantitative beta- HCG was 41,428 mIU/mL. A transvaginal ultrasound was performed and did not find an intrauterine pregnancy. An ectopic pregnancy was considered the most likely cause of her positive HCG.

The patient's past medical history consisted of chronic abdominal pain and chronic hypertension. She had undergone two cesarean deliveries due to preterm severe preeclampsia and had a pomeroy tubal ligation with her second. Three days post partum; she developed a low grade fever and underwent computed tomogram of the abdomen revealing a 6x10 cm right dermoid cyst. She was asymptomatic and was discharged but did not follow-up with gynecology until this admission. She had been evaluated by surgery for her chronic abdominal pain and had a second abdominal computed tomogram scan in 2008 revealing the 6 x 10 cm midline dermoid lesion, nonobstructing right nephrolithiasis, and cholelithiasis. She underwent a laparoscopic cholecystectomy in 2008. Other prior surgeries included a total thryroidectomy for hyperthyroidism. She was currently on thyroid replacement and an antidepressant. Her family history was remarkable for diabetes and hypertension. She did not desire future childbearing. Once she discovered the positive home pregnancy test, she went to the emergency room for evaluation. The transvaginal ultrasound or emergency room pelvic exam did not demonstrate an ovarian mass and the previous computed tomogram scan report was unavailable.

The plan was a diagnostic laparoscopy with possible oopherectomy or salpingectomy to identify and remove the presumed ectopic pregnancy. Laparoscopic findings included a modestly enlarged anteverted uterus with a large right ovary containing an 11 x 9 x 4.5 cm cyst. The left ovary appeared normal and both fallopian tubes displayed prior tubal ligation and did not demonstrate a tubal pregnancy. She underwent a laparoscopic right salpingo-oopherectomy and endometrial curettage. The specimen required a minilaparotomy for removal. Pathology reported that the 11 cm grey-tan specimen was a benign mature cystic teratoma. Sectioning of the cyst found caseous material, hair, and partially calcified areas. The endometrial pathology was also evaluated and demonstrated a benign hypersecretory endometrium without atypia. There was no evidence of chorionic villi on either specimen.

Following the operation, the patient's HCG concentration was halved to 25,427 mIU/mL and was monitored weekly. One week post-operatively, her HCG was reported at 12,953 mIU/mL; three weeks post-operatively her HCG was 35.4 mIU/mL; and four weeks it was 5.9 mIU/mL. The patient continued to have her HCG levels monitored for two more negative results.

Discussion

The differential diagnosis for elevated human chorionic gonadotropin levels is pregnancy, gestational trophoblastic neoplasia (GTN), and ovarian tumors. This patient's presenting symptoms were suspicious for an extra-uterine pregnancy following tubal ligation. However, the negative pelvic ultrasound and endometrial curretage made GTN and ectopic pregnancy unlikely.

Dermoid cysts or mature cystic teratomas are usually an inactive, benign combination of all three embryonic germ cell layers, containing sebaceous fluid, hair, and even teeth. Common in the second and third decades, these cysts may present with symptoms depending on their size and susceptibility for torsion. Approximately one percent of dermoid cysts contain malignant cells that develop into squamous cell carcinoma later in life and the patient's extremely high HCG level warranted serious concern. Choriocarcinoma was a possible source of her elevated HCG but the negative endometrial curettage with decreasing HCG levels was reassuring.

This patient's dermoid cyst was particularly unusual for several reasons. It was missed at the time of her repeat cesarean section and again at the time of her cholecystectomy. The higher fat content of a larger dermoid cyst typically provides easier visualization on CT scan; conversely, its greater buoyancy may make the ovary high in the peritoneal cavity and not palpable by pelvic exam. She had undergone two prior surgeries and the large dermoid cyst was not visualized. In the case of her cesarean section, the ovary was pushed high in the upper abdomen by the gravid uterus and was missed by the operating surgeon. During her cholecystectomy, she was placed in reverse Trendelenburg resulting in the dermoid cyst returning to a pelvic location and was missed by the general surgeon. Second, the cyst's reported size in 2007was large, but it continued to grow in the subsequent three years. On average, a dermoid cyst grows 1.8 mm each year.[5]

Finally, this cyst appeared to have secreted significant amounts of HCG and rather suddenly since the patient never complained of amenorrhea or pregnancy-like symptoms in the past two years. This benign dermoid's HCG production simulating an ectopic pregnancy resembles two similar published cases.[5,6] Downey et. al. published the first case in London in 1989 and very few cases have been reported since then.[7] (See Table 1 for a comparison between this

Table 1: Dermoid cyst comparison between a previously published case and this case

Dermoid Cyst	Dawley 2010	Pothula 1994
Patient	31-year old	24-year old
Size	11x9x4.5 cm	14x8x6 cm
HCG Level	41,428 HCG	Positive, unreported value

case's cyst and a previously reported cyst.) Laparoscopic removal of the dermoid resulted in an immediate decrease in HCG concentration further suggesting ectopic HCG production by the cyst. Furthermore, cyst removal eliminated the patient's abdominal discomfort, pregnancy-like symptoms, and risk of torsion.

The origin of the high HCG levels could not be confirmed; pathology was unable to perform HCG staining on the preserved specimen. The lack of a gestational sac or chorionic villi within the specimen made an ectopic pregnancy or GTN unlikely. Because the patient's HCG concentrations immediately decreased upon removal of the right ovary, the dermoid most likely produced the extremely high HCG levels.

Fortunately, the patient's symptoms have resolved and the dramatic decrease in her serum HCG concentration was reassuring. Because the oopherectomy and pathology reported a benign cystic teratoma that coincided with normalization of HCG levels, it was presumed that a rare occurrence of an HCG secreting dermoid cyst was the source of production of her high beta-hCG levels that mimicked an ectopic pregnancy. This case demonstrates the need to perform a thorough exam of intra-abdominal structures during scheduled surgical procedures to avoid missing significant pathology resulting in an additional future surgical procedure for treatment.

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Gender and Geographic Differences in CAD Risk Factors and $CHADS_2$ Scores in Atrial Fibrillation Patients

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Abstract

Atrial fibrillation (AF) is a cardiac arrhythmia associated with a wide range of other co-morbid medical conditions. The state of West Virginia has a higher prevalence of coronary artery disease (CAD) and CAD risk factors compared to the national average. We hypothesized that West Virginians with atrial fibrillation would also have a higher prevalence of CAD risk factors and higher $CHADS_2$ stroke risk scores. This is particularly important since Louisiana is the only high CAD risk southern state included in the original verification of the $CHADS_2$ risk scoring system (i.e. California, Connecticut, Louisiana, Maine, Missouri, New Hampshire, and Vermont). Accordingly, we performed a retrospective analysis of the association between AF and CAD, CAD risk factors and $CHADS_2$ scores in a cohort of men and women in the West Virginia University Hospital population. We report a greater positive association between AF and hypertension, diabetes mellitus and obesity than the national average. AF was seen more commonly among men. But, $CHADS_2$ scores were higher among women as a result of a higher prevalence of diabetes mellitus. This study indicates that AF is associated with a greater prevalence of CAD risk factors and higher $CHADS_2$ scores among West Virginians in comparison with the rest of the nation.

Introduction

Atrial fibrillation (AF) is an arrhythmia associated with a wide range of cardiac conditions and is an independent predictor of heart failure and stroke.[1,2] Hypertension (HTN) and coronary artery disease (CAD) are the most common co-morbidities associated with AF.[3,4,5] According to the 2007 Behavioral Risk Factor Surveillance System survey results, the state of West Virginia has a higher prevalence of CAD and CAD risk factors compared to the national average (HTN- 33.3% vs 27.8%, diabetes mellitus (DM)- 10.8% vs 8.0%, Obesity- 68% vs 62.9%, smoking- 26.9% vs 19.8%).[6] We hypothesized that West Virginians with atrial fibrillation would also have a higher prevalence of CAD risk factors and higher $CHADS_2$ stroke risk scores. This is particularly important since Louisiana is the only high CAD risk southern state included in the original verification of the $CHADS_2$ risk scoring system (i.e. California, Connecticut, Louisiana, Maine, Missouri, New Hampshire, and Vermont).[7] Accordingly, we performed a retrospective analysis of the association between AF and CAD, CAD risk factors and $CHADS_2$ scores in a cohort of men and women in the West Virginia University Hospital population.

Methods

This retrospective, observational study was conducted at West Virginia University Hospital after receiving the approval of the Institutional Review Board for the Protection of Human Subjects. A total of 8,986 consecutive EKGs were analyzed and screened for the diagnosis of atrial fibrillation (AF) between October 2009 and March 2010. After excluding duplicates, 541 patients with the diagnosis of AF on EKG tracing formed our study population. The patients' demographic characteristics (age, gender, weight, height, clinical risk factors and medications) were assessed from the medical records of each of the 541 patients.

The stroke risk index was calculated based on the risk factors identified from chart review using the $CHADS_2$ score.[7] We calculated $CHADS_2$ scores by adding 1 point for each of the following: recent CHF, hypertension, age 75 years or older, and DM—and 2 points for a history of stroke or TIA. Therefore, $CHADS_2$ is an acronym for the major risk factors and their scoring. For instance, a 78-year-old (+1) patient who had diabetes mellitus (+1) and hypertension (+1) would have a $CHADS_2$ score of 3. A score of 0 identified patients at "low risk", 1 to 2 at "moderate risk" and 3 to 6 at "high risk" for stroke. $CHADS_2$ is commonly used by physicians to estimate the risk of stroke in patients with AF and decide about antithrombotic therapy based on patient-specific risk of stroke.

Body Mass Index of < 25 kg/m^2 was considered "normal", 25 to < 30 kg/m^2 as "overweight" and ≥ 30 kg/m^2 as "obese".[8] HTN was defined as blood pressure greater than 140/90 mm Hg or a history of hypertension and being on antihypertensive medication. The differences between men and women were evaluated

using Student's t test for continuous variables and chi-square test for categorical variables. The results were considered statistically significant at a p value <0.05.

Results

Five hundred forty one patients' charts were reviewed. Baseline characteristics are listed in Table 1. The sample cohort consisted of a greater number of men than women (p value <0.005). The average age of the women included in the analyses was higher than the average age of the men (73.6 vs 67.8 years). Over 80% of the patient population was overweight or obese. There were no significant gender differences in the percentage of overweight and obese individuals. A history of cigarette smoking was documented in 46% of the patient cohort. The prevalence of cigarette smoking was significantly higher in men than women (57% vs 27%, p <0.005). The average ejection fractions (EF) of the women

Table 1: Clinical characteristics of the study population:

Characteristic	Total	Male	Female	P value
Number of patients	541	307	234	<0.005
Age, mean ± SD, yr	70.3±12	67.8±12.3	73.6±10.8	<0.005
Age group, n(%)				
<40	7(1.3)	7(2.3)	0	0.02
40-65	171(31.6)	117(38.1)	54(23)	<0.005
>65	363(67.1)	183(59.6)	180(77)	<0.005
BMI, mean ± SD, kg/m²	31.5±7.4	31.5±6.1	31.45±8.8	0.42
Normal (<25)	103(19)	43(14)	60(25.6)	<0.005
Overweight (25 to <30)	146(27)	92(30)	54(23)	0.07
Obese (>30)	286(54)	169(55)	117(50)	0.24
EF, mean ± SD, %	53±15.8	51.2±16.3	55.3±14.8	<0.005
DM, n(%)	226(42)	108(35.1)	118(50.4)	<0.005
HTN, n(%)	479(89)	272(88.6)	207(88.5)	0.96
CAD, n(%)	211(39)	123(40)	88(37.6)	0.56
Valvular etiology, n(%)	51(9.4)	28(9)	23(9.8)	0.78
Non-valvular etiology, n(%)	490(90.6)	279(90.1)	211(90.1)	0.78
CHF, n(%)	155(28.6)	86(28)	69(29.5)	0.7
Stroke/TIA, n(%)	63(11.6)	33(10.7)	30(12.8)	0.45
Smoking, n(%)	246(46)	174(57)	62(27)	<0.005
$CHADS_2$ stroke risk, n(%)				
Mild (score 0)	34(6.3)	23(7.5)	11(4.7)	0.18
Moderate (score 1-2)	302(55.8)	187(61)	115(49.1)	0.006
High (score 3-6)	205(37.9)	97(31.6)	108(46.1)	<0.005
Medication, n(%)				
Warfarin	302(56)	180(58.6)	122(52.1)	0.13
Rate Control	453(84)	255(83)	198(84.6)	0.62
Rhythm Control	115(21.2)	64(20.8)	51(21.7)	0.79

BMI= body mass index, CAD= coronary artery disease, CHF= congestive heart failure, DM= diabetes mellitus, EF= ejection fraction, HTN= hypertension, TIA= transient ischemic attack

Figure 1.
Distribution of AF in patient population by age and gender.

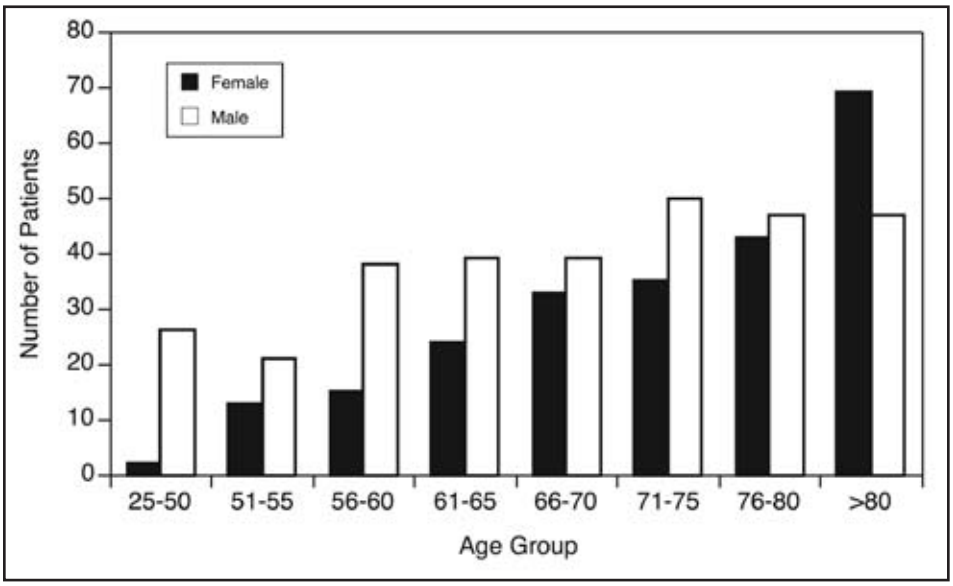
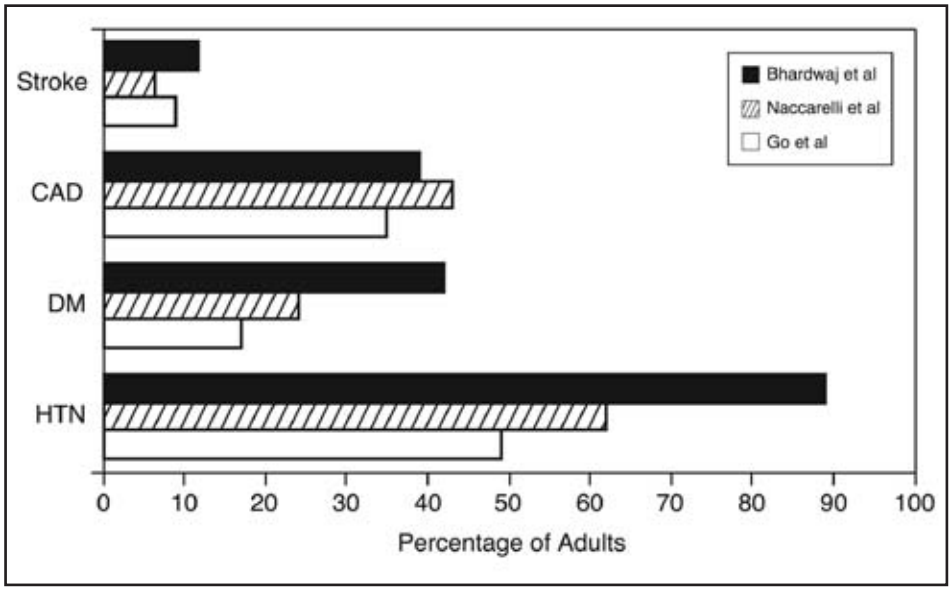


Figure 2.
Comparison of selected risk factors and co-morbid conditions between West Virginia and United States.



was significantly higher than that of the men (51.2±16.3 vs 55.3±14.8, p <0.005). DM was more common in women than men (p <0.005). Hypertension was diagnosed in 90%, coronary artery disease (CAD) in 39% and TIA/CVA in 11.6% of the cohort. A little over half the patients (56%) received warfarin therapy. Women had the greatest number and percentage of high risk $CHADS_2$ scores (p <0.005). Moderate risk $CHADS_2$ scores were more common in men. The etiology of the AF was identified as non-valvular in 90% of the patient population,

Discussion

There were more men with AF in our single center study. This observation contrasts with the national data where the absolute number of AF is nearly equally divided between men and women.[9] In addition, our men were diagnosed with AF at a younger age compared to women. There was also a greater proportion of older women with AF than older men (Figure 1). An equally very high percentage (81%) of both men and women were overweight or obese. Not surprisingly, the rate of DM was reportedly higher than national average in this patient population, as well (42% vs 17% and 24%).[3,10] (Figure 2) Importantly, a greater percentage of women in this AF cohort were diabetic; despite having similar rates of obesity. More number of women in higher age group can be one of the factors for this gender difference.

Eighty nine percent of both the men and women were diagnosed with hypertension (HTN). This rate of HTN is considerably higher than the 49% and 62% reported nationally.[3,10] The prevalence of CAD in both men and women (39%) was similar to a larger national study (35% and 43%).[3,10] Both men and women in our cohort had a significantly higher rate of stroke than the national average for AF (11.6% vs 6.5 to 8.9%).[3,10] The greater percentage of higher risk $CHADS_2$ scores seen in women appears to be largely due to the higher prevalence of DM and older age among women in our cohort.

Apart from structural heart diseases, common cardiovascular risk factors like HTN and DM predispose to AF which is an independent risk factor for stroke.

Although antithrombotic and antiarrthymic therapy is helpful in reducing the risk of stroke, however it is frequently contraindicated in elderly due to significant associated morbidity. There is no causative relationship of AF with HTN and DM, but it is hypothesized that aggressive management of these modifiable risk factors may be the safest and most effective approach to prevent the occurrence of AF and associated morbidity and mortality.

Conclusion

The association of AF with CAD risk factors (e.g. HTN, DM and obesity) and the incidence of TIA/CVA was significantly greater in our single WV cohort than the previously reported national average.[7,9,10] The association of AF with CAD, however, is still similar to the study using the larger national sample.[10] Further study is warranted to identify potential gender and regional differences in outcomes for patients with atrial fibrillation.

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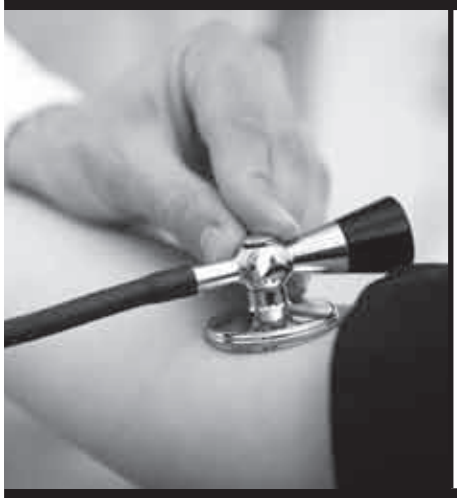

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Identification of Genes Contributing to Cardiovascular Disease in Overweight and Obese Individuals from West Virginia

The Appalachian Cardiovascular Research Network*

Individual author listing and affiliation appear at the end of the paper.

Abstract

Excess weight is a known risk factor for coronary artery disease (CAD) and a large percentage of overweight and obese individuals ultimately develop CAD. The objective of this study was to identify human genes associated with CAD in a subgroup of overweight and obese individuals using population-based association methods. Logistic regression analyses were used to test the association between single nucleotide polymorphisms (SNPs) in 34 candidate genes and the CAD phenotype with age, gender, and BMI as covariates. Two SNPs in the *Apolipoprotein B* (*Apo B*) gene [rs1042031 and rs1800479], one in the *Cholesterol Ester Transfer Protein* (*CETP*) gene [rs5880], and one in the *Low Density Lipoprotein Receptor* (*LDLR*) gene [rs2569538] met the 0.01 significance level for association with CAD. Based on these findings, we conclude that variants within the *CETP* and *Apo B* genes conferred susceptibility to CAD in overweight individuals and that a variant with the *LDLR* gene conferred susceptibility in an obese group.

Introduction

Coronary artery disease (CAD) is the leading cause of death and premature disability in the United States.[1, 2,3] In its most recent update on heart disease, the American Heart Association reported that 16.8 million US adults are afflicted with CAD and that the estimated CAD patient care costs for 2009 are $165 billion.[3] The primary cause of CAD is atherosclerosis, a progressive multifactorial disease characterized by the accumulation of lipids and fibrous elements in the large arteries.[4] Evidence from animal studies, epidemiological studies and clinical correlations strongly suggest a role for dietary cholesterol as an environmental promoter of atherosclerosis.[2,3] A genetic etiology for atherosclerosis is indicated by familial aggregation of the trait and heritability estimates of contributing factors (e.g. LDL- and HDL-cholesterol levels) that range from 20% to 80%.[2,5]

Several significant causal genes have been identified by studying Mendelian disorders that either cause or confer susceptibility to CAD.[5] Genome-wide linkage scans have revealed CAD susceptibility loci on chromosomes 1p34-36, 2q, 3q13, 13q12-13, 14q32, 16p13, and 17.[(6, 7 and reviewed in 8)] Several genome-wide association studies for CAD have been performed based on single nucleotide polymorphisms (SNPs).[6] Although some identified regions were replicated (3q12-13, 9p21), most of the known findings of regions associated with CAD could not be replicated. A recent replication study on 85 previously identified variants in genetic risk factors for acute coronary syndrome found that only one of these variants (in the β-fibrinogen promoter) was validated as a risk factor.[9] Additional candidate gene association studies in different subpopulations are needed in order to confirm the associations with these SNPs and identify new SNPs associated with CAD.

Overweight and obesity have become global epidemics in both children and adults[10] and are known to contribute to CAD, heart failure, and sudden cardiac death.[4,5,11] Since a significant number of overweight individuals go on to develop CAD, we hypothesized that one or more genes could cause or confer susceptibility to the development of CAD in this group. We sought to identify genes associated with CAD in overweight and obese individuals by screening for SNPs in a set of cardiovascular disease candidate genes using case control association methods. We identified SNPs within three genes [*Apo B* (apolipoprotein B), *LDLR* (low density lipoprotein receptor) and *CETP* (cholesterol ester transfer protein)] that were associated with CAD phenotype. The *Apo B* and *CETP* SNPs have been identified in previous CAD association studies,[12,13] while the *LDLR* SNP is a novel association.

Methods

Human Subjects and CAD Phenotype

Human subjects were enrolled according to Institutional Review Board protocols approved by the following West Virginia institutions: Marshall University Department of Cardiovascular Services, Charleston Area Medical Center, Lincoln Primary Care Center, Tri-County Clinic, Tug River Clinic, and Valley Health Systems.

The CAD phenotype was predicated on known indicators of the disease: angina, myocardial infarction, cardiac artery stenosis, and acute coronary syndrome. Individuals were classified as affected with CAD if one or more of the following conditions were present: (1) at least one vessel with at least 50% stenosis as determined by cardiac catheterization, (2) acute myocardial infarction diagnosed either by elevation of creatine phosphokinase myocardial band or by diagnostic electrocardiogram, (3) coronary artery bypass graft,

Table 1: ***Candidate genes for CAD with corresponding number of genotyped SNPs***

Candidate Gene	Number of SNPs
ABCA1 (ATP-binding cassette)	6
AGT (angiotensinogen preprotein)	8
ALOX5A (arachidonate 5-lipoxygenase-activating protein) protein)	1
Apo B (Apolipoprotein B)	8
Apo C2 (Apolipoprotein C-II)	1
Apo E (Apolipoprotein E)	1
BHMT (betaine-homocysteine methyltransferase)	3
CETP (cholesteryl ester transfer protein)	14
F5 (coagulation factor V)	5
HDLBP (high density lipoprotein binding protein)	3
HNF4A (hepatocyte nuclear factor 4, alpha)	2
LDLR (low density lipoprotein receptor)	7
LIPA (lipase A, lysosomal acid, cholesterol esterase)	11
LIPG (lipase, endothelial)	2
LRP1 (low density lipoprotein-related protein 1)	3
LRP1B (low density lipoprotein-related protein 1B)	7
LRP5 (low density lipoprotein receptor-related protein 5)	8
LPR8 (low density lipoprotein receptor-related protein 8)	7
MPO (myeloperoxidase)	1
MSR1 (macrophage scavenger receptor 1)	2
MTHFR (5,10-methylenetetrahydrofolate reductase)	5
MTR (5-methyltetrahydrofolate-homocysteine)	1
MTRR (5-methyltetrahydrofolate-homocysteine)	1
NOS3 (nitric oxide synthase 3)	3
PLTP (phospholipid transfer protein)	2
PPARA (peroxisome proliferative activated receptor)	6
SHMT1 (serine hydroxymethyltransferase 1)	2
SCARB1 (scavenger receptor class B, member 1)	5
SERPINB2 (serpin peptidase inhibitor, clade B)	1
TCN2 (transcobalamin II)	4
TNFSF4 (tumor necrosis factor superfamily, member 4)	2
USF1 (upstream stimulatory factor 1)	1
USF2 (upstream stimulatory factor 2)	1
VWF (von Willebrand factor)	2
Total: 34	136

(4) percutaneous coronary intervention, (5) documented cerebral vascular disease, or (6) documented peripheral arterial disease. Individuals without any of these symptoms or interventions who did not report any history of CAD and who were at least 40 years of age were classified as controls.

Participants with Body Mass Index (BMI) ≥ 25 were placed in the overweight category while those with BMI ≥ 30 were considered obese. Of the 261 Caucasian participants, we identified 243 who were overweight. In this group of individuals, 104 had evidence of CAD and 92 were controls. Forty seven individuals did not meet our criteria for cases or controls and were excluded from analysis. Of these 47 exclusions, 33 clinically normal individuals were younger than age forty and 14 individuals had an indeterminate disease phenotype. Obese (BMI ≥ 30) individuals accounted for 141 of the 196 overweight individuals.

Candidate Genes and SNP Selection

Thirty four candidate genes for CAD were selected from three different sources of cardiovascular disease susceptibility genes: Online Mendelian Inheritance in Man (www.ncbi.nlm.nih.gov/omim), CardioGenomics (cardiogenomics.med.harvard.edu), and Comparative Genomic Resources for Cardiovascular Research (Berkeley Programs for Genomic Applications; pga.jgi-psf.org/) (Table 1).

Selection of candidate gene SNPs was performed in a two phase approach. In the first phase, we selected a minimal set of tagging SNPs within each candidate gene using the HapMap Genome Browser and Haploview software.[14,15] Only SNPs with a minor allele frequency (MAF) ≥ 5% were selected for analysis. When MAFs were not available from the SNP databases, we calculated the frequency based on our study population. SNPs for which a TaqMan Allelic Discrimination assays were available were pre-selected prior to application of the aggressive tagging protocol. Haplotype blocks were identified by Haploview analysis of HapMap data. In the second phase of the SNP selection, additional SNPs were genotyped for genes in which statistically significant associations were identified in the first phase. These additional SNPs were genotyped in order to maximize the coverage of the gene and better define the area of interest. One hundred thirty six SNPs from thirty-four selected candidate genes were tested for an association with CAD as described below.

Genotyping Methods

Genomic DNA was purified from patient whole blood samples using Qiagen Blood and Cell Culture DNA Maxi Kits. SNPs were genotyped using either pyrosequencing or TaqMan Allelic Discrimination methods. In the pyrosequencing method, specific loci were amplified from 25 nanograms of genomic DNA by the polymerase chain reaction (PCR). Pyrosequencing reactions were carried out as described by Nyren et al.[16] using a Biotage PSQ96MA Pyrosequencing System. Allelic Discrimination analyses were performed on either an ABI Model 7000 or Model 7500 Sequence Detection Systems as described by Livak et al.[17] ABI Sequence Detection System Absolute and Allelic Discrimination software was used to determine the genotype.

Statistical Methods

A series of conditional logistic regression analyses with age, gender, and BMI as covariates were performed to identify SNPs associated with the CAD phenotype. Statistical analyses were performed using statistical analysis software (SAS) release 9.2. *p*-values less than or equal to 0.01 were considered to be statistically significant. A chi-square test was used to determine if SNP alleles were in Hardy-Weinberg Equilibrium (HWE). Three of the 136 genotyped SNPs (rs289714, rs4823613, and rs891512) were found to be not in HWE at significance level of 0.05, and were excluded from further statistical analyses.

Table 2: ***Mean age (in years), BMI, and gender differences between CAD and control subjects. Data are given as means ± standard deviation (SD). NS stands for not significant.***

	CAD Subjects	Control Subjects	*p*-value
Total number of subjects (*n*)	104	92	
Mean age (in years)	63.5 ± 10.7	56.3 ± 9.8	< 0.001
Mean BMI	33.4 ± 6.2	35.6 ± 7.5	< 0.05
Number of males/females	70/34	24/68	< 0.001
Mean age for males	63.4 ± 9.8	57.1 ± 9.7	< 0.01
Mean age for females	63.8 ± 12.7	55.9 ± 9.9	< 0.01
Mean BMI for males	32.3 ± 5.4	32.5 ± 4.6	NS
Mean BMI for females	35.7 ± 7.2	36.7 ± 8.1	NS

Table 3: ***Association with Atherosclerosis (Allelic Model). The at-risk allele is given in bold. CI stands for confidence interval, OR stands for odds ratio.***

BMI ≥ 25							
SNP	Gene	Allele Frequencies				*p*-value	OR [95% CI]
		Cases (*n* = 96)		Controls (*n* = 91)			
		A	G	A	G		
rs1042031	*Apo B*	0.30	0.70	0.13	0.87	0.0054	**A** 2.44 [1.30, 4.57]
		Cases (*n* = 100)		Controls (*n* = 90)			
		C	G	C	G		
rs1800479	*Apo B*	0.71	0.29	0.87	0.13	0.0079	**G** 2.33 [1.25, 4.34]
BMI ≥ 30							
		Cases (*n* = 65)		Controls (*n* = 65)			
		A	G	A	G		
rs2569538	*LDLR*	0.18	0.82	0.06	0.94	0.0049	**A** 4.29 [1.56, 11.8]

The remaining 133 SNPs passed the HWE significance test at 0.05.

Results

Demographic data of the individuals used in this study are given by age, gender, and BMI in Table 2. Out of 196 overweight individuals, 94 (48%) were males and 102 (52%) were females. The average age of the patients entering the study was 60.1 years with a standard deviation of 10.9 years. Both case and control groups were composed of non-Hispanic, Caucasian populations from West Virginia. Since there were significant differences in age, gender, and BMI between cases and controls, logistic regression analyses were performed with age, gender, and BMI as covariates.

Using the allelic model, we identified two SNPs (rs1042031 and rs1800479) within the *Apo B* gene that were associated with CAD at significance level below 0.01 (Table 3). SNP rs1042031 is located within *Apo B* exon 29 and substitution of the reference allele G by the minor allele A results in a substitution of the wild type glutamine (GLU) with lysine (LYS) at amino acid 4181. For overweight individuals, each occurrence of A at rs1042031 conferred an increased likelihood of 2.44 fold for developing CAD compared to individuals with a G substitution. *Apo B* SNP rs1800479 is an intronic SNP about 2kb up stream of rs1042031 SNP. For overweight individuals, each occurrence of the minor allele, G, at rs1800479 conferred an increased likelihood of 2.33 fold for developing CAD compared to individuals with a C substitution. Six other SNPs analyzed within the *Apo B* gene region did not show significant association with CAD (Table 4).

SNP rs2569538 in the *LDLR* gene was significantly associated with CAD in a subgroup of obese individuals under both the allelic (*p*-value = 0.005, Table 3) and the genotypic model (*p*-value = 0.007, Table 5). Obese individuals who are A/G heterozygotes at rs2569538 were four times more likely to develop CAD than G/G homozygotes. This SNP is located inside intron 15 within the second haplotype block of *LDLR* gene. Six other *LDLR* SNPs were genotyped but did not show significant relationship with CAD (Table 4).

Using the genotypic model in the overweight group, we identified a SNP within the *CETP* gene on chromosome 16 (rs5880) that was associated with CAD at a significance level of 0.008 (Table 5). SNP rs5880 represents a nonsynonymous change which results in substitution of proline for the normally occurring alanine at position 373 in the processed protein (position 390 in the precursor protein). Overweight individuals who were G/G homozygotes at rs5880 were 5.56 times more likely to develop CAD than C/G heterozygotes. SNP rs5880 was also found to be associated (*p*-value = 0.006) with CAD in a sample of overweight individuals in which participants with type II diabetes were excluded (data not shown). None of twelve additional *CETP* SNPs were associated with the CAD phenotype in overweight and obese groups (Table 4).

Discussion

Two *Apo B* SNPs, rs1042031 and rs1800479, met our criterion for association with CAD. Based on their physical map location both SNPs are located in the first haplotype

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Table 4: *Apo B* **(Chromosome 2),** *LDLR* **(Chromosome 19), and** *CETP* **(Chromosome 16) SNPs. Location of each SNP was identified through the HapMap project Database. Minor Allele Frequencies (MAFs) were either found through the HapMap project or the dbSNP web site. SNPs in bold were genotyped in the second phase of SNPs selection.**

Apo B SNP	Position (bp)	MAF	*p*-value	SNP type	Location	Substitution
rs1367117	21,175,542	0.267	NS	nonsynonymous	exon 4	T98I
rs520354	21,171,254	0.475	NS		intron 6	
rs679899	21,162,556	0.490	NS	nonsynonymous	exon 14	A618V
rs11676704	21,156,000	0.158	NS		intron 18	
rs693	21,143,837	0.492	NS	synonymous	exon 26	T2515T
rs1800479	21,139,025	0.174	0.008		intron 27	
rs1042031	21,137,395	0.208	0.005	nonsynonymous	exon 29	E4181K
rs1042034	21,136,923	0.192	NS	nonsynonymous	exon 29	S4338N

LDLR SNP	Position (bp)	MAF	*p*-value	SNP type	Location	Substitution
rs2228671	11,071,902	0.100	NS	synonymous	exon 2	C27C
rs1799898	11,088,544	0.150	NS	synonymous	exon 12	L575L
rs5927	11,094,931	0.275	NS	synonymous	exon 15	R744R
rs2738456	11,097,794	0.250	NS		intron 15	
rs2738459	11,099,463	0.431	NS		intron 15	
rs2569538	11,099,538	0.108	0.0049		intron 15	
rs1433099	11,103,648	0.300	NS		3'UTR	

CETP SNP	Position (bp)	MAF	*p*-value	SNP type	Location	Substitution
rs1800775	55,552,727	0.425	NS		promoter	
rs9926440	55,560,154	0.250	NS		intron 2	
rs1532625	55,562,792	0.380	NS		intron 7	
rs12708974	55,563,041	0.133	NS		intron 7	
rs289717	55,566,879	0.333	NS		intron 10	
rs289718	55,567,423	0.370	NS		intron 10	
rs289719	55,567,432	0.279	NS		intron 10	
rs4784744	55,568,676	0.333	NS		intron 10	
rs5880	55,572,582	0.050	0.008	nonsynonymous	exon 12	A373P
rs5882	55,573,583	0.305	NS	nonsynonymous	exon 14	V405I
rs9923854	55,574,493	0.125	NS		intron 14	
rs289741	55,574,965	0.288	NS		intron 15	
rs1801706	55,575,153	0.200	NS		3'UTR	

block of *Apo B*.[14,15,18] Two other SNPs (rs1042034 and rs693) within the first haplotype block of *Apo B* were not associated with CAD.

Apo B is the principal protein component of several low density lipoproteins (LDLs) and is the main apolipoprotein of chylomicrons. Defects in the Apo B gene are the cause of familial ligand-defective apolipoprotein b-100 (fdb), an autosomal dominant disorder that leads to hypercholesterolemia and increased susceptibility to coronary artery disease. Causal mutations map to exon 26 of Apo B and lead to substitution of glutamine for arginine 3500 or substitution of cysteine for arginine 3532.[19] In contrast to the fdb genotype-phenotype correlation, a meta-analysis of 30 case control studies failed to find an association between CAD and the exon 26 XbaI restriction fragment length polymorphism (RFLP).[12] This study did report a significant association with an EcoR1 RFLP located in exon 29 which is identical to SNP rs1042031. Based on the location of the two associated *Apo*

B SNPs found in this study and the meta-analysis, we hypothesize that a susceptibility locus for CAD is located near *Apo B* exon 29.

Binding of LDLs to the LDLR is mediated by interactions between the LDLR and the Apo B-100 lipoprotein. Over 1000 mutant alleles within the *LDLR* gene are known to cause familial hypercholesterolemia, and a class of these alleles is known to disrupt the binding of LDLR to Apo B.[20] We identified a single SNP (rs2569538) within intron 15 of the *LDLR* gene that was associated with CAD in a group of obese individuals under both the allelic and genotypic models (Tables 3 and 5). Although allele A was found to be a risk allele for susceptibility to CAD under the allelic (additive) model, the A/A genotype was not significantly different from the G/G genotype under the genotypic model. It is possible that small sample size may not have provided sufficient power for the analysis in the case of the genotypic model. Additional studies are needed to determine if SNP rs2569538 directly affects LDLR function or is linked to a variant that reduces LDLR function.

CETP catalyzes the transfer of cholesterol esters and triglycerides from high density lipoprotein (HDL) to ApoB containing particles like LDL and very low density lipoprotein. The role of CETP in CAD has been vigorously debated by a number of reviewers and its ultimate action may depend on genetic, metabolic and environmental factors.[21] Several studies point to a model in which lower CETP levels are anti-atherogenic because HDL-C is more abundant and results in improved cholesterol efflux via ABCG1.[22] For example, in a large meta-analysis, three CETP genotypes that showed moderate reductions in CETP activity were associated with reduced coronary risk.[23] However, the connection between increased CETP and CAD risk is weakened by other studies. In a prospective community-based sample,[24] lower plasma CETP activity was associated with greater CAD risk.

SNP rs5880 results in the substitution of proline for the normally-occurring alanine at position 373 (A373P) in the processed CETP protein.[25] In a linker scanning mutagenesis study, insertional substitutions of amino acid positions 373-379 severely impaired cholesterol ester transfer activity without dramatic impairment of secretion.[26] This study suggests that the A373P substitution would result in a CETP variant with reduced activity that could raise HDL-C levels and lower CAD risk. However, three studies[13,25,27] showed that the rs5880 minor allele (A373P) and/or a linked polymorphism form a CETP variant that reduces HDL-C levels and presumably result in higher CAD risk. We show that the normal allele (G) of rs5880 is associated with the disease phenotype. This association has not been reported in previous studies but is consistent with the pro-atherogenic effects of a fully functional CETP.

Although obesity is recognized as a risk factor for cardiovascular disease,[28] the underlying physiological or metabolic basis for the increased risk is unknown. Several authors have speculated that this may be due to abnormal lipid profiles, hypertension, type II diabetes or increased cardiovascular workload in obese individuals.[11,28] Although we did not measure serum lipid levels in our patient population, relative weight is positively correlated with both LDL cholesterol and triglyceride levels.[29,30] The observation that the deleterious effects of elevated CETP levels are manifested only in patients with elevated triglycerides[21,30] may explain the association of the *CETP* variant with CAD in our overweight group.

Conclusions

We have shown that variants within two CAD candidate genes (*CETP* and *Apo B)* play a role in CAD in overweight individuals. *Apo B* SNP rs1042031 or a linked variant confers susceptibility to CAD in both the overweight population in our study and several general populations.[12] *CETP* SNP rs5880 appears to confer susceptibility to CAD in overweight individuals perhaps because elevated triglycerides in this group are more rapidly converted to atherogenic LDL cholesterol. The *LDLR* SNP was only associated in our obese population and has not been identified in previous studies. These results suggest that genetic mutations in *Apo B*, *CETP*, and *LDLR* genes contribute to development of CAD in overweight individuals. Further investigations of these genes are needed in order to identify the specific mutations and understand their diagnostic values. Although the diagnostic value of individual genetic markers identified in association studies of complex traits is generally very low, the identification of rare variants and use of combinations of genetic markers could potentially improve predictive value.

Glossary

Linkage analysis: Genetic linkage describes the tendency of gene loci to be inherited together. Linkage analysis relies on this tendency to determine the location of genes on chromosomes.

Association studies: determine whether a specific allele is present at an increased frequency in individuals with a given disease compared to the frequency in individuals without the disease.

Single Nucleotide Polymorphisms: a variation in a DNA sequence consisting of a single base.

Acknowledgments

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Table 5: ***Association with Atherosclerosis (Genotypic Model). The at-risk genotype is given in bold. CI stands for confidence interval, OR stands for odds ratio.***

BMI ≥ 25									
SNP	Gene	Genotype Frequencies						*p*-value	OR [95% CI]
		Cases (*n* = 101)			Controls (*n* = 89)				
		GG	CG	CC	GG	CG	CC		
rs5880	*CETP*	.94	.05	.01	.84	.16	.00	0.0080	**GG**:CG 5.56 [1.57, 19.6]
BMI ≥ 30									
		Cases (*n* = 65)			Controls (*n* = 65)				
		AA	AG	GG	AA	AG	GG		
rs2569538	*LDLR*	.03	.31	.66	.00	.12	.88	0.0072	**AG**:GG 4.14 [1.47, 11.7]

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Strongyloides Hyperinfection Syndrome Complications: A Case Report and Review of the Literature

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Abstract

Strongyloidiasis is a major global health challenge that is often underestimated in many countries. In immuno-compromised hosts, an autoinfection can go unchecked with large numbers of invasive Strongyloides larvae disseminating widely and causing hyperinfection, with fatal consequences. This review will highlight a case of gram negative bacteremia complicated by meningitis and Adult Respiratory Distress Syndrome (ARDS) as a fatal outcome of Strongyloides hyperinfection, commonly known to occur in the setting of immunosuppression.

A middle aged female with chronic lymphocytic leukemia and hypogammaglobulinemia presented with severe respiratory distress requiring intubation. *She had been on intermittent corticosteroids and multiple courses of antibiotics for the past six months for COPD exacerbations*. Bronchoalveolar lavage showed Strongyloides stercoralis. Blood cultures grew Vancomycin Resistant Enterococci and a few days later Vancomycin Sensitive Enterococcus was found in the CSF. Afterwards, she grew Vancomycin Sensitive Enterococcus in the blood. She was treated with Ivermectin and Albendazole for Strongyloides and Linezolid and Vancomycin for these two different strains of E. faecium. After initial resolution of bacteremia and meningitis, she relapsed three weeks later with the same organism growing in the CSF. The clinical course continued to deteriorate with the development of significant neurological dysfunction. Poor nutritional state and ventilator associated pneumonia contributed to this downward trend. After a detailed discussion with the family, life support was discontinued and the patient succumbed to her illness.

Introduction

Strongyloides stercoralis is a soil transmitted nematode, endemic in tropical and subtropical areas. Due to increasing immigration from countries endemic with strongyloides, physicians in developed countries may also encounter this condition. Infection usually results in asymptomatic chronic disease of the gut, which can go undetected for decades. Eosinophilia and larvae in stools are often the only indicatiors of infection. The disease is classified as 'acute', 'chronic' and 'severe' strongyloidiasis and commonly manifests with cutaneous, pulmonary and intestinal features. Common clinical features of acute strongyloidiasis include maculopapular rash involving the feet, epigastric discomfort, diarrhea, occasional nausea and vomiting. Other manifestations include cough, dyspnea, wheezing, low grade fever or constipation.

Strongyloides stercoralis is also capable of causing autoinfection in the host. Strongyloides Hyperinfection (SH) is a life threatening complication of chronic strongyloidiases and usually occurs in the setting of immunocompromised state (patients with malignancy, organ transplantation or concurrent human T-cell-lymphocytic virus 1 infection or those on corticosteroid therapy). Mortality is largely due to gram negative bacteremia leading to adult respiratory distress syndrome and rarely, meningitis. We present a unique case of a patient with SH complicated by simultaneous occurrence of vancomycin resistant enteroccus bacteremia and vancomycin susceptible enterococcus bacteremia and meningitis.

Case Report

A 68-year-old diabetic female with chronic lymphocytic leukemia was transferred from an outside facility with severe respiratory distress. She was admitted to the outside hospital three days prior to transfer, with complaints of fever, shortness of breath, cough with yellow sputum, wheezing, and generalized weakness. *She had been on intermittent corticosteroids and multiple courses of antibiotics for the past six months for suspected COPD exacerbations. Her recent antibiotics included cephalosporins, fluoroquinolones and macrolides*. Her initial white cell count was 38.0 (thou/ul) and hemoglobin was 7.7 g/dl for which she received 2 units of packed red blood cells. Her chest x-ray showed bilateral infiltrates.

On presentation to our facility, her temperature was 38.4 C, pulse was 111 beats per minute, respirations were 22/min, blood pressure was 100/60 mmHg. The oxygen saturation was 88% on 2 liters nasal cannula. On physical examination, the patient appeared tired and in mild distress. She had a diffuse maculopapular rash. Heart rhythm was irregularly irregular. Lungs had bilateral crackles and wheezes. The remainder of the physical examination including head and neck, abdominal, musculoskeletal and neurologic examination was normal.

The initial work up at our institution showed a WBC count of 57.7 (thou/ul) with neutrophils 33%, lymphocytes 64% (Table 1). The ABG results showed pH 7.45,

PCO2 78, PO2 50, Bicarbonate 45, *PaO_2/FiO_2 ratio of 114*. Chest X-ray revealed increased interstitial opacities and mild bronchial wall thickening with suggestion of bronchiectasis (Figure 1). CT head showed no acute intracranial process. CT chest demonstrated bilateral areas of ground-glass opacity with reticular and nodular thickening. Interlobular septal thickening with areas of geographic sparing and traction bronchiectasis were also noted (Figure 2). A transthoracic echo showed left ventricular ejection fraction in the range of 65 % to 70 %. Features were consistent with mild diastolic dysfunction. There was very mild aortic valve stenosis with a mean gradient of 11mm Hg. Estimated peak right ventricular systolic pressure was in the range of 45 mmHg to 50 mmHg.

Due to progressive respiratory failure, the patient was intubated and transferred to our medical intensive care unit. She was started on broad spectrum antibiotics including vancomycin, ciprofloxacin, tobramycin and caspofungin. Bronchoscopy was performed the next day and bronchoalveolar lavage showed a worm which was later identified as Strongyloides stercoralis (Figure 3). The patient continued to remain unresponsive and a spinal tap was performed, that showed a pyogenic CSF picture and grew Vancomycin Sensitive Enterococci.

Her blood culture drawn on the day of admission grew Vancomycin Resistant Enterococci and a few days later, she grew a strain of Vancomycin Sensitive Enterococci in her CSF. She was treated with Albendazole and Ivermectin for SH for two weeks, Linezolid for vancomycin resistant Enterococcus (VRE) bacteremia and vancomycin for vancomycin Sensitive Enterococcus (VSE) meningitis. She was also started on IVIG due to low levels of immunoglobulins.

A few days after she had completed a two week course of antiparasitic drugs, she developed peripheral blood eosinophilia but without any redemonstration of Strongyloides in respiratory secretions. However, she was still treated with one more week of Ivermectin, after which the eosinophilia resolved.

The patient started to show a clinical response and was neurologically stable with clearing of CSF (Table 2). However, she decompensated again due to respiratory failure. She was found to have reoccurence of VSE bacteremia (Table 3) and CSF analysis showed a pyogenic process that again grew VSE.

A tracheostomy was performed for her long term ventilation. A

Table 1: Laboratory data on admission

Variable	Value (Reference values)
White blood cell count (thou/ul)	57.7 (3.5-11.0 THOU/UL)
Hemoblobin (g/dl)	10.0 (11.2-15.2 g/dL)
Hematocrit (%)	31.4 (33.5-45.2 %)
Platelets (thou/ul)	180 (140-450 THO/UL)
Neutrophils (%)	33 (40-75 %)
Lymphocytes (%)	64 (20-45 %)
Eosinophils (%)	0 (1-6 %)
Metamyelocytes (%)	1 (0)
Monocytes (%)	2 (4-13 %)
Basophils (%)	0 (0-1%)
PT (sec)	20.5 (9.1-11.2 Sec)
INR	2.2 (0.8-1.2)
PTT (sec)	23.2 (22.5-32.0 Sec)
Sodium (mmol/l)	132 (136-145 mmol/L)
Potassium (mmol/l)	3.9 (3.5-5.1 mmol/L)
Chloride (mmol/l)	74 (96-111 mmol/L)
Bicarbonate (mmol/l)	44 (22-32 mmol/L)
Urea nitrogen (mg/dl)	22 (6-20 mg/dL)
Creatinine (mg/dl)	0.86 (0.49-1.10 mg/dL)
AST (U/liter)	33 (5-30 U/L)
ALT (U/liter)	74 (6-35 U/L)
Amylase (u/l)	122 (<128 U/L)
Lipase (u/l)	17 (6-51 U/L)
CK (u/l)	10 (24-170 U/L)
Troponin (ng/ml)	.048 (<0.050 ng/mL)
Digoxin (ng/ml)	0.9 (0.8-2.0 ng/mL)
Lactic acid (mmol/l)	2.8 (0.5-2.2 mmol/L)
IgA (mg/dl)	26 (69-309 mg/dL)
IgG (mg/dl)	185 (613-1295 mg/dL)
IgM (mg/dl)	9 (53-334 mg/dL)
Cortisol (ug/dl) 7:55 AM	8.1 {7.0-25.0 ug/dL (AM Sample)
Uric acid (mg/dl)	6.6 (2.5-6.6 mg/dL)
BNP (pg/ml)	421 (<100 pg/mL)
Albumin (g/dl)	3.5 (3.2-4.4 g/dL)
Calcium (mg/dl)	8.9 (8.5-10.4 mg/dL)
Magnesium (mg/dl)	1.9 (1.7-2.5 mg/dL)
Phosphorus (mg/dl)	3.1 (2.4-4.7 mg/dL)
Triglyceride (mg/dl)	177 (<150 mg/dL)
TSH cascade (uIU/ml)	0.6 (0.300-5.900 uIU/mL)

repeat bronchioalveolar lavage showed Pseudomonas infection and therefore, she was started on Imipenem. After 2 weeks of treatment with Vancomycin, her CSF continued to show pleocytosis and culture persistently grew the same enterococcus species. Because of significant neurological dysfunction, underlying hematological malignancy, poor nutritional state and persistently positive CSF cultures, we discussed the patient's grim prognosis with the family and it was decided to withdraw life support after six weeks of hospitalization.

Discussion

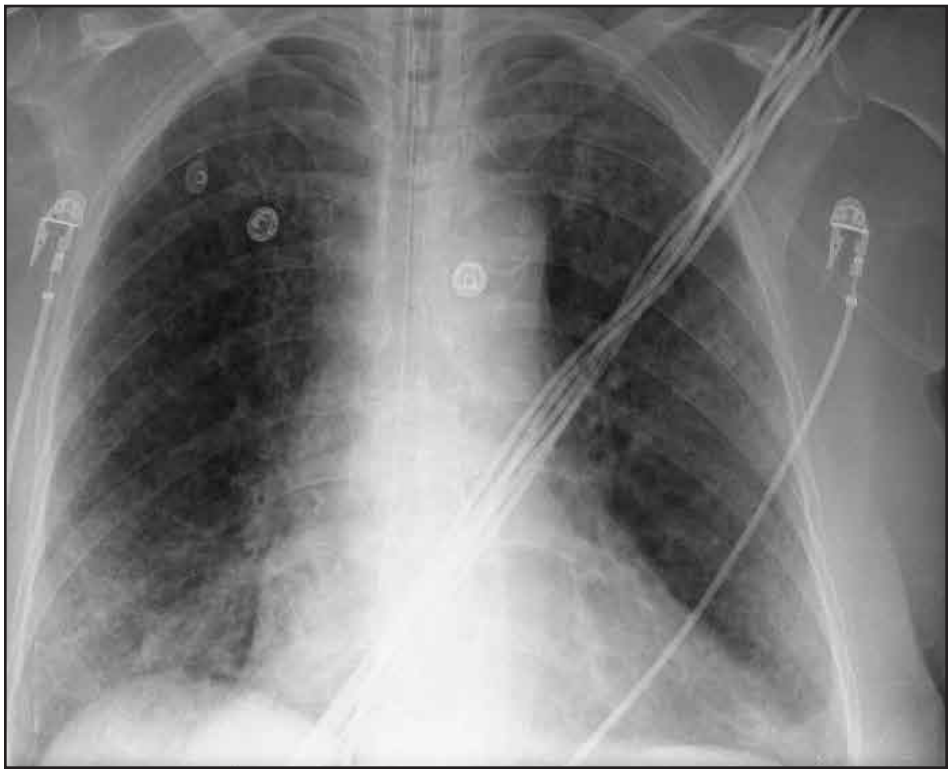
Strongyloides stercoralis is a soil transmitted intestinal nematode that is endemic in many tropical and subtropical areas of the world.[1] However, a large surveillance report from a US Cancer Center showed Strongyloides infection of 0.8/10000 cases.[2] The prevalence has risen due to increased immigration to North America particularly in areas considered non-endemic in the past.[3] In United States, this infection is prevalent in Appalachia, mainly rural Tennessee and Eastern Kentucky with a prevalence of 3% and 4% respectively.[4] This parasite remains quiescent in the human intestine for as long as 30 years[5] and becomes apparent in the setting of immune dysfunction.

Strongyloides stercoralis has the ability to reproduce itself in humans. A filariform larva is transmitted from the soil and penetrates into the skin. After exposure, it can migrate to the respiratory system via bloodstream. The parasite is, then, swallowed and penetrates the duodenal wall where rhabditiform larvae hatch from the eggs to be expelled in feces; and restart the asexual cycle in soil. Rhabditiform larvae mature and penetrate the skin in perianal area, leading eventually to autoinfection.[6]

In immunocompromised patients, however, the larvae change rapidly into infectious, filariform larvae and reinvade the gut, resulting in a cycle of autoinfection. During passage of this large burden of parasites through the gut wall, bacteria may be carried along, occasionally resulting in polymicrobial bacteremia.

The term hyperinfection is used to denote Strongyloides autoinfection

Figure 1.
Increased interstitial opacities and mild bronchial wall thickening with suggestion of bronchiectasis. Consider congestive heart failure versus an infectious process.



with a multi-log increase in parasite burden. Worms are detectable in extra intestinal sites, especially the lungs.[7] Patients with impaired cell mediated immunity such as those on long-term corticosteroids, HIV and HTLV infected patients and those with hematological malignancies are at particular risk.[8] Corticosteroids are the most widely used immunosuppressants and are specifically associated with transformation of chronic strongyloidiasis to hyperinfection.[9] The diagnosis becomes even more challenging since many of these patients present with symptoms mimicking COPD.[10] Strongyloidiasis is difficult to diagnose because the parasite load is low and the larval output is irregular. Review of literature showed that WBC count is usually within the reference range in acute and chronic strongyloidiasis and elevated in severe strongyloidiasis. During acute

Figure 2.
Bilateral areas of ground-glass opacity, reticular and nodular thickening, and an interlobular septal thickening with areas of geographic sparing and traction bronchiectasis.

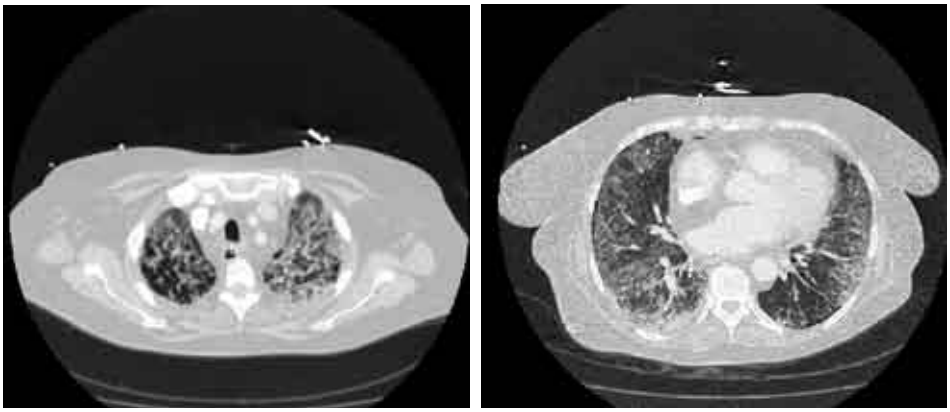


Figure 3.
Strongyloides stercoralis in the BAL.

infection eosinophilia is common, intermittent during chronic infection, and frequently absent in severe strongyloidiasis. Microscopically identifying S. stercoralis larvae in stool is a definitive diagnostic test. However, results of a single stool examination by use of conventional techniques fail to detect larvae in up to 70% of the cases due to fluctuating larval exretion and, therefore, consecutive stool examinations have been recommended to increase the yield.[9] Blood cultures in strongyloidiasis often yield growth of enteric pathogens, most commonly Escherichia coli and/or Klebsiella species. Strongyloides serology (enzyme immunoassay, indirect fluorescent antibody) has 88-95% sensitivity. Sensitivity may be lower in severely immunocompromised patients. This test however, cannot differentiate between past and present infection.[8]

Strongyloides stercoralis is a unique parasite that can cause fatal disease years after the exposure, often in the setting of SH, with mortality as high as 87%.[6] Lam et al. carried out a retrospective study and evaluated the characteristic features of seven patients. All the patients left the endemic area more than 20 years ago.[11] Mortality is mainly due to gram negative, often polymicrobial bacteremia and meningitis because of leakage of gut flora from the ulcerated bowel mucosa or bacteria carried on the surface of the larvae as they migrate to extra intestinal sites. A review published in 1999 identified 38 case reports of bacterial sepsis complicating strongyloidiasis, 68% of those patients had bacteremia out of which 12% were polymicrobial.[12]

Gram negative bacterial meningitis has been reported in Strongyloides hyperinfection especially in association with immunosuppression.[13] Our patient had active chronic lymphocytic leukemia with hypogammaglobulinemia and was on intermittent steroids for six months, which explains her predisposition to SH. *In addition, she received multiple courses of antibiotics to treat COPD exacerbation including cephalosporins, flouroquinolones and macrolides, which predisposed her to VRE bacteremia.* Vancomycin resistance is found to be an independent predictor of mortality in severe enterococcal bacteremia. [14] Furthermore, patients infected with Enterococcal faecium have a worse prognosis than those with E. faecalis.[15] Our case is unique for its rarity. Although association of Enterococcus faecium meningitis with SH has been reported,[16] to our knowledge there are no reported cases of concomitant VSE and VRE bacteremia in a patient with SH in literature.

Table 2: Summary of CSF Analysis

Day	WBC count	Neutrophils (%)	Lymphocytes (%)	Protein	Glucose	Culture	Event in History
4	1950	9	4	143	13	Vancomycin Susceptible Enterococcus Faecium Group D	Initiation of Vancomycin
6	214	74	13	79	37	Vancomycin Susceptible Enterococcus Faecium Group D	Response to Vancomycin
11	12	0	70	38	75	Culture Negative	Documented Clearance of Organism
27	385	41	32	84	55	Vancomycin Susceptible Enterococcus Faecium Group D	Recurrence of Enterococcus -Vancomycin Restarted
34	26	6	87	108	45	Negative	Documented Clearance of Organism
38	3750	77	14	97	16	Vancomycin Susceptible Enterococcus Faecium Group D	Recurrence of Enterococcus
42	25	9	68	98	73	Gram positive cocci in pairs-no growth on culture	Failure to clear the organism

A concern arising from this discussion may relate to the use of Linezolid, a static drug, for VRE bacteremia in this time and era of Daptomycin availability. A recent retrospective study was published in Journal of antimicrobial chemotherapy, which showed that Linezolid was as effective as Daptomycin in the treatment of VRE bacteremia. [17] However, it has been found that appropriate therapy against VRE bacteremia results in no improvement in long term survival in patients with this infection since these patients are extremely sick at onset of bacteremia.[18]

We report a rare case of SH in order to highlight the clinical suspicion and awareness needed by clinicians, to detect and treat this potentially fatal condition in a timely manner.

Conclusion

Patients with underlying risk factors should be suspected of having strongyloidiasis as the outcome can be fatal. Immunosuppressed patients who experience any unusual gastrointestinal or pulmonary symptoms or suffer from unexplained Gram-negative sepsis should be suspected of having strongyloidiasis. Early identification by enzyme-linked immunosorbent assay serology, stool testing or duodenal aspiration may prevent the fatal complications of SH. Early treatment of strongyloidiasis in these patients would improve morbidity and mortality.

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Table 3: Summary of Blood Cultures

Day	Blood culture result
1	Vancomycin resistence Enterococcus Faecium Group D
3	No growth
5	No growth
7	Vancomycin Susceptible Enterococcus Faecium Group D
10	No growth
21	No growth
27	No growth
35	No growth
40	No growth
42	No growth

histopathological study on the duodenum of Strongyloides stercoralis hyperinfection. *World J Gastroenterol.* 2008;14(11):1768–1773.)

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In With The New

Educating the public and those in the health care professions regarding issues of importance to the delivery of health care in WV.

The West Virginia State Medical Association Alliance has always been a proponent for improving the health of West Virginians. We renew this pledge for 2012 by supporting initiatives for the safe and proper disposal of unwanted medications. The Food and Drug Administration (FDA) and the Drug Enforcement Administation (DEA) are at the forefront of these efforts nationally.

At the Alliance's recent fall board meeting, plans to undertake this project were outlined by board members. Michael O'Neil, PharmD., Chairman, West Virginia Controlled Substance Advisory Board and Associate Professor, Department of Pharmacy Practice, University of Charleston School of Pharmacy presented a step by step process in initiating a 'Drug Take Back Program' for the Medical Alliance beginning with obtaining approval from the DEA. He discussed the types of medications that will be collected, who will be involved, where the drugs will go after collection, and how are they destroyed.

Plans for additional projects were addressed by Chris Vaught, CEO of Vaught, Inc. and inventor of the Element MDS (medical disposal system). Element MDS products contain an MDS powder packet which when mixed with unwanted medications and tap water hold the medication in suspension and form a solid gel, making the medication undesirable. Now widely used in West Virginia, The Hospice for Southern West Virginia was the first to use this product.

The Raleigh County Medical Alliance will distribute brochures on the safe disposal of medication in an effort to create public awareness on the importance of safe disposal of medication to prevent drug abuse, protect the environment, and prevent identity theft.

Health projects are great ideas, and members are the movers. As 2012 begins, the WVSMA Alliance is faced with the challenge of increasing its membership. How do we make volunteer work a fulfilling experience? The WVSMA Alliance is a special group of physician spouses, bonded by a vision and mission of keeping healthy West Virginians. Members get together for fellowship; enjoying the camaraderie of members from different counties, and networking with other physician spouses of various professional, business, and cultural backgrounds. We look forward to having a core group of both the dedicated long-time members and the new generation of young physician spouses.

Rose Romero
WVSMAA President

WVU Healthcare welcomes new heart surgeon

Dr. Anthony Holden joins WVU Heart Institute

Anthony Holden, MD

Heart surgeon Anthony Holden, M.D., has joined the WVU Heart Institute. He specializes in cardiac surgery, including coronary artery bypass grafting, aortic valve surgery, surgery for atrial fibrillation and mitral valve repair surgery.

"I'm excited to be a part of the WVU Heart Institute," Dr. Holden said. "The people of West Virginia are fortunate to have a unique, multidisciplinary group of physicians at WVU, including cardiologists and cardiac surgeons. Together, we individualize each patient's care with a collaborative, team approach."

Holden earned his medical degree from Northeastern Ohio Universities College of Medicine and completed specialty training in general surgery at the University of Arizona Health Science Center and in thoracic surgery at University Hospital SUNY, Syracuse, NY. Holden is board certified in general and thoracic surgery.

The medical team at the WVU Heart Institute provides comprehensive heart care, including intervention, management and rehabilitation for cardiac patients. WVU heart and thoracic surgeons continually make advances in treating patients with cardiothoracic diseases, performing hundreds of open-heart and thoracic surgeries each year. The team specializes in complex cardiac surgery cases, including all aspects of cardiac valve surgery and surgery for heart arrhythmia.

WVU Healthcare offers new lung cancer screening program

WVU Healthcare is offering a new low-cost screening program to help patients who are at risk for lung cancer.

The Lung Cancer Screening Program is a multidisciplinary effort aimed at catching the disease in its early stages by offering low-dose helical chest CT scan and smoking cessation counseling for $99.

The rationale for the creation of the program stems from results of the National Cancer Institute's National Lung Screening Trial, published in the *New England Journal of Medicine* in August 2011.

"This study showed an earlier detection of lung cancer and demonstrated a 20 percent reduction in lung cancer mortality, among current and former smokers, when screened with low-dose helical chest CT versus chest x-ray," Harakh V. Dedhia, MD, professor in the Department of Medicine, Section of Pulmonary and Critical Care said. "Early detection of lung cancer is critically important because symptoms associated with this disease usually do not occur until the cancer has advanced and is more difficult to treat."

To qualify for the screening program, patients must be 55 to 74 years old, and either an active smoker with at least a 30 pack-year history, or have quit smoking within the past 15 years.

Eligible patients need to visit their primary care physician to obtain a referral and an order for the low-dose helical chest CT scan, which will be interpreted by a board certified radiologist at WVU. The primary care physician can order the scan and FAX the request to 304-598-6375. The patient should call 1-855-WVU LUNG, option 1 to schedule an appointment. A nurse will call the patient two or three business days following the CT scan and the results will be mailed to the patient and primary care physician for continuity of care and optimized communication. If the results are abnormal, the patient may choose to consult with their primary care physician regarding follow-up care or be referred to a WVUH specialty clinic.

WVU is the only major cancer center in West Virginia to offer the new low cost screening program.

For information on the WVU Healthcare Lung Cancer Screening Program call Kim Yow, RN or Christina Ayers, RN at 304-293-9525 or 304-293-2288.

Meaningful Use – Becoming a "Meaningful User"

The American Recovery and Reinvestment Act of 2009 (Recovery Act) was signed into law by President Obama on February 17, 2009. The law includes the Health Information Technology for Economic and Clinical Health Act, or the "HITECH Act," which established programs under the Centers for Medicare and Medicaid Services (CMS) to:

- Establish a set of specific requirements to be considered "certified" electronic health record (EHR) technology;
- Establish a series of criteria to which healthcare providers and hospitals must adhere in order to qualify as meaningful users of health information technology (HIT) and receive incentive payments;
- Establish a series of quality measures on which providers and hospitals must report in order to receive the incentive payments.

A Meaningful Use workgroup was charged with developing recommendations to the HIT Policy Committee on how to define meaningful use in the short and long-term, including: 1) the ways in which EHRs can support meaningful use, and 2) how providers can demonstrate and receive financial incentives for meaningful use.

On July 13, 2010, the US Centers for Medicare and Medicaid Services (CMS) released a Final Rule establishing the criteria with which eligible professionals (EPs), other health providers and hospitals must comply in order to qualify for the incentive payments that are available with clinicians through the American Recovery and Reinvestment Act. Providers are not required to begin participating in the incentive program in 2011; however, providers must begin receiving payment no later than 2016.

As the US rolls out its largest ever investment in HIT, meaningful use (MU) promises to dramatically transform the delivery of care. One of the primary benefits of image access in the electronic medical record (EMR) is patient education.

CMS's goal is for the definition of meaningful use to be consistent with applicable provisions of Medicare and Medicaid law while continually advancing the contributions certified EHR technology can make to improving health care quality, efficiency, and patient safety. To accomplish this, CMS' final rule would phase in more robust criteria for demonstrating meaningful use in three stages.

Stages for Meaningful Use:

Stage 1: Establish criteria for Meaningful Use. Stage 1 has been completed.

Stage 2: Would expand upon Stage 1 criteria in the areas of disease management, clinical decision support, medication management support, patient access to their health information, transitions in care, quality measurement and research, and bi-directional communication with public health agencies which is not yet finalized. Stage two will further enhance state public health operations. This stage will allow for the meaningful exchange of public health data with state data systems for syndromic surveillance, electronic laboratory reporting and immunization encounter reporting. The West Virginia Statewide Immunization Information System (WVSIIS) is a 12 year old system that provides a single record for a person, from records that are entered or submitted from multiple sources. This process is somewhat time consuming, but bi-directional data exchange using HL7 version 2.5.1 will allow data to be sent to and from WVSIIS using the physician's EMR. Bi-directional data exchange allows both parties to have the most up-to-date records and saves physicians time in researching a patient's immunization history while ensuring that all persons are age-appropriately immunized.

Stage 3: Would focus on achieving improvement in quality, safety and efficiency, focusing on decision support for national high priority conditions, patient access to self management tools, access to comprehensive patient data, and improving population health outcomes.

Loretta Haddy, PhD, MS
State Epidemiologist and
Director, Office of Epidemiology
and Prevention Services
WVDHHR/Bureau for Public Health

Joan D. Skaggs, RN, MSN
Coordinator for Clinical Services
Division of Primary Care
Office of Community Health
Systems and Health Promotion
WVDHHR/Bureau for Public Health

Translational Genomic Research Institute dedicated

Allison Wolf, MU Biomedical Sciences PhD candidate

Marshall dedicated its new Charles H. McKown, Jr., MD, Translational Genomic Research Institute in a ceremony Dec. 6.

The institute will allow Marshall's Biomedical Sciences Graduate Program researchers to conduct more investigator-initiated clinical trials. In addition to laboratories dedicated to cancer research, the TGRI will also house the West Virginia Cancer Genomics Network, a partnership of Marshall and West Virginia University. The network is developing a database of genomic information that will allow researchers to compare the genes of multiple patients suffering from the same types of cancer, which could help doctors and researchers predict response to targeted therapies.

Studies taking place in the institute's laboratories focus heavily on nutrition and cancer.

Dr. Pier Paolo Claudio studies the effects of dietary agents on cancer, with emphasis on growth and metastasis, and uses targeted gene therapy to improve the efficacy of cancer treatment. He also recently launched a Phase I clinical trial at the TGRI, seeking to determine the effectiveness of existing chemotherapy treatments for patients with small cell lung cancer.

Dr. Elaine Hardman studies the effects of omega-3 fatty acids on the development of cancer. Her published research indicates that, in animal models, a diet high in omega-3 fatty acids can prevent the development or slow the growth of multiple cancer types. To extend this research to humans, she and Dr. Oscar Ballester have conducted a human clinical trial in which patients with early stage chronic lymphocytic leukemia consumed supplemental omega-3 fatty acids.

Dr. Richard Niles' research focuses on vitamin C and the fact that different tissues in the body and various tumors show altered ability to take up and use the vitamin as a cofactor for enzymatic reactions. He and Dr. Sarah Miles, a postdoctoral fellow in his lab, are involved in a translational project with Dr. Jose Pulido, an ophthalmologist at the Mayo Clinic. This research has led to a provisional patent for a diagnostic test.

Nanoparticles in fuel additives associated with liver damage

Recent studies conducted at Marshall have demonstrated that nanoparticles of cerium oxide – common diesel fuel additives used to increase the fuel efficiency of automobile engines – can travel from the lungs to the liver and that this process is associated with liver damage.

The data in the study by Dr. Eric R. Blough and his colleagues at Marshall's Center for Diagnostic Nanosystems indicate there is a dose-dependent increase in the concentration of cerium in the liver of animals that had been exposed to the nanoparticles, which are only about 1/40,000 times as large as the width of a human hair. These increases in cerium were associated with elevations of liver enzymes in the blood and histological evidence consistent with liver damage. The research was published in the Oct. 13 issue of the peer-reviewed *International Journal of Nanomedicine*.

Cerium oxide is widely used as a polishing agent for glass mirrors, television tubes and ophthalmic lenses. Cerium oxide nanoparticles are used in the automobile industry to increase fuel efficiency and reduce particulate emissions. Some studies have found that cerium oxide nanoparticles may also be capable of acting as antioxidants, leading researchers to suggest these particles may also be useful for the treatment of cardiovascular disease, neurodegenerative disease and radiation-induced tissue damage.

PHOTOS BY RICK HAYE

Johannes Fahrmann, MU Biomedical Sciences PhD candidate

Obituaries

The WVSMA remembers our esteemed colleagues...

John Blair Morton II

Dr. John Blair Morton II, 47, of Charleston passed away Wednesday, Nov. 30, 2011, at home after a long illness, surrounded by his loving family.

John was a physician, specializing in gastroenterology. He returned to Charleston with his family in 2007 and became a partner in Charleston Gastroenterology Associates.

He served in the U.S. Navy as a commissioned officer from 1987 to 1992.

John was a 1982 graduate of George Washington High School. He graduated with high honors from the University of Virginia in chemical engineering in 1986. In 1996, he graduated from the West Virginia University School of Medicine.

He completed a gastroenterology fellowship at Oschner Clinic Foundation, New Orleans, La.

He was an avid runner, enjoyed traveling, loved spending time with his children and really enjoyed life.

John was preceded in death by his father, William A. Morton Sr.

He is survived by his wife, Erma Morton of Charleston; son, John "Jack" Morton III, age 6; daughter, Margaret "Maggie" Elizabeth Morton, age 5; mother, Barbara O' Connor Morton of Charleston; sisters, Julia Anne Morton and Mary Leslie Morton of Charleston; and brother, William A. and his wife, Yvonne Fay Morton, of Whittier, Calif.

John leaves behind his loving family and caring friends.

As his final wish, his body was donated to the West Virginia University School of Medicine Human Gift Registry, Morgantown, to further medical research.

In lieu of flowers, donations may be made to his children's college fund, Harford Smart 529 Plan, c/o Heritage Investment Group, 318 5th Ave., South Charleston, WV 25303, or First Presbyterian Church, 16 Leon Sullivan Way, Charleston, WV 25301.

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Carrie Cox, FYMS
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Shayne Gue, FYMS
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Raleigh County Medical Society

Omar Hasan, MD

Please direct all membership inquiries to: **Mona Thevenin, WVSMA Membership Director at 304.925.0342, ext. 16 or mona@wvsma.com.**

Disability Insurance:
Residual/Recovery Benefit

by Joe Noca, Union Central, and Josh Wood, WV Medical Insurance Agency

In our last edition, we discussed the merits of an own occ definition of disability versus the modified own occ or own occ and not working definition of disability. The definition of disability is clearly the most important contract benefit in a disability policy. A very close second as far as benefits within a disability policy are concerned is the Residual/Recovery benefit.

The basic purpose of a residual rider is to help supplement current income when an insured is returning to work from being off on a claim. In the case of Union Central, a residual claim is initiated when an insured can perform some but not all of the substantial and material duties of their occupation and has a loss of income of at least 15%, or is unable to work in their occupation more than 80% of the time as was usual prior to the start of their claim. If the insured has at least a 75% loss in pre-disability earnings, it is considered a total loss and their full benefit is paid. For the first six months of a residual claim, at least 50% of their total disability benefit will be paid. The residual disability benefit amount is calculated as follows:

> Loss of monthly earnings (current income)/(divided by) prior monthly earnings (before the claim) x your base monthly benefit = Residual Monthly Benefit

Let's illustrate that formula with real numbers in the following example:

Dr. Smith is a pediatrician that had been earning $240,000 annually prior to his heart attack two years ago. Dr. Smith has rehabbed himself to the point of being able to return to work, however, his physician is only allowing him to work 20 hours per week initially. In this case, here is how the residual benefit is calculated:

At 20 hours per week, Dr. Smith's income is $10,000/mo. His income prior to his disability claim was $20,000/mo. With an annual income of $240,000, Dr. Smith qualified for $10,600/mo in disability benefits. Using the above formula, the calculation is

> $10,000/mo in current earnings/ (divided by)$20,000 in pre-disability earnings x $10,600/mo in disability benefits = $5,300/mo in a residual monthly disability benefit

As long as Dr. Smith continues to experience an income loss of 15%-20% while working part time he will collect a residual monthly benefit until such time he is back to earning 80%-85% or more of his pre-disability earnings.

The more significant application of the Residual/Recovery benefit is if the insured has returned to work and is performing the substantial and material duties of their occupation more than 80% of the time as was usual prior to the start of their disability claim, a residual monthly benefit will continue to

be paid as long as they continue to experience an income loss of at least 15%. This residual/recovery benefit will continue to be paid until such time they no longer have the 15% loss in income or they reach the end of their benefit period.

The built in recovery benefit as part of the residual rider itself is a critical component of the language in a disability policy. Several carriers in the disability marketplace today have very limited recovery benefits as part of their policies. A few of the carriers, including Union Central, have a recovery benefit built in to their Enhanced Residual Rider as a benefit in the policy. With several carriers, their recovery benefit has to be added by rider.

Not all residual/recovery benefits are alike. Most residual riders are trigger benefits with either a 15% or 20% loss in pre-disability income. When it comes to the recovery benefit, it can vary significantly from carrier to carrier. In the case of Union Central, an insured can potentially be carried on a recovery claim for their entire benefit period. There are a few other carriers with similar benefits, some of which are built in and some which have to added by rider. Still, other carriers have very limited recovery benefits in their policies, from six months to a maximum of three years. For medical professionals, the recovery benefit in a disability policy should be considered a difference maker when evaluating disability policies. If a medical professional will never be able to return to their pre-disability earning power because of limitations resulting from their claim, the recovery benefit is the benefit that will continue to supplement their income for potentially as long as the remaining portion of their benefit period. If the recovery benefit is limited from a low of 6 months to a maximum of 36 months, as with a few carriers, the insurance company will cease paying the supplemental recovery benefits at the end of those time frames. That could produce a significant reduction in total monthly earnings.

Our recommendation is to look at your current policy to see if there is language that mentions anything about a recovery benefit. If so, check to see if there is a time limitation (12 months, 24 months, 36months, etc) or is there language supporting the potential for the "remaining benefit period" (if you have an age 65 benefit period, and age 67 benefit period, or an age 70 benefit period as part of your policy).

If it has been some time since you last reviewed your disability policy, especially to confirm whether or not you have a Residual/Recovery benefit in the policy, we encourage you to do so. As part of the services being offered by the West Virginia Medical Insurance Agency and its partnership with Union Central, Josh Wood can make a quick review of your disability policy and help you better understand this feature/benefit of your policy. You may reach Josh at 304-925-0342 x33 or josh@wvsma.com
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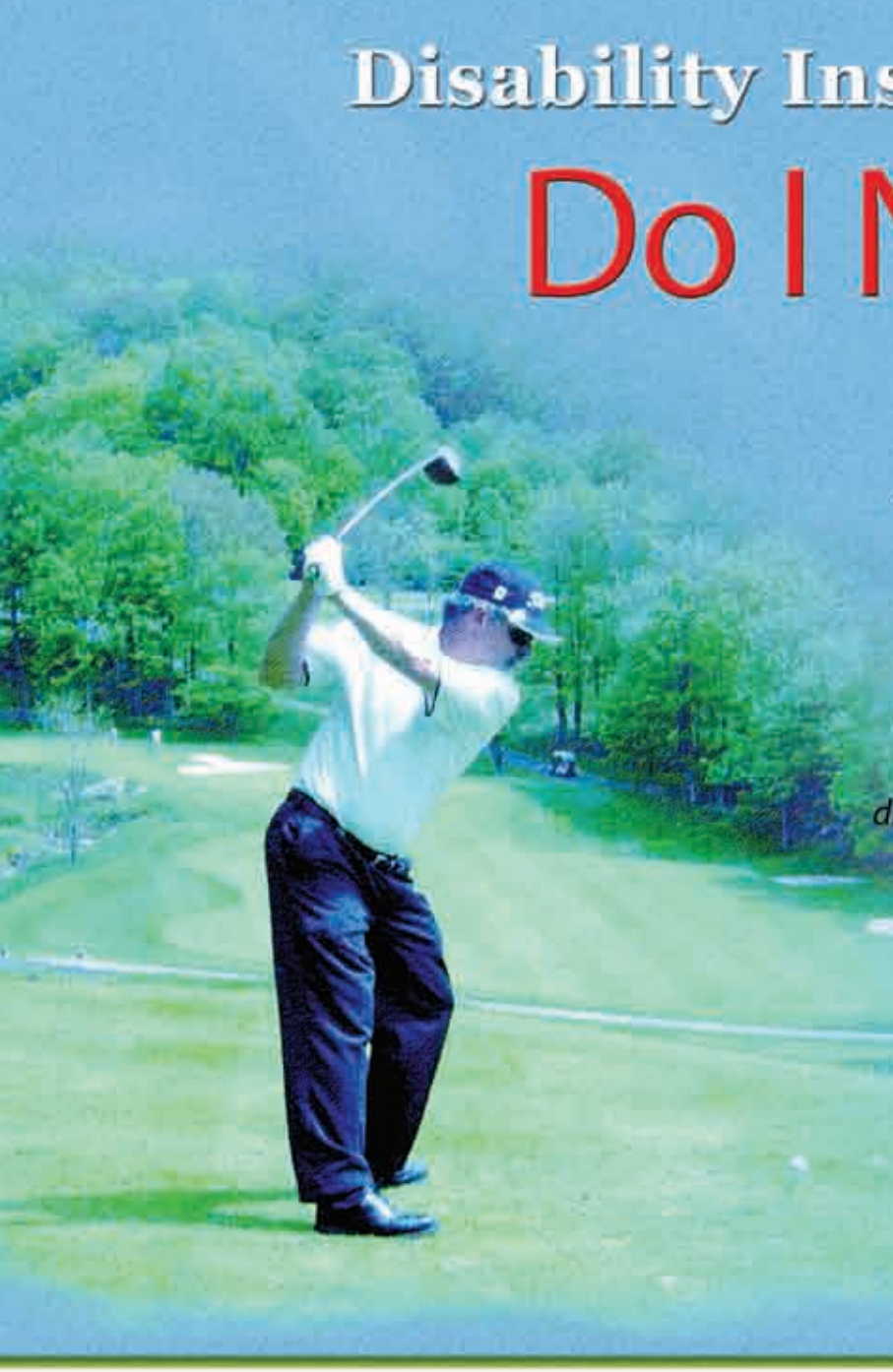
Disability Insurance

Do I Need It?



"The Social Security Administration estimates that 3 out of 10 Americans will become disabled before they retire." *

+

"Disability insurance industry statistics report that fewer than 1 out of 10 long-term disability claims actually result from injuries." *

+

"Ninety percent say they value their ability to earn income, but almost 40% said they haven't thought about how they would protect this ... financial resource." *

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*Source: CDA 2010 Consumer Disability Awareness Study.

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WEST VIRGINIA
RESPONDER EMERGENCY DEPLOYMENT INFORMATION SYSTEM
REDI

West Virginia Responder Emergency Deployment Information

What is WV REDI?

West Virginia Responder Emergency Deployment Information system

- WV REDI is a web-based registration system developed to facilitate health and medical response through identification of West Virginians willing to serve in public health emergency and non-emergency situations

Who can register?

- Registration is open to West Virginia's health and medical professionals, and others who live or work in West Virginia

How can I help?

- You can help by being willing to assist during a health related emergency or event and by registering in WV REDI

What if I can't go when called?

- Please remember that "volunteer" truly means volunteer. You can choose, at any time, to decline any request that you receive for deployment

How do I register?

- To register go to **www.wvredi.org** and click on "register now"

Where do I get more information?

- For more information, call **304-558-6900 ext. 2009**

Register today to be prepared for tomorrow!

Visit the www.wvredi.org homepage and click on "register now."

WEST VIRGINIA Department of Health & Human Resources

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