Evidence-Based Fetal Referrals for Congenital Heart Surgery

Cynthia Elaine Battiste, M.D.[1], Margaret Helen O'Hara, M.D.[2],
Steven Wayne Allen, M.D.[1]
University of Kansas School of Medicine-Wichita
[1]Department of Pediatrics, [2]Department of Obstetrics and Gynecology

Abstract

Background. The outcomes of fetal referrals to congenital heart disease centers for delivery and postnatal surgery prior to discharge over a two-year period were reviewed. Cost differences between fetal referrals and neonatal transports were investigated.

Methods. A retrospective chart review was conducted on 17 fetal referrals to two congenital heart disease centers from 01/01/2007 to 12/31/2008. The two centers were contacted to obtain their neonatal transport charges.

Results. Of the 17 fetal referrals, 10 patients underwent congenital heart surgery prior to postnatal discharge. Only one patient who underwent surgery died. Third party payers saved approximately $13,600 or $36,600 in neonatal transport costs to these centers.

Conclusions. There was only one death of a patient with hypoplastic left heart syndrome and a restrictive atrial septum, which has a poor prognosis. There was a significant cost differential between fetal referral and neonatal transport.

KJM 2012; 5(1):1-7.

Introduction

Congenital heart disease occurs in 9 of 1000 livebirths.[1] Critical congenital heart disease, which requires interventional catheterization or surgery in the first year of life, occurs in about 25% of these children. Antenatal diagnosis of critical congenital heart disease and referral of the mother for confirmation and planned delivery at a congenital heart disease center in these cases may allow for optimum outcomes[2,3] with referrals in favor of the best centers.[4]

A prenatal diagnosis of congenital heart disease did not result in savings in cost, length of hospitalization, or survival in the relatively small geographic area of New England, which lends itself to rapid patient transfer.[5] However, a study of three referral centers in Northern California reported that most infants without a prenatal diagnosis of congenital heart disease require one or more transports to congenital heart disease centers with ventilation and prostaglandin therapy.[6]

Allen and colleagues[7] reported superior outcomes in patients requiring congenital heart surgery by selectively referring to high-volume surgical centers based on published or "apparent" low mortality rates for specific congenital cardiac surgical procedures. Congenital heart surgery has not been done at our center since 1998. All of our patients are referred to major congenital heart surgery centers. Using Allen and colleagues' model for superior surgical outcomes, our institution developed and used an evidence-based referral system for in utero diagnosis of congenital heart disease likely to require early intervention.

Parents are counseled about the intervention and the option of referral to an evidence-based demonstrated congenital heart surgical center in cases most likely to require intervention prior to postnatal discharge. These centers are long distance, 200 miles (center 1) and 900 miles

(center 2), from our institution. Patients that we believe will have a good outcome are referred to center 1. Center 2 is nationally known as one of a few centers with the lowest mortality (less than 10%) for complex congenital heart disease requiring the Norwood procedure. Therefore, patients likely to require the Norwood procedure are referred to center 2.

This study was a two-year retrospective review of fetal referrals undergoing post-natal congenital cardiac surgery prior to discharge. Mortality outcomes and the cost differences between fetal referral and neonatal transport to the two centers were investigated.

Methods

From 01/01/2007 to 12/31/2008, a perinatologist referred 81 patients to one of two pediatric cardiologists for a comprehensive fetal echocardiogram. The pediatric cardiologists obtained the fetal echocardiograms at the perinatologist's office with one of two certified obstetrical sonographers. The fetal echocardiograms were performed on a Voluson Expert 730 with an AC 2-5 transducer until May, 2008, when a GE-E8 with a 4C transducer was used.

A retrospective chart review of these 81 patients was completed. Seventeen patients were identified whose parents chose evidence-based referral to one of these two centers. The following data were extracted from these 17 charts: date of comprehensive fetal echocardiogram, fetal gestational age, maternal age, pediatric cardiologist, reason for referral, chromosomal anomaly, extracardiac anomaly, echocardiography findings, congenital heart surgical center where the patient was referred, and outcome.

The two centers were contacted to obtain their charges for neonatal transport. The cost of driving to these centers was estimated. The average cost of a motel at center 2 was estimated using an American Automobile Association (AAA) travel book. The cost of flying to center 2 was obtained from an AAA travel agent.

Results

Ten patients underwent congenital heart surgery procedures prior to discharge. Two patients underwent other interventions. Two patients did not require intervention prior to discharge. One patient's mother had premature rupture of membranes and delivered at her local hospital. Two patients were lost to follow-up.

The two patients who were lost to follow-up were seen initially at center 1. One had aortic valve stenosis, a dilated left ventricle, and a patent foramen ovale. The other one had severe tricuspid valve hypoplasia, pulmonary valve stenosis, infundibular stenosis, a restrictive ventricular septal defect, a secundum atrial septal defect, and a hypoplastic right ventricle. There was no record of them being admitted to that center after birth.

One patient with an absent pulmonary valve, severe pulmonary insufficiency, right atrial enlargement, and right ventricular hypertrophy was seen at center 1. That patient has not had any intervention. One patient with a small left ventricle was thought to have a probable severe coarctation on fetal echocardiogram. Only a secundum atrial septal defect was found after birth at center 2, and that patient did not require intervention.

The fetus, whose mother had premature rupture of membranes with delivery at the local hospital, had a complete atrio-ventricular block secondary to maternal lupus. The infant was followed by a pediatric electrophysiologist at center 1 and has not had a pacemaker implanted yet.

One patient with pulmonary valve atresia underwent radio-frequency perfor-

ation and balloon dilation prior to discharge from center 1. That patient had undergone two subsequent balloon dilations. One patient with levo-transposition of the great arteries, a ventricular septal defect, pulmonary valve stenosis, and complete atrioventricular block underwent permanent pacemaker implantation prior to discharge from center 1.

Details of the 10 patients who underwent congenital heart surgery prior to discharge are shown in Table 1. In some cases, subsequent congenital heart surgical procedures were known. The patient with hypoplastic left heart syndrome and a restrictive atrial septum, which has a poor prognosis, was profoundly cyanotic at birth. The patient was immediately evaluated and taken to the operating room for a hybrid procedure. This was the only patient who died. Thus, a 10% mortality was observed for our 10 patients who underwent congenital heart surgical procedures.

In review of the expected costs of travel for the parents, there were no flights from our city to center 1. The cost of driving to either center was estimated using 15 miles per gallon at $3 per gallon. The parents should not have had to stay overnight when going to center 1. The parents would incur transportation costs at the initial evaluation and again when returning to center 1 for delivery. However, the second trip was likely not a cost difference as at least one parent would have to drive to center 1 after delivery at our institution if the baby underwent a neonatal air transport to center 1. The estimated cost for both parents to drive to center 1 was $110.

Similarly, at least one parent would have to drive or fly to center 2 after delivery at our institution if the baby underwent a neonatal air transport to center 2. As mentioned, the cost of a motel at center 2, and the cost of roundtrip airfare from our city to the closest airport to center 2 was per AAA. There was an additional estimated cost of a roundtrip shuttle from the airport to center 2. The estimated costs for both parents to drive to center 2, stay at a motel for four nights, and eat for five days was $1,210. The estimated costs for both parents to fly to center 2, use an airport shuttle, stay at a motel for two nights, and eat for three days was $1,447.80. Center 1 charged approximately $13,600 for neonatal air transport. Center 2 charged approximately $36,600 for neonatal air transport. Table 2 shows comparative costs.

Discussion

In our retrospective review to determine the effects of evidence-based fetal referral on mortality and cost, a reduction in expected mortality and lower total cost was observed with the use of evidence-based referral for fetally detected congenital heart disease requiring surgery prior to discharge.

In a retrospective review, Yeager et al.[8] reported that cardiac patients transported from adjacent obstetric facilities compared to cardiac patients transported from other inpatient medical facilities were more likely to have been diagnosed prenatally with more complex disease and had higher mortality. A study from Boston Children's Hospital found that a prenatal diagnosis of hypoplastic left heart syndrome or transposition of the great arteries improves the preoperative condition of these patients, but it may not significantly improve preoperative mortality or early postoperative outcome among neonates managed at a tertiary center.[9] However, a University of California-San Francisco study of patients with hypoplastic left heart syndrome found that all patients diagnosed prenatally and who underwent surgery survived.[10] Of 38 patients diagnosed postnatally who under-

Table 1. Congenital heart surgical procedures and outcomes.

Center	Gestational Age (weeks/days)	Diagnosis	Initial Intervention	Subsequent Interventions	Outcome
1	24	Tricuspid valve atresia, VSD[1], Normal great arteries	Blalock-Taussig shunt	Bidirectional Glenn shunt	Alive
1	27	VSD[1], DORV[2], d-malposition[3], Pulmonary valve stenosis	Blalock-Taussig shunt	Blalock-Taussig shunt, Bidirectional Glenn shunt	Alive
2	35	Coarctation	Repair with patch	None	Alive
2	23	HLHS[4]	Norwood	None	Alive
2	34	Hypoplastic aortic arch, Coarctation, Small aortic valve	Norwood	Coarctation repair (elsewhere)	Alive
2	23	Tricuspid valve atresia, VSD[1], Normal great arteries	Blalock-Taussig shunt, Atrial septectomy	Hemi-Fontan, Fenestrated Fontan	Alive
2	36	HLHS[4]	Norwood	Hemi-Fontan, Fenestrated Fontan	Alive
2	25	HLHS[4], Restrictive atrial septum	Atrial stent (embolized), Stent removal, Atrial septectomy, Bilateral branch pulmonary artery bands	None	Dead
2	23	DILV[5], Right atrioventricular valve atresia, l-TGA[6]	Atrial septectomy, Pulmonary artery band	Hemi-Fontan, Fenestrated Fontan	Alive
2	28	TV atresia, VSD[1], d-TGA[7], Hypoplastic aortic arch	Damus-Kaye-Stansel procedure	Bidirectional Glenn shunt	Alive

[1]VSD (ventricular septal defect), [2]DORV (double-outlet right ventricle), [3]d-malposition (dextro-malposition of the great arteries), [4]HLHS (hypoplastic left heart syndrome), [5]DILV (double-inlet left ventricle), [6]l-TGA (levo-transposition of the great arteries), [7]d-TGA (dextro-transposition of the great arteries).

Table 2. Cost comparisons.

Center 1		
Fetal Referral		**Neonatal Transport**
Gasoline	$80	$13,600
Food	$15/person	
Center 2		
Fetal Referral		**Neonatal Transport**
Gasoline or Airline Airport Shuttle	$360 $438.90/person $50/person	$36,600
Motel	$100/night	
Food	$45/person/day	

went surgery, only 25 survived. Patients diagnosed prenatally had a lower incidence of preoperative acidosis, tricuspid regurgitation, and ventricular dysfunction. They were less likely to need preoperative inotropic medications or bicarbonate.

Sharland et al.[11] in a retrospective review, found difficulties in diagnosing coarctation prenatally. Of 87 fetuses, coarctation was diagnosed correctly in 54, suspected but unproved in 24, and overlooked prenatally in 9. They concluded that although a combination of echocardiographic features can identify aortic arch anomalies in the fetus, none, either alone or in combination, could distinguish between real and false positive cases, particularly in late gestation. As reported above, one false positive case was observed in our study.

Jenkins et al.[12] developed a consensus-based method of risk adjustment for in-hospital mortality among children younger than 18 years after surgery for congenital heart disease (designated RACHS-1). Their data sources were the Pediatric Cardiac Care Consortium (PCCC) and hospital discharge data sets. The PCCC includes 32 congenital heart surgery centers. The three statewide hospital discharge data sets were from Illinois, Massachusetts, and California.

Coarctation repair less than 30 days of age is a risk category 2 procedure with an expected mortality rate by PCCC data of 3.8% and hospital discharge data of 3.3%. The Blalock-Taussig shunt and the pulmonary artery band are risk category 3 procedures with an expected mortality rate of 8.5% and 6.8% respectively. Atrial septectomy, a risk category 4 procedure, has an expected mortality rate of 19.4% and 16.4% respectively. Finally, the Norwood operation and the Damus-Kaye-Stansel procedure are risk category 6 procedures. The mortality rate in this category for PCCC data is 47.7% and for hospital discharge data is 41.5%.

In our study, one patient was in risk category 2, three patients in risk category 3, two patients in risk category 4, and four patients in risk category 6. Using the data of expected mortality in RACHS-1, a mortality of 22-26% was expected. Only one death was observed in a patient with hypoplastic left heart syndrome and a restrictive atrial septum undergoing an emergent hybrid procedure for a mortality of 10%.

As mentioned previously, Copel et al.[5] did not find that a prenatal diagnosis of congenital heart disease resulted in cost savings. Although Friedberg et al.[6] stated that the need to transport critically ill

neonates to a referral center potentially compromises their hemodynamic stability and is costly, they did not report the actual costs of transports to the three Northern California centers or the transport distances.

Our study was limited by being retrospective. Cases may have been omitted or missed, but we are unaware of any such cases. Lack of follow-up data in two cases in such a small series was a limitation. Our institution is small with only two pediatric cardiologists making for possible limitations in the wider use of this referral pattern. Statistical power was limited by not having large numbers of fetuses with critical congenital heart disease which require surgery prior to discharge. However, only one patient died of those with follow-up whose parents chose to deliver at the evidence-based congenital heart surgery centers recommended by the pediatric cardiologist.

In conclusion, lower mortality than expected was demonstrated in this small group of patients. By selectively referring patients requiring the highest risk procedures to a center with the lowest mortality, our patients achieved mortality rates as good as the best centers and better than the RACHS-1 estimates. Centers in the RACHS-1 study probably do not refer to other centers.

Third party payers would incur the costs of a perinatology consult, a pediatric cardiology consult, a fetal echocardiogram, and possibly a congenital heart surgeon's consult at the time of the initial referral. However, these costs would be much less for third party payers than those for neonatal transport. The parents incurred additional travel expense by having to travel to the congenital heart disease center for confirmatory fetal echocardiogram and arranging delivery at the referral center. The costs for the parents were greater if they traveled to the more distant center.

Potentially with these types of data, third party payers would consider paying the travel expenses for the parents, which would be less expensive and a more cost effective use of resources. Based on the perceived advantage in outcomes and demonstrated cost savings, our institution continues to refer patients fetally diagnosed with congenital heart disease and likely to require early intervention for delivery at the evidence-based surgical centers.

Acknowledgements:
We gratefully acknowledge the technical assistance of Michelle Mense, BSRT, RDMS and Tara Rupke, BS, RDMS, RVT.

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Keywords: fetal heart, referral and consultation, cardiac surgical procedures, outcome assessment, costs and cost analysis

Impetigo Associated with Cyanobacteria Exposure at a Kansas Lake: An Adolescent Case Series

Kari Harris, M.D., Kerri Meyer, M.D.,
Teolinda Milsap, M.D.
University of Kansas
School of Medicine-Wichita
Department of Pediatrics

Introduction

Cyanobacteria, or blue-green algae, have existed for about 3.5 million years and are common inhabitants of terrestrial, fresh, brackish, or marine waters.[1,2] They are important organisms in biodiversity and contribute greatly to the pharmaceutical and human health fields.[1]

Cyanobacteria have the capacity to produce a diversity of toxins, some being the most powerful toxins known.[3] The literature reports 150 known types of cyanobacteria, 50 of which inhabit freshwater. One-third of the freshwater inhabitants are toxigenic and have the potential to cause adverse health conditions in both humans and animals.[1,4] This toxicity was first reported over 120 years ago, when several livestock animals died within hours of drinking from a lake containing cyanobacterium.[2]

Adverse human health conditions include headache, myalgia, oral blistering, allergic reactions, skin rashes and gastrointestinal symptoms as well as potential hepatotoxicity.[1,2] Furthermore, there remains concern that exposure to cyanotoxins produced by these bacteria potentially could be carcinogenic and/or neurotoxic.[1,3-5] Toxic exposure can occur by direct contact, ingestion, or inhalation of recreational or untreated water as well as by deliberate ingestion of herbal supplements containing cyanobacteria.[6-8]

Several case reports have described a range of clinical sequelae developing after exposure to recreational waters contaminated with cyanobacteria. The most commonly reported were allergic-like symptoms, skin rashes, and gastrointestinal symptoms, all of which were self-limited.[2] The mild and self-limited nature of these manifestations makes it likely that underdiagnosis and misdiagnosis of cyanobateria-related health effects occur.[2] Much information is available about types of symptoms associated with blue-green algae, however, little exists on how medical professionals should evaluate and treat patients presenting with these complaints.

In 2011, the Kansas Department of Health and Environment issued a public advisory or warning for many lakes around Kansas regarding the potential harm associated with exposure to cyanobacteria.[9,10] We report three adolescent female patients who presented with similar impetiginous rashes after exposure to the toxic algae at Cheney Lake in south central Kansas. All three cases began within days after swimming in Cheney Lake during the time that the public health announcement was released.

Case Series

Case 1. A 15-year-old female presented to clinic two weeks after a rash started on her elbow (see Figure 1). She had been swimming in Cheney Lake on the day prior to the rash. The lesion on her elbow started

as a red blistering rash and progressed to involve her other arm and both legs. Her only associated symptom was some itchiness on the skin where the rash was located. She denied any fever, respiratory symptoms, nausea, or vomiting. Her vital signs were all within normal limits and her exam was only significant for multiple erythematous lesions over her arms and legs some with superficial ulcerations. The lesion that was most involved was located around her left elbow with some serous fluid drainage as well as honey-crusting noted circumferentially. The patient was started on oral cephalexin and the rash improved.

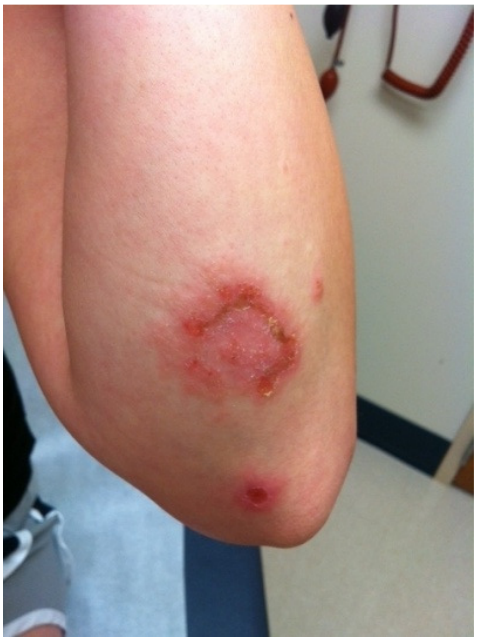

Figure 1. Honey-crusted lesion with fluid drainage.

Case 2. A 14-year-old female presented for a follow-up appointment after being treated at a local emergency department for what was diagnosed as a spider bite. The lesion had started 2-3 weeks prior, two days after swimming at Cheney Lake. The lesion existed primarily on her right knee, but had spread to involve her left ear lobe and left face at her follow-up appointment. The lesions itched and she admitted to scratching and picking at them prior to the rash spreading. She denied any fever, respiratory symptoms, nausea, or vomiting. On exam, her vital signs were unremarkable. On her right knee, she had what appeared to be a healing abscess that had drained and had remaining erythema with superficial scabbing present. There were several smaller satellite lesions with honey-crusting present surrounding the larger lesion on her knee. She had similar lesions with surrounding erythema and honey-crusting on her left ear lobe and cheek (directly adjacent to her left ear lobe). She was started on oral cephalexin and her rash resolved after treatment.

Case 3. A 16-year-old female presented to the clinic after a lesion began under her nose three days prior. She had been swimming at Cheney Lake approximately three weeks before she presented. Directly after swimming, she had nasal congestion that worsened until her presentation. The skin lesion began as a red sore on her upper lip. A similar lesion formed under her left naris two days before presentation and a third lesion began inside her left naris on the day of her appointment. She also had symptoms of a sore throat for the three days before presentation and one episode of diarrhea. She denied nausea or vomiting and had no history of fever. On exam, she was afebrile and vital signs were within normal limits. She had a 1.5 cm, honey-crusted, erythematous macule under her left naris and an approximately 0.5 cm circular, crusted lesion on her left upper lip at the vermillion border. The remainder of her exam was unremarkable. She was started on amoxicillin as treatment for sinusitis and topical mupirocin as treatment for her impetigo. Her symptoms improved with treatment.

Discussion

Multiple advisories and warnings have been posted for recreational lakes in Kansas

during 2011 because of the cyanobacteria in the water.[9,10] Depending on the amount of cell counts, or the presence of specific toxins, the Kansas Department of Health and Environment release either an Advisory or a Warning to the public stating the potential harm and recommended actions. At the time of submission of this article, eight Public Health Warnings and five Advisories had been released for lakes around Kansas.[9] Many people often are unaware of these public health announcements, or may ignore them altogether, thus exposing themselves to the toxic algae. Health care professionals are left to diagnose and treat the subsequent symptoms patients develop from this exposure. However, little information is available on how these illnesses should be diagnosed and managed.

The true incidence of human illnesses associated to toxic algae exposure is unclear. Many symptoms mimic other self-limited illnesses and could go unnoticed or misdiagnosed. Even in our three patients, if they had not presented within such a short time frame from exposure to the same contaminated water, we may not have tied the symptoms to the algae exposure. Because no diagnostic testing was performed, we only can link the skin lesions to the toxin exposure by the patients' temporal association with recreation at that specific lake and the similarity of their presentations.

All three patients were treated conventionally for bacterial impetigo with good response indicating that routine management for future lesions would be appropriate. In fact, supportive care for many manifestations linked to cyanobacteria exposure would likely be appropriate given their mild and self-limited nature.

The relevance for our cases lies in that Kansas has many lakes affected by cyanobacteria and such exposure should be considered when a patient presents with these types of symptoms. It is critical to get a thorough history which should include recent recreational activities, exposure to lake or pond water, and locations of summer camps or other outdoor activities. When exposure to cyanobacteria has been identified, it is important that the health care provider is aware of the possible manifestations of toxin exposure including the potentially more severe complications.

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Keywords: cyanobacteria, impetigo, case reports, Kansas, lakes

Metabolic Acidosis in Acetaminophen Overdose without Concurrent Liver Toxicity

Michael D. Chacey, M.D.[1], Michael S. Crosser, M.D.[2], Elliott D. Crouser, M.D.[1]

[1]The Ohio State University Medical Center, Division of Pulmonary, Allergy, Critical Care and Sleep Medicine, Dorothy M. Davis Heart & Lung Research Institute, Columbus, OH

[2]University of Kansas Medical Center, Division of Pulmonary and Critical Care Medicine, Kansas City, KS

Introduction

Metabolic acidosis and coma are common complications of acetaminophen overdose. These affects are usually attributed to massive hepatic necrosis caused by *N*-acetyl-*p*-benzoquinoneimine (NAPQI), a toxic metabolite of acetaminophen. We describe an unusual case of lactic acidosis and coma in a patient with acetaminophen toxicity without associated hepatocellular damage as the identifiable cause.

Case Report

A 47-year-old female in otherwise good health, presented after a suicide attempt involving the ingestion of 213 extra strength (500 mg) acetaminophen gel capsules. She was taken to the nearest emergency department, where her serum acetaminophen level was determined to be 810 mcg/ml. Her toxin screen was otherwise negative. Intravenous N-acetylcysteine (NAC) was initiated approximately 90 minutes after the ingestion of the capsules. Charcoal and sorbitol were administered via nasogastric tube, and the patient was transferred to our university hospital for further evaluation.

Upon arrival to our facility, she was obtunded with a Glasgow coma score of 7 (opens eyes to painful stimuli, made no verbal noises, and withdrew to painful stimuli). She was afebrile with a respiratory rate of 28 bpm, heart rate 115 bpm, blood pressure 134/87 mmHg, with peripheral oxygen saturation of 97% while on 6 liters of oxygen by nasal canula. Her physical exam was remarkable for obesity and diminished mental status. Her pupillary reflexes were intact. The patient had very diminished cough and gag reflexes. Her examination was otherwise unremarkable. She was endo-tracheally intubated due to concerns relating to airway protection.

Admission laboratory results were not suggestive of significant hepatocellular damage. The liver panel showed normal aspartate aminotransferase (AST: 22 u/L; normal range 5-34), alanine aminotransferase (ALT: 20 u/L; normal range 10-4), and alkaline phosphatase (ALP: 81 u/L; normal range 38-126). Her prothrombin time was 15.2 seconds (normal range 12.5-15.5). Arterial blood gases showed a pH of 7.14 (normal range 7.35-7.45), pC02 of 33 mm Hg (normal range 32-48), and p02 of 180 mm Hg (normal range 83-108) on 6 liters of oxygen by nasal canula (prior to endotracheal intubation), with serum bicarbonate and lactic acid levels of 12 mmol/L (normal range 21-31) and 7.2 mg/dL (normal range 5-20), respectively. The calculated anion gap was 18 (normal range 3-12). An extensive evaluation was conducted to identify possible

etiologies of her lactic acidosis, including evaluation for infections consisting of chest and abdominal imaging, blood and urine cultures, and a lumbar puncture. Urine toxicology screening was negative, and serum toxicology screening was only notable for acetaminophen. All other laboratory results were within normal limits.

Clinical course. The patient's acidosis resolved and her acetaminophen level decreased to an undetectable level within 36 hours. The results of relevant laboratory studies are summarized in Table 1, demonstrating no signs of liver damage or impaired synthetic function at any time. The NAC was discontinued after 48 hours and she was liberated from ventilator support on hospital day three, at which time her mental status was completely normal.

Table 1. Serial blood chemistry measurements during hospital stay.

	Admit	12 hours	24 hours	36 hours	48 hours
Apap (mcg/mL)	810	600	106	>10	>10
pH	7.14	7.23	7.24	7.48	7.43
Anion Gap	18	13	11	6	7
Lactate (mmol/L)	7.2	4.5	1.9	1.4	1.1
Protime (sec)	15.2	13.8	13.2	12.8	13
AST (u/L)	22	16	17	17	15
ALT (u/L)	20	16	19	19	20
Alk Phos (u/L)	81	62	64	61	59

Apap - Acetaminophen; Protime - Prothrombin Time; AST - aspartate aminotransferase; ALT - alanine aminotransferase; Alk Phos - alkaline phosphatase.

Discussion

Overdose with acetaminophen is a common cause of ICU admission and is the leading cause of acute fulminant liver failure in the United States.[1] Morbidity and mortality frequently occur during acetaminophen toxicity due to overwhelming liver failure caused by NAPQI, a toxic metabolite. NAPQI rapidly binds to and depletes glutathione stores.

Glutathione is essential for detoxifying peroxides, and its absence leads to hepatic damage from oxidative stress.[2] Chronic alcoholism, hepatitis, low protein diets, malnutrition, and smoking have been associated with lower baseline glutathione levels[3,4] and patients with these risk factors may be at increased risk for ill effects of NAPQI. Once glutathione is no longer available to bind NAPQI, this metabolite covalently bonds to sulfhydryl-containing proteins causing further damage to hepatocytes,[1,5] culminating in loss of hepatic function, massive acidosis, organ failure, and in approximately 500 cases per year, death.[6]

In addition to hepatotoxicity, NAPQI inhibits mitochondrial respiration by blocking electron transport between the cytochrome B/C complex and the cytochrome oxidase complex within the electron transport chain.[7] Early administration of NAC maintains stores of glutathione, which conjugates NAPQI thereby alleviating its toxic effect. While NAC serves as an effective antidote to a toxic metabolite of acetaminophen, it has no effect on the intact drug.[8]

Cases similar to this one have been reported previously.[9-13] However, careful documentation of the timing of acetaminophen levels with recovery from acidosis and coma, such as reported herein, was lacking. In all reported cases, the common finding

was high levels of unmetabolized acetaminophen. Mechanistically, the acidosis and coma could be explained by inhibition of mitochondria respiration by unmetabolized acetaminophen. In this regard, *in vitro* studies demonstrated dose-dependent inhibition of mitochondrial electron transport and ATP formation by acetaminophen.[14]

Animal studies reported accelerated rates of glycolysis in response to acetaminophen overdose, even when hepatocellular injury was prevented with NAC, presumably related to inhibition of aerobic (mitochondrial) respiration. Namely, acetaminophen toxicity in animal models was associated with inhibition of electron transport via NADH dehydrogenase (Complex I)[7] and depletion of cytochrome b (a Complex III subunit) in vital organs.[14] Consequent reductions in aerobic respiration increases reliance on ATP production through glycolysis.[15]

Compared to mitochondria-mediated aerobic respiration, glycolysis is much less efficient, producing a fraction of the ATP for each molecule of glucose consumed. Hence, more glucose is needed to maintain adequate ATP formation during anaerobic metabolism. Moreover, ongoing glycolysis in the absence of mitochondrial respiration leads to the build-up of pyruvate (see Figure 1) which, in turn, is reduced to lactate.[16]

The accumulation of lactate leads to an anion gap acidosis, as was observed in our patient. Furthermore, the relatively low levels of ATP produced as a result of impaired mitochondrial respiration and increased reliance on glycolysis, likely contributes to diminished organ function, particularly in tissues with high basal metabolic rates, such as the brain. In this regard, acetaminophen also has been shown to cross the blood brain barrier and reach significant levels in cerebral spinal fluid.[17] Although a direct link remains to be established, it is reasonable to speculate that acetaminophen could inhibit the function of central nervous system mitochondria and contribute to the neurologic impairment seen in patients with acetaminophen overdose.

The direct effects of elevated serum lactate on mental status in humans is unclear,[11] however, animal models suggest that elevated local lactate concentrations could undermine cognitive functions. Intrathecal injection of DL-lactate in calves results in more dramatic alterations of behavior and mentation than does a treatment with hydrochloric acid to achieve the same pH. It was reasoned that d-lactate, and to a lesser extent L-lactate, block neuronal glucose metabolism and alter the membrane potential in neurons.[18] Thus, direct neurological effects of lactate represent another potential mechanism by which acetaminophen overdose compromises cognition.

Despite efforts to intervene as early as possible with NAC treatment, most individuals presenting with acetaminophen overdose experience some degree of hepatocellular insult, ranging from mild elevation in transaminases to complete loss of synthetic function and hepatic failure.[1,6] This hepatic damage typically is associated with overt clinical manifestations, including encephalopathy, metabolic acidosis, and altered synthetic function (e.g., coagulopathy). It is likely that most patients being treated for acetaminophen-induced liver failure also experience a "type B" lactic acidosis (i.e., relating to interference with mitochondrial function).

This notion is supported by the documentation of metabolic acidosis prior to the onset of overt hepatocellular injury in a series of patients presenting with acetaminophen toxicity.[11,19] A two-stage acidosis sequence is proposed, initially related to inhibition of mitochondrial respiration by unmetabolized acetaminophen followed by a second phase of acidosis

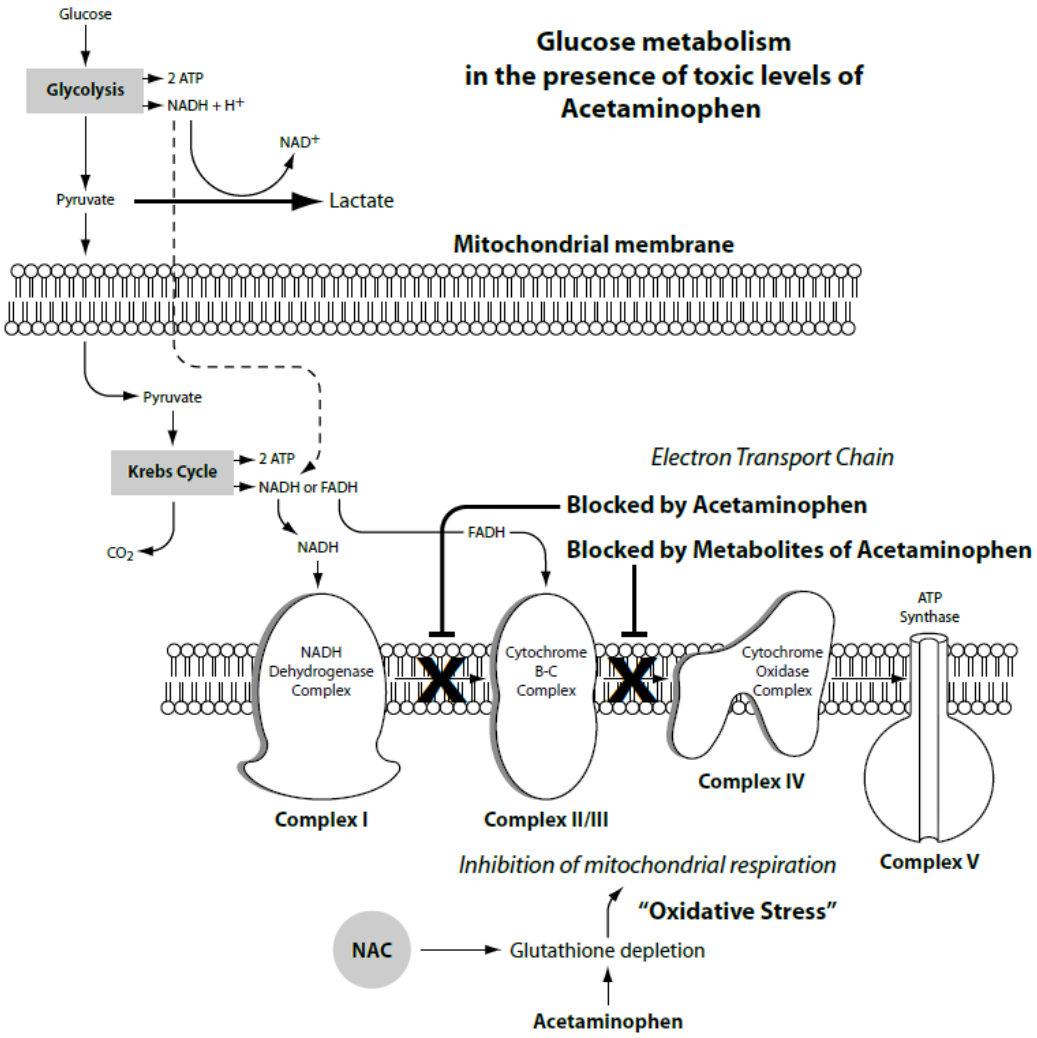

Figure 1. The breakdown of glucose and how it is inhibited by acetaminophen and its metabolites.

caused by overt hepatocellular necrosis, resulting in impaired lactate clearance and, presumably, ongoing mitochondrial inhibition. This scenario is substantiated by *in vitro* studies wherein exposure of hepatocytes to toxic doses of acetaminophen resulted in an inhibition of mitochondrial respiration 3-4 hours prior to the onset of detectable hepatocellular damage.[20]

Another rare cause of anion gap acidosis in the setting of acetaminophen overdose is accumulation of 5-oxoproline.[21] Excessive levels of 5-oxoproline can occur in the presence of acetaminophen overdose due to depletion of glutathione. This mechanism was unlikely to contribute to our patient's anion gap acidosis, as rapid administration of NAC would have prevented depletion of hepatic glutathione, and there would have been signs of hepatocellular injury. In this regard, glutathione levels need to drop by 80% in hepatocytes before significant accumulation of 5-oxoproline can occur.[22] 5-oxoproline is more likely to cause gap acidosis in acetaminophen toxicity from chronic use and is not believed to contribute to the sudden onset lactic acidosis seen in acute overdose.[21]

Our patient provided an unusual opportunity to observe the metabolic manifestations of massive acetaminophen overdose (977 mg/kg) in the absence of hepatocellular damage. It is evident from this case that acetaminophen can cause acute lactic acidosis and coma which resolve as the drug levels normalize, presumably relating to acute, reversible mitochondrial inhibition. Given the critical role of mitochondria and ATP as determinants of cell viability,[23] particularly in the context of acetaminophen toxicity,[24] it is reasonable to postulate that acetaminophen-induced mitochondrial inhibition predisposes to subsequent hepatocellular damage (e.g., relating to glutathione depletion).

Lactic acidosis is seen commonly in patients with sepsis, shock, renal failure, and inter-abdominal ischemia. Even in the presence of acetaminophen overdose, these clinical signs should be considered before ascribing the metabolic abnormality to acetaminophen.

While a comprehensive review of the management of lactic acidosis is beyond the scope of this article, several excellent reviews on the subject exist.[25-26] As discussed in these reviews, every effort was undertaken to consider alternative explanations and to prevent lactic acidosis, including optimization of hemodynamic variable, exclusion of severe infection, and appropriate supportive care.

Since our patient's renal and hepatic functions were preserved, she was able to clear the excess lactate soon after the acetaminophen levels normalized. While this case emphasizes the utility of timely NAC administration, it also identifies the early manifestations of acetaminophen toxicity, and leads us to consider opportunities to avoid further hepatocellular injury through avoidance of mitochondrial toxins (e.g., antimicrobial agents) commonly administered in the hospital setting.[27]

Acknowledgments. The authors would like to thank Timothy Eubank, Ph.D. for his assistance in creating the figure for this article.

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Key Words: acidosis, acetaminophen, overdose, coma, lactic acid

Langerhans Cell Histiocytosis Presenting with Headache and Sellar Mass in an Adult

Vaishali Patel, M.D., Aradhana Pandey, M.B.B.S., Kathy Newell, M.D., Rajib K. Bhattacharya, M.D.
Kansas University Medical Center
Department of Internal Medicine,
Division of Endocrinology, Metabolism, and Genetics
Kansas City, KS

Introduction

Langerhans Cell Histiocytosis (LCH) is a rare disease characterized by aberrant proliferation of a specific dendritic (Langerhans) cell belonging to the monocyte macrophage system.[1] These cells can infiltrate virtually any organ without inducing dysfunction.[2] LCH is encountered more often in children, with a peak age range of 1-3 years and an incidence of 3-5 cases per million per year and a male to female ratio of 2:1.[3] LCH is rare in adults and the incidence may be underestimated due to the fact that many cases likely go undiagnosed.

In order of decreasing frequency, the presenting symptoms are skin rash, dyspnea or tachypnea, polyuria and polydipsia, bone pain, lymphadenopathy, weight loss, fever, gingival hypertrophy, ataxia, and memory problems.[4] Regarding the endocrine system, LCH has a particular predilection for involvement of the hypothalamo–pituitary axis (HPA), leading to diabetes insipidus (DI) in up to 50% of cases. In a recent analysis, DI was the most common and permanent consequence of LCH, occurring in 24% of patients.[5] Other endocrine deficiencies can develop in up to 20% of patients.[5,6] Endocrine manifestations include DI followed by growth hormone deficiency with a median latency of about one year, followed by gonadotropin deficiency with a median latency of about seven years from the diagnosis of DI. ACTH and TSH deficiency also have been described.[7]

The length of time from the first symptom(s) to diagnosis is frustratingly long. Many patients wait one to four years before the correct diagnosis is made, and others have symptoms for 5 to 20 years.[8] The difficulty in making an accurate diagnosis is reflected in the long time from symptom onset to diagnosis, lack of clinical suspicion, and the variable characteristics of the disease. Diagnosis is based on electron microscopy or immunohistochemistry (positivity for S100 protein and CD1a).[9-11] Treatment is based on the extent of the disease and the site of involvement.[12]

We report a case of a woman who had symptoms of diabetes insipidus for many years before she presented with headache and subsequently was diagnosed with LCH.

Case Report

A 53-year-old post-menopausal female presented to her primary care physician with complaints of headache and blurry vision for two to three months. An MRI of the brain revealed an enhancing lesion in the suprasellar hypothalamic area extending into the brain stem measuring 2.8 cm (AP) x 2.4 cm (transverse) x 1.6 cm with hyperintensity on FLAIR (see Figure 1). During this time frame, the patient also was diagnosed with hypothyroidism. In retrospect, the patient had

polyuria, compensated with polydipsia, for a few years preceding the headache. An MRI-guided right fronto-temporal craniotomy was completed with guided biopsy.

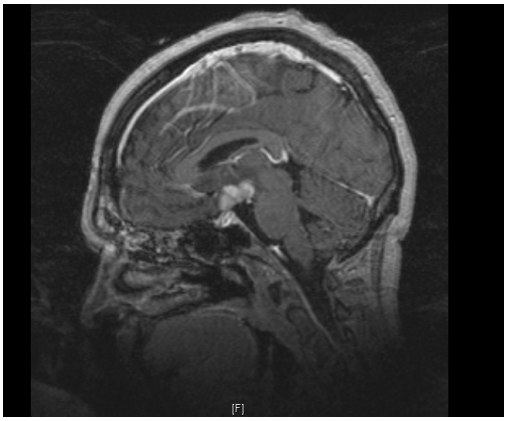

Figure 1. MRI of the brain showing the lobulated enhancing mass centered in the suprasellar location.

Pre-biopsy biochemical evaluation revealed normal sodium (140 mmol/L). Post-operatively, while in recovery room, the patient had greater than 800 ml of urine output over the course of three hours. Over the next two hours, she became lethargic, developed respiratory acidosis, and was intubated for respiratory failure. She had urine output of about nine liters over a period of 12 hours. Her blood chemistry 12 hours post-biopsy revealed hypernatremia with serum sodium of 166 mmol/L. An endo-crinologist was consulted to manage diabetes insipidus.

The patient initially was treated with DDVAP 1 mcg subcutaneously every eight hours with resultant improvement in polyuria. Fluids were replaced first with a combination of quarter-normal saline and half-normal saline with the addition of free water via naso-gastric feeding tube and later replaced with half-strength saline only. With these measures, her sodium improved to 146 mmol/L over a span of 48 hours. At this point, she was extubated. Serum sodium was maintained in normal range with oral maintenance fluids and DDAVP 0.2 mg by mouth twice daily. Perioperatively while she was intubated, she received dexamethasone, and IV levothyroxine 50 mcg daily.

The pathology report revealed gliosis with scattered atypical cells, patchy chronic inflammation, and Rosenthal fibers. Histiocytic infiltrate was present consistent with Langerhans cell histiocytosis. A patchy polymorphous inflammatory infiltrate consists of small lymphocytes, plasma cells, eosinophils, sometimes multiple per high power field, and larger histiocytes with clefted "C" to horseshoe-shaped nuclei (immunoreactive with CD1a). A few multinucleated cells including one Touton-type giant cell was noted, but no well-formed granulomas were found. No emperipolesis was noted. No necrosis was detected. CD1a stains were positive for multiple of the cells with abundant cytoplasm and C-shaped nuclei. S100 highlighted frequent immunoreactive cells, inclusive of, yet more than, the CD1a population of cells (see Figure 2). CD20 highlighted multiple small lymphocytes (see Figure 3). No CD117 immunoreactive cells were identified ruling out CNS germinoma. CNS lymphoma was ruled out with appropriate stains. The consulting oncologist recommended chemotherapy as an outpatient.

Additional workup during hospital stay revealed panhypopituitarism. Dexametha-sone was discontinued post-extubation and the 8 am cortisol level, more than 48 hours later, was 1.0 mcg/dl indicating adrenal insufficiency. FSH and LH were low at 0.7 µU/mL and 0.2 µU/mL respectively, which in a post-menopausal female was suggestive of pituitary dysfunction. TSH was 0.07 µU/mL and free T4 was 1.0 ng/dL presenting a picture of central hypothyroidism. The dose of levothyroxine was changed from 50 mcg intravenously daily to her home dose of 112 mcg daily by mouth. Physiological hydrocortisone replacement was started at 20

mg in the morning and 10 mg in the evening. DI was treated with a maintenance dose of DDVAP 0.2 mg by mouth twice daily. Eventually she underwent rehabilitation and was discharged home.

After discharge, the patient was treated with chemotherapy. Following treatment, she had about 33% shrinkage of the tumor size on MRI. Her visual symptoms have resolved but she continued to have pan-hypopituitarism and was on adequate pituitary hormone supplements.

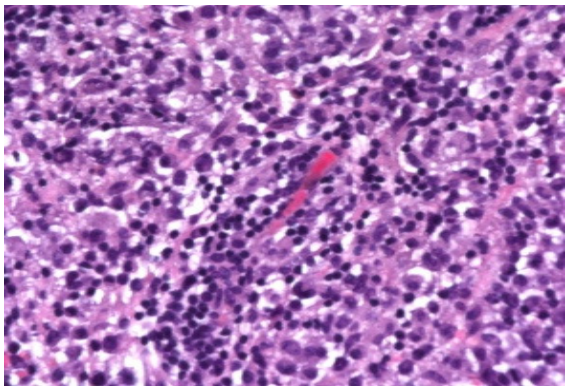

Figure 2. Numerous Langerhans cells were confirmed immunohistochemically (anti-CD1a, original magnification x200).

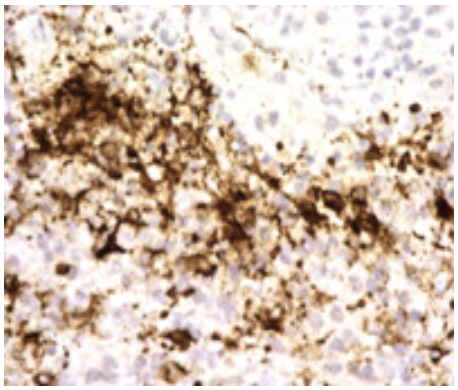

Figure 3. A biopsy from the suprasellar mass contained patchy areas of a cellular lymphohistiocytic infiltrate, including scattered Langerhans cells with typical C-shaped nuclei.

Discussion

LCH is a rare disorder characterized by idiopathic proliferation of specialized bone marrow derived Langerhans cells. LCH may be systemic or localized and its clinical manifestations are variable. In adults, infiltration is seen most frequently in bones (52%), lungs (40%), and skin (7%); whereas involvement of liver, spleen, lymph nodes and bone marrow is less frequent.[4,13,14] In view of the non-specific symptoms, LCH usually is misdiagnosed or under diagnosed.

This case was unique as her symptoms of LCH were related only to pituitary involvement. The patient had symptoms of DI for a few years, but the diagnosis was delayed until the patient had symptoms from the pituitary mass including headache and visual complains. By then, the patient had lost anterior and posterior pituitary hormone functions including antidiuretic hormone, thyroid, gonadotropic hormones, and cortico-trophin hormones. The long mean time from symptom onset to diagnosis was due, in part, to lack of clinical suspicion related to the low incidence of the disease.

Diagnosis of LCH is based on electron microscopy or immunohistochemistry (positivity for S100 protein and CD1a). Treatment is based on the extent and site of disease involvement. Options include conservative therapy with topical steroids, hormone replacement therapy, or local excision versus aggressive therapy including radiation, chemotherapy, anti-CD1a mono-clonal antibodies and/or organ or stem cell transplantation.[15-17]

This report attempted to identify evolution of pituitary dysfunctions, histopathological picture, and progress of the disease. Health care professionals should be aware of LCH as a possible cause of DI. An increased awareness could lead to early

diagnosis and treatment before more permanent damage occurs. The quality of life may be impaired by long-term sequelae including orthopedic problems, deafness, pituitary insufficiency, neurological defects, and impaired liver function. Most reported cases have systemic involvement.[8,15] Patients that initially present with DI have had subsequent abnormalities of other pituitary hormones that might take a few years to manifest. Thus, an increased suspicion and evaluation of other anterior pituitary hormone dysfunction on initial evaluation and follow-up are needed.

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Keywords: Langerhans cell histiocytosis, headache, case report

Editor's Note

The following article, **Margaret Mitchell's Lost Letter to a Kansas Horse & Buggy Doctor,** by Jane F. Knapp, M.D. and Robert D. Schremmer, M.D., provides a glimpse into the history of medicine in Kansas. It was published originally in **Missouri Medicine** in the November/ December 2011 issue. We appreciate Dr. John Hagan, Editor of **Missouri Medicine**, for allowing the Kansas Journal of Medicine to reprint it.

PERSPECTIVE FEATURE

Arthur Hertzler at his desk. Courtesy of the Kansas Learning Center for Health.

Margaret Mitchell's Lost Letter to a Kansas Horse & Buggy Doctor

by Jane F. Knapp, MD
& Robert D. Schremmer, MD

The correspondence of Arthur Emanuel Hertzler, MD, included an unpublished letter from *Gone With the Wind* author Margaret Mitchell. In it she offers reasons why she never wrote a second novel.

A career in medicine is a journey that can take many paths. A few years ago, inspired by a poster symposium at the annual Pediatric Academic Societies meeting, we got hooked on exploring the history of Midwestern pediatrics. Specifically, we wanted to focus on people and events relating to children's health care in our home states of Missouri and Kansas.[1-4] In 2010, we decided to profile Arthur Emanuel Hertzler, a small town Kansas physician who in his day enjoyed an international reputation following the publication of his 1938 bestseller *The Horse and Buggy Doctor*.[5]

Once we started our research, information on Hertzler's life and in particular the pediatric aspects of his practice weren't hard to find. He started his medical career in Halstead, Kansas, on May 1, 1895, the same day a tornado hit the town.[6] His practice was varied, broad, and spanned over 50 years. He cared for all the common childhood ailments of the time and quite frequently performed, "kitchen table surgery" on children and adults alike. His stories on the ravages of diphtheria are chilling and his account of the house call he made to drain an empyema on a 14-year-old boy is as graphic and dramatic as anything we might encounter today.[5] He was a prolific writer who kept records on all his patients and authored 20 medical textbooks, several in popular literature and over 100 scientific papers. Our studies of his books and collected papers from the Clendening History of Medicine Library at the University of Kansas School of Medicine uncovered a man of strong opinions and rambling prose who never shied away from speaking his mind in public or in print.

The last step in our research was a journey to Halstead, population 2085 (www.halsteadks.com). We wanted to spend time talking to the locals, see the place where Hertzler built a clinic and a hospital, and review the remaining archives on his life now stored at the Kansas Learning Center for Health (KLCH).

Halstead is a three-hour drive southwest of Kansas City into farm country. Entering the town on Kansas Highway 89, renamed the Hertzler Memorial Highway, we found a typical small Midwestern community. Grain elevators bordered Main Street and flanked the inevitable railroad tracks. A water tower rose in the distance framed by nothing more than the vivid blue expanse of cloudless prairie sky.

The KLCH is in a new building just down the road. It was founded through the Hertzler Research Foundation by Dr. Irene Koeneke, Hertzler's wife. We were warmly greeted and showed to the piles of scrapbooks and boxes stacked for our visit on a table next to the 4 ft high eyeball

exhibit. It was quiet because there weren't any school tours that day; a perfect time for poring through old records.

It didn't take long to discover the letter from Margaret Mitchell on her personalized stationary dated September 7, 1944. (See Figure 1, next page.) Our first thoughts inevitably were, "*The Gone With the Wind* Margaret Mitchell?" It was soon apparent that it was indeed *the* Margaret Mitchell, and that she was a fan as she put it "of Hertzler's pungent writing style." Based on our collective knowledge of Arthur's writing, we easily related. The letter was obviously from one writer to another and typified her special talent as a storyteller. She began by referring to Hertzler's book *Ventures in Science of a Country Surgeon*.[7] Toward the end of the book, in a chapter entitled, "The Writing of Books," he notes that he had been introduced to Margaret Mitchell, and described her as, "the most remarkable person I have ever met." [7]

Margaret Mitchell, circa 1941.
Source: U.S. Library of Congress.

The next to last paragraph piqued our curiosity. In her letter, Margaret Mitchell tells Arthur Hertzler why, as of 1944, she had not written another book. On further reading we learned that biographers have well chronicled her father Eugene Mitchell's ill health, protracted decline and Margaret's immersion in his care.[8,9] They have also recounted multiple other stressors, including her struggle to cope with the notoriety and complexities of her life following the publication of *Gone With the Wind*, her own poor health, and her husband's frailty. Interestingly, after her death in 1949 her husband and brother wrote to her correspondents requesting that they destroy her letters[9] but Arthur had died in 1946 soon after retirement. That letter, tucked away in Kansas for decades, provides the opportunity to revisit Margaret's thoughts on writing again with the clarity and poignancy of her own words. In a touch of irony she ended by urging him to write more.

The letter from Margaret Mitchell wasn't the only find. There was a copy of a letter from Albert Einstein dated June 24, 1944, in which he thanks Hertzler for sending him a copy of *The Grounds of an Old Surgeons Faith*.[10] A retinue of the 1941 Chicago Cubs sent a letter autographed by players, coaches, the manager, trainer, and newspapermen thanking him for the steaks he supplied to their dining car during a train trip through Wichita. They also sent along a thick packet of autographed individual and group pictures; there's a good one of Dizzy Dean. Fellow Kansan Karl Menninger sent a letter congratulating Hertzler on his career achievements when Arthur retired in 1946. The letters left us flush with the thrill of discovery, but also struck by this sturdy and enduring form of communication much richer in composition than the hastily deleted e-mails and superficial texts and tweets of today.

Ultimately, the most rewarding part of this journey into history was the visit to Halstead. For it was there that we gained an understanding of Arthur Hertzler, the person behind the books. Before we left we viewed the glass display cases filled with memorabilia in the back of the museum. There among the old medical instruments was a large leather bound copy of *De Humani Corporis Fabrica Libri Decem* the anatomy text by Adriani Spigelii (also known as Adriaan van den Spiegel), published in Venice in 1627.[11] From signatures in the front of the book it appears to have once been owned by Franz Leydig. Hertzler was a serious student of anatomy. In 1899, he took a two-year hiatus from his practice to study anatomy and surgical pathology with Virchow and Waldeyer in Berlin. In the *Horse and Buggy Doctor* he writes of his great respect for his teachers and notes that, "no American teacher ever showed me the many favors that many of these German professors did." [5] We saw the picture of his beloved daughter, Agnes, the black-eyed girl that he refers to several times in *The Horse and Buggy Doctor*. Agnes, we learned through personal communication with KLCH staff, died at 18 during an appendectomy being performed by her father. The story of her tragic death supplied the heretofore

MARGARET MITCHELL

Atlanta, Georgia
September, 1944

Dear Doctor Hertzler:

Last night I began picking about in "Ventures in Science of a Country Surgeon," for I have the bad habit of never starting a book at the beginning and reading it to the end. As a child I was reproved for picking all the raisins out of puddings and eating them first, and I have not improved much since then. After eating the raisins I always ate all the pudding, too, so I could never understand why my practice was reprehensible. While putting in my fingers to pull out a medical raisin, whom should I find but myself. To say I was surprised is a very great understatement. To say I was pleased and flattered at what you said is such an understatement I scarcely have the courage to put it down. I ate this raisin immediately and enjoyed it very much and thank you so much for your forthright remark.

I not only get information from your medical books but I get vast entertainment. I do not know anyone who writes as pungently as you do. Nor do I know anyone who can use a meat exe on the pompous or the misguided or the overstuffed with such deadly aim. I know I should not get so much pleasure and laughter from books as serious as yours, but I do and must confess it. I think you must be an extraordinarily able teacher with never a dull moment in your classes, for you have a vigorous mind and you certainly speak it.

I had enjoyed Chronic Appendicitis enormously, for I have the rare good luck of having an old fashioned doctor for a friend and I have heard him express himself in similar terms on this same subject. I read parts of it to my husband, who listened with interest equal to mine. Then, picking about in the section, Ventures in Therapeutics, my eyes fell upon the words "sciatica and compressed nerves." I read this section aloud, too, and I cannot tell you how enchanted my husband and I were by what you wrote. I would like to say that I "rolled on the floor" at your remarks about the specialists and their work upon the spine, but, dear Doctor, I do not roll on the floor these days, nor roll anywhere, because I am one of those people who had my intervertebral disks worked on eighteen months ago and am in far worse shape than before. However, I suppose that I am mentally in fine condition, for I can laugh about this section of your book when too deep a laugh is not very pleasant. The doctor who yanked out my disk is inviting me back to the hospital to do the operation over, and when he issues his next invite I think I'll quote him, line and page, from your book. After I had read my husband the part about you and the hash and the stomach pump and the cardia, he had to take off his glasses and wipe them because he had laughed till he had cried. He said that you must be one of the most remarkable people in shoe leather to be able to make your point about the strength of these muscles with such vividness. "The Doctor is a salty cuss," he said, "and you certainly were lucky to meet him. I only wish I had the chance to know him myself."

I did not write you after I had read your book on the "Diseases of the Thyroid Gland," but it was not through lack of interest. I read it slowly and with care, harassing the old fashioned friend I mentioned above for meanings of medical terms and explanations of surgical technique which no layman can know. That is an impressive volume, impressive especially when I think of the many years' study and thought which went into making it. If you had no other monument except this it would be a greater monument than most men can ever hope for, but here you go along writing other books just as good!

I had intended to write you about the thyroid book, but my father died in June and I did not have time or the heart. He had been ill so long---six years in all, and the last three in the hospital. He would not have a kidney stone removed many years ago when he was in excellent health and he delayed far too long in having a prostatic operation. Three years ago we did not expect him to live another week, and for his sake I wish it had been that way. He had the constitution of an ox and just how he stayed alive his doctors did not know. I'm sure you've seen uremia and abscessed kidneys and toxemia and pneumonia enough so that I do not have to tell you what those years were. When people ask why I have not written another book, I look at them in wonder, for how can one do creative work in a constant worry like this or when physical fatigue reaches the point of exhaustion every day. I hope that my own health will improve now that I do not have to bend over high hospital beds or fix pillows or lift or strain. I've had it on my mind so often to thank you for that book, for I really got a lot out of it.

You do not fool me at all and I do not think you are fooling yourself by your statement in the front of your "Ventures"---"this is probably my last book." I know there'll be plenty of others.

Cordially,
Margaret

missing perspective into Arthur's pungent writing style. It also provided us insight into the personal loss that we now understood, from other papers we examined at the KLCH, haunted him throughout his life.

Our poster on *The Life and Times of a Kansas Horse and Buggy Doctor and His Recollections on the Care of Children* was presented at the 2011 Pediatric Academic Societies Meeting.[12] It focused on Arthur's professional career as a physician on the Kansas prairie in a time when it took stamina and grit to reach your patients and skill, experience and ingenuity once you got there. It recounted stories of his care for children whom he said, "always came first."[5] But, our poster didn't tell the less public story we found preserved in the letters, scrapbooks, displays and oral history of Halstead. It seemed a shame not to share it.

Hertzler Memorial Highway sign on the outskirts of Halstead, KS. Photo by R. Schremmer, MD.

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Acknowledgment

The authors would like to acknowledge the assistance of Brenda Sooter, Executive Director, the staff and the Board of Directors of the Kansas Learning Center for Health for their assistance in our research and the preparation of this manuscript.

Figure 1 (opposite page)
Scanned copy of Margaret Mitchell's letter to Author Hertzler. Courtesy of the Kansas Learning Center for Health. Recreated for Missouri Medicine.

Jane F. Knapp, MD, MSMA member since 1989, is Chair or the Department of Medical Education and Associate Chair of Pediatrics at Children's Mercy Hospitals and Clinics in Kansas City, and Associate Dean at the University of Missouri-Kansas City School of Medicine. Robert D. Schremmer, MD, is Associate Professor of Pediatrics in the Division of Emergency Medicine and Urgent Care Services at UMKC.
Contact: jknapp@cmh.edu

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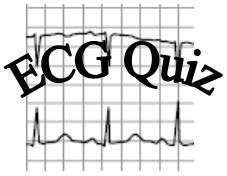
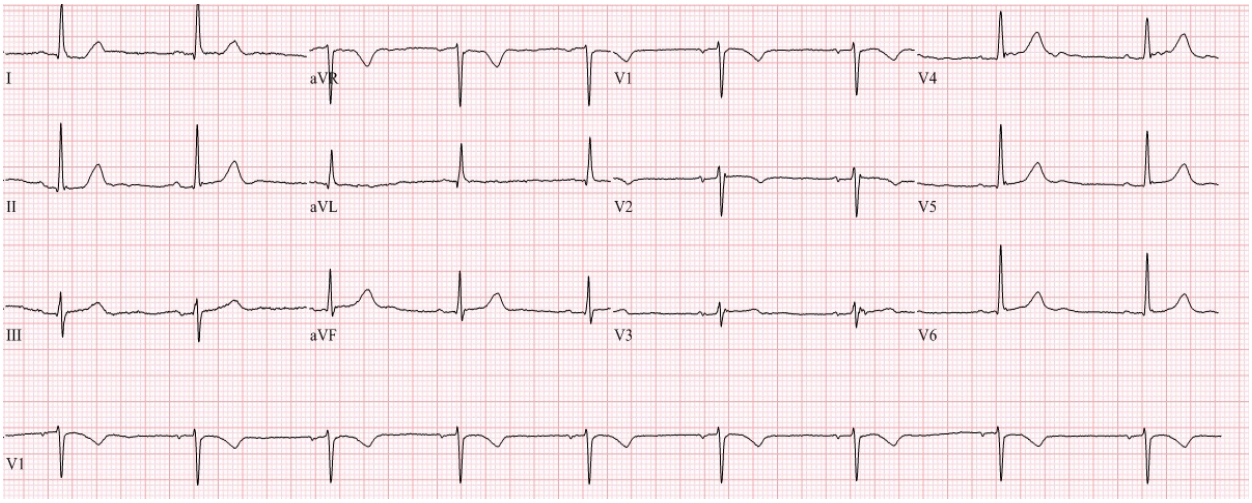


Quick or Slow Rhythm?

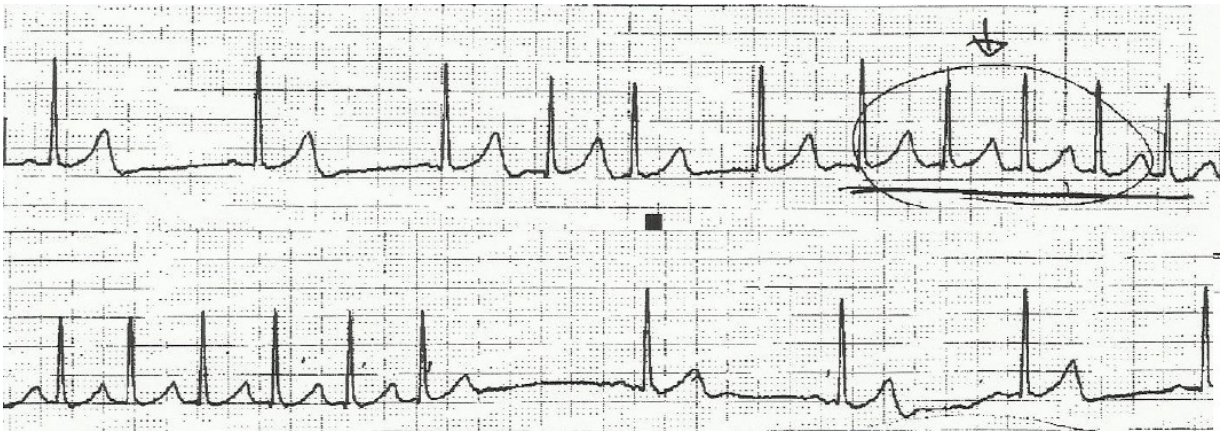
Elie Chalhoub, M.D.[1], Wassim Shaheen, M.D.[1,2],
Boutros El-Haddad, M.D.[1]
[1]University of Kansas
School of Medicine-Wichita
Department of Internal Medicine
[2]Heartland Cardiology, Wichita, KS

A 74-year-old Caucasian male presented with recurrent pre-syncopal episodes. He reported having diaphoresis as a prodrome, then feeling "about to lose consciousness" without actual loss of consciousness. These symptoms occurred more frequently in the past three weeks. He reported no visual disturbances, and the duration of each episode was only a few minutes. He denied any history of recent head trauma. He denied chest pain, palpitations, shortness of air, or orthopnea. His physical examination revealed normal heart sounds with no murmurs. Bradycardia (55 bpm) was present. Otherwise, the physical exam was unremarkable, including normal orthostatic vitals. Labs showed a normal complete blood count and comprehensive metabolic panel. His thyroid-stimulating hormone level was 9.3 μIU/ml and his free thyroxine and free triiodothyronine levels were normal.

The initial ECG:



Telemetry while asymptomatic and sleeping:



What is the diagnosis?

A) Supraventricular tachycardia
B) Atrial fibrillation
C) Variable AV block
D) Tachycardia-bradycardia syndrome - Sick sinus syndrome

Answer on next page…

Correct Answer: D

Sick sinus syndrome (sinus node dysfunction) is a group of cardiac rhythm disturbances characterized by abnormalities of the sinus node including: (1) sinus bradycardia, (2) sinus arrest or exit block, (3) combinations of sinoatrial or atrioventricular conduction defects, and (4) alternating paroxysmal supraventricular tachyarrhythmias (tachycardia-bradycardia syndrome) that result in atrial rates that are inappropriate for physiologic needs.[1] Table 1 shows the intrinsic and extrinsic factors in the etiology of sick sinus syndrome.

Treatment of sick sinus syndrome is directed at symptoms.[2] Some patients may benefit from antiarrhythmic drugs and beta-blockers. Indications for pacemaker insertion are summarized in Table 2. Our patient underwent a permanent pacemaker insertion. At one-month follow-up, he reported resolution of his pre-syncope and absence of other significant cardiovascular symptoms.

Table 1. Etiology of sick sinus syndrome.[3]

Intrinsic	Extrinsic
Hypothyroidism	Trauma, including cardiac surgery
Fibrocalcific degeneration	Drugs - Calcium channel blockers
Increased vagal tone	- Beta-blockers
Congenital mutations	- Digoxin
Scleroderma	- Antiarrhythmics
Amyloidosis	- Lithium
Chagas disease	

Table 2. Indications for pacemaker insertion for patients with sinus node dysfunction.[2]

Class I indications
Documented symptomatic bradycardia, including frequent sinus pauses that produce symptoms (level of evidence: C)
Symptomatic chronotropic incompetence (level of evidence: C)
Symptomatic sinus bradycardia that results from required drug therapy for medical conditions (level of evidence: C)
Class IIa recommendations
Heart rate greater than 40 bpm when a clear association between significant symptoms consistent with bradycardia and the actual presence of bradycardia has not been documented (level of evidence: C)
Syncope of unexplained origin when clinically significant abnormalities of sinus node function are discovered or provoked on electrophysiological studies (level of evidence: C)
Class IIb recommendations
Minimally symptomatic patients with chronic heart rate greater than 40 bpm while awake (level of evidence: C)
Class III recommendations
Permanent pacemaker implantation is <u>not</u> indicated for sinus node dysfunction in asymptomatic patients (level of evidence: C)
Permanent pacemaker implantation is <u>not</u> indicated for sinus node dysfunction in patients for whom the symptoms suggestive of bradycardia have been clearly documented to occur in the absence of bradycardia (level of evidence: C)
Permanent pacemaker implantation is <u>not</u> indicated for sinus node dysfunction with symptomatic bradycardia due to non-essential drug therapy (level of evidence: C)

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Keywords: sick sinus syndrome, electrocardiography, presyncope