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ABSTRACT & COMMENTARY

Studies Find Cognitive Decline Reversible, Even if Patients Are ApoE4 Positive

By Joseph E. Scherger, MD, MPH

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Dr. Scherger reports no financial relationships relevant to this field of study.

SYNOPSIS: Insulin resistance is associated with cognitive decline and Alzheimer's disease. Patients who are positive for the apolipoprotein E4 gene are at increased risk for Alzheimer's disease. This risk may be reversed by treating insulin resistance.

SOURCE: Johnson LA, Torres ER, Impey S, et al. Apolipoprotein E4 and insulin resistance interact to impair cognition and alter the epigenome and metabolome. *Sci Rep* 2017;7:43701.

The incidence of cognitive decline and Alzheimer's disease is increasing parallel with the increase in insulin resistance and type 2 diabetes.[1] Researchers are establishing a causative association between these conditions.[2] Treating insulin resistance and normalizing blood sugar may reverse cognitive decline and early Alzheimer's disease.[3]

Patients who test positive for the apolipoprotein E4 (ApoE4) gene demonstrate an increased incidence of Alzheimer's disease.[4] Johnson et al studied mice and the biological connection of the ApoE4 gene and insulin resistance. The presence of insulin resistance produces cognitive changes in ApoE4-positive mice, which is reversible if insulin resistance is resolved through dietary change.

■ COMMENTARY

2017 was a breakthrough year for understanding and treating cognitive decline and Alzheimer's disease. Previously, this condition was thought to be irreversible. Three credible books, published between August and November 2017, were about research on nutrition and other lifestyle measures to reverse

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cognitive decline in separate clinical trials.[2,5-6]

Dale Bredesen, MD, is a visiting professor of neurology at UCLA and founding president of the Buck Institute for Research on Aging. His protocol for preventing and reversing cognitive decline is called ReCODE (reverse cognitive decline). ReCODE calls for at least 12 hours of daily fasting to achieve nutritional ketosis and a healthy Mediterranean diet of nuts, seeds, and vegetables, including avocado, olive oil, and wild caught fish. The book covers foods in detail, along with the supplements Bredesen recommends.[2] Other parts of the protocol are exercise, sleep, and stress reduction. Bredesen's research regarding reversing Alzheimer's disease has been published since "patient zero" in 2014.[7]

Dale Sherzai, MD, and Ayesha Sherzai, MD, are neurologists at Loma Linda University. Co-directors of the Brain Health and Alzheimer's Prevention Program at Loma Linda University Medical Center, they developed the NEURO (Nutrition, Exercise, stress reduction [Unwind], Restorative sleep, and Optimize brain function) protocol, which is similar to ReCODE. Patients also engage in multiple cognitive exercises.[5] NEURO differs from ReCODE in that NEURO is a whole food, plant-based diet (vegan or vegetarian). The creators of ReCODE and NEURO made similar discoveries, which means patients could use ReCODE, NEURO, or possibly a combination of each.

Daniel Amen, MD, is a psychiatrist who operates six clinics that treat various brain diseases. He has written many articles and books and uses imaging and comprehensive testing to design treatment protocols. His latest book, *Memory Rescue: Supercharge Your Brain, Reverse Memory Loss, and Remember What Matters Most*, is about an approach that includes nutrition, some supplements, and lifestyle adjustments.[6]

Reversing cognitive decline is a game changer for medicine. No longer do clinicians simply help patients and families cope with a progressive disease that is irreversible. Intensive low-carbohydrate and anti-inflammatory nutrition and lifestyle change are skill sets that have become vitally important to good primary care practice. ■

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BRIEF REPORT

L-methylfolate for Bipolar Disorder

By David Kiefer, MD

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Dr. Kiefer reports no financial relationships relevant to this field of study.

SYNOPSIS: L-methylfolate improves some symptoms in major depression in people with type 1 bipolar disorder.

SOURCE: Nierenberg AA, Montana R, Kinrys G, et al. L-methylfolate for bipolar I depressive episodes: An open trial proof-of-concept registry. *J Affect Disord* 2017;207:429-433.

L-methylfolate (LMF) is surfacing as a treatment for many health conditions, but the details remain: Who would most benefit, for which diagnoses, and what is the best dose? There is a dearth of methodologically sound clinical trials to help answer these questions, but the researchers of this proof-of-concept study begin the process of adding important clinical data to the fund of knowledge.

This study was an extension of prior placebo-controlled research showing that 15 mg of LMF daily can lead to improvements in symptoms of major depression.[1] This treatment approach had not been extended to depression in people with bipolar disorder, although such depression can be just as debilitating and associated with polypharmacy. Thus, although potential adjunctive therapies are necessary, they are limited. The research participants were adults who had to be on a maintenance medication (mood stabilizer or atypical antipsychotic) for type 1 bipolar disorder. The participants could not be taking antidepressant medications, yet per a scale (Mini International Neuropsychiatric Interview) had to be classified as having major depression. There was also a long list of exclusion criteria, including (interestingly) no history of multivitamin use within the last 12 weeks or dietary supplements with known central nervous system effects.

The 10 participants who satisfied the inclusion and exclusion criteria received 15 mg daily of LMF and continued on their bipolar medication for six weeks. Visits with the study clinicians occurred every two weeks for six weeks. Numerous tools were used to quantify symptoms of mania, depression, and overall functioning, as well as life satisfaction and bipolar severity. Baseline scores of these measures and final mean scores were tallied and compared using Cohen's d statistical analysis (to establish the effect size). Of the 10 original participants, nine made it to week 4, and eight finished the six-week trial. Of all the measures, researchers highlighted that the Montgomery-Åsberg Depression Rating Scale (MADRS), a score of 9 or lower indicating remission, decreased significantly ($P = 0.027$) from a baseline of 23.4 to 13.9 at six weeks (effect size 1.19).

Researchers also mentioned that the Quick Inventory of Depression Symptomatology-Self Report improved by 35% with an effect size of 0.92, although no P values were provided. Also, other scales hinted at improvements in cognition, functioning, and suicidal ideation; again, P values were not indicated for the numbers provided. There was a low baseline level of mania per the Young Mania Rating Scale, but one patient showed a worsening of manic symptoms and possibly a manic episode. On this note, a large list of side effects were followed; it is unclear whether the changes noted between baseline and study endpoint were statistically significant. The most common side effects were dry mouth, headache, and fatigue. This was an open-label, uncontrolled study. Obviously, clinicians need a placebo-controlled, randomized trial to abscribe the findings here to LMF. That goes for the benefits seen and the side effects described (most alarming was the possible manic episode).

[Methylene tetrahydrofolate reductase polymorphisms may decrease the formation of 5-methyltetrahydrofolate, a methyl donor in the formation of methionine from homocysteine.]

I wonder about the demographic, those people with major depression associated with type 1 bipolar disorder who currently receive adequate treatment for their depressive symptoms. These patients may indeed represent a psychiatric need and, should LMF prove to be safe and effective, LMF might be able to provide such patients some relief. There is some prior clinical work on depression that would support the results seen here, and the mechanism is plausible and compelling. The researchers cited work showing that LMF modulates and increases monoamine neurotransmitters, such as dopamine, serotonin, and norepinephrine. Furthermore, it appears to freely cross the blood-brain barrier, and addresses the fact that those people suffering from depression are more likely to possess polymorphisms in the methylene tetrahydrofolate reductase (MTHFR) gene, which LMF can bypass and more directly affect physiological processes. More specifically, MTHFR polymorphisms may decrease the formation of 5-methyltetrahydrofolate, a methyl donor in the formation of methionine from homocysteine.[1] This irregular folate metabolism and build-up of homocysteine seems to correlate with (cause?) an expanding list of conditions, including major depression,[1] multiple sclerosis,[2] chronic kidney disease,[3] cardiovascular disease,[3] and infertility.[4] ■

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BRIEF REPORT

Newer Guidelines for Influenza Testing This Season

By Carol A. Kemper, MD, FACP

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Dr. Kemper reports no financial relationships relevant to this field of study.

SOURCES: California Department of Public Health. Testing and treatment for patients hospitalized with suspected influenza. Oct. 2, 2017.

Merckx J, Wali R, Schiller I, et al. Diagnostic accuracy of novel and traditional rapid tests for influenza infection compared with reverse transcriptase polymerase chain reaction: A systematic review and meta-analysis. *Ann Intern Med* 2017;167:394-409.

As we approach flu season, I like to remind providers that rapid influenza diagnostic tests are imperfect — and before ordering a rapid flu test, consider the likelihood of a positive result. Do they plan to treat the patient or the test result?

Merckx et al performed a meta-analysis of more than 162 diagnostic studies, comparing the diagnostic accuracy and sensitivity of rapid influenza diagnostic tests (RIDTs) with immunoassays (DIAs) and nucleic acid amplification tests (NAATs) in children and adults with influenza-like illness (ILI). The overall results confirm what we already know: RIDTs are helpful in providing a rapid result for many patients, but false-negative results are common. Pooled sensitivities for detecting Influenza A using RIDTs were 54%, compared with 80% for DIAs and 91.6% for NAATs. Pooled sensitivities for detecting Influenza B were similar: Using RIDTs, they were 53%, compared with 77% for DIAs and 95% for NAATs. Pooled sensitivities generally were higher in pediatric patients compared with adults. Keep in mind that false negatives are common when flu is more frequent in your community. False positives are more common when flu is less frequent.

The California Department of Public Health and the CDC have recommended that, regardless of the results of prior rapid influenza testing, empiric therapy with a neuraminidase inhibitor should be administered promptly to patients hospitalized with ILI or suspected influenza, and not necessarily discontinued simply because an RIDT result may be negative. NAAT testing or RT-PCR testing should be performed in all suspect cases, and many hospitals maintain an RT-PCR panel for respiratory virus, which can be helpful. Although treatment has shown the greatest benefit when initiated within 48 hours of onset of illness, evidence supports the administration of antiviral therapy when begun later than 48 hours in those hospitalized with severe flu. ■

BRIEF REPORT

Travelers Unaware of the Need for Pre-travel Vaccinations

By Carol A. Kemper, MD, FACP

Clinical Associate Professor of Medicine, Stanford University, Division of Infectious Diseases, Santa Clara Valley Medical Center

Dr. Kemper reports no financial relationships relevant to this field of study.

SOURCE: Hyle EP, Rao SR, Jentes ES, et al. Missed opportunities for measles, mumps, rubella vaccination among departing U.S. adult travelers receiving pre-travel health consultations. *Ann Intern Med* 2017;167:77-84.

Outbreaks of measles continue to occur in the United States, mostly because of imported cases. More than half of these occur as the result of inadequately vaccinated returning U.S. travelers who acquire measles infection abroad. And the problem is not limited to those returning to the United States. On any given day, only 86% of persons at Disneyland have received MMR vaccine, far below the threshold for herd protection in the event of an outbreak. The recent measles outbreak at Disneyland in 2014-2015 resulted in 125 measles

infections, 110 of which occurred in Californians. Nearly half (45%) were unvaccinated, most for non-medical exemption.

Investigators surveyed 54,100 departing U.S. adult travelers for measles immunity and eligibility for MMR between 2009 and 2014. Travelers were evaluated at one of 24 sites with Global TravEpiNet, which is a consortium of travel clinics, 14 of which are based at academic centers and 10 at primary care practices, public health facilities, or pharmacies. Travelers born before 1957 were considered immune and excluded from analysis (n = 13,290 adults). Of those remaining, the median age was 33 years (range, 26-44 years). The most common travel destinations included Africa (35%) or Central or South America (28%), and the median duration of planned travel was two weeks. Most travelers born after 1957 were deemed to be measles-immune (84%), based on a history of receiving two doses of measles vaccine (73%), serologic testing (10%), and/or a history of measles infection (3%), and/or provider judgment (18%). Only a small number (0.3%) were ineligible for vaccination for medical reasons. The remaining 16% were eligible for MMR. MMR was offered to anyone eligible for vaccination; 53% did not receive MMR during their visit. The most common reason was patient refusal (48%). In 28% of cases, vaccination was not provided based on provider decision — 94% of the time because the provider thought the vaccine was unnecessary and 6% of the time because of insufficient time before travel. "Health system barriers" were listed as the reason for non-vaccination in 24% of cases, largely due to referral to an outside provider. For the 1,698 travelers who refused the vaccine, three-fourths indicated they were "not concerned about illness," 20% were concerned about vaccine safety, and a small percentage (6%) were concerned about vaccine cost.

Many travelers remain unaware of the risks of illness abroad and the need for good travel advice and immunization. Too often, I've argued with patients who weigh the imagined risk of illness against the inconvenience and expense of vaccination, and lost the argument. This survey also demonstrates that at least one-fourth of missed MMR vaccine was the result of provider decision, suggesting travel clinic providers would benefit from additional education about the benefits and need for MMR vaccination in eligible travelers. ■

PHARMACOLOGY UPDATE

Buprenorphine Extended-release Injection (Sublocade)

By William Elliott, MD, FACP, and James Chan, PharmD, PhD

Dr. Elliott is Assistant Clinical Professor of Medicine, University of California, San Francisco.
Dr. Chan is Associate Clinical Professor, School of Pharmacy, University of California, San Francisco.

Drs. Elliott and Chan report no financial relationships relevant to this field of study.

The FDA has approved the first once-monthly injectable buprenorphine, a partial opioid agonist, for the treatment of moderate-to-severe opioid use disorder. Buprenorphine is formulated in a biodegradable polymer and biocompatible solvent (Atrigel) designed to deliver the drug at a controlled rate over a one-month period after subcutaneous administration. The FDA assigned this product a priority review and a fast-track designation. It is marketed as Sublocade.

INDICATIONS

Buprenorphine extended-release injection is indicated for the treatment of moderate-to-severe opioid use disorder in patients who have initiated treatment with a transmucosal buprenorphine-containing product, followed by dose adjustment for a minimum of seven days.[1] The manufacturers recommend using the product as part of a complete treatment program that includes counseling and psychosocial support.

DOSAGE

The recommended dose is two monthly subcutaneous injections of 300 mg, followed by 100 mg monthly maintenance doses.[1] The maintenance dose may be increased to 300 mg monthly if benefits outweigh risks.

The product should be prepared and administered by a healthcare provider. Buprenorphine extended-release injection is available as prefilled syringes of 100 mg/0.5 mL and 300 mg/1.5 mL.

POTENTIAL ADVANTAGES

Buprenorphine extended-release injection provides another treatment option that reduces the burden of daily medications. It can be used for patients on up to 24 mg/day of transmucosal buprenorphine. The previously approved buprenorphine implant is only for patients on transmucosal buprenorphine doses < 8 mg/day.[2]

POTENTIAL DISADVANTAGES

Serious harm or death could result if buprenorphine extended-release injection is administered intravenously as a solid mass develops on contact with body fluids, which may cause occlusion, local tissue damage, or thromboembolic events, including life-threatening pulmonary emboli.[1] Other side effects (5-8.5%) include constipation, nausea, vomiting, headache, drowsiness, injection site pain/itching, and elevation of liver enzymes.[1]

COMMENTS

Buprenorphine extended-release injection was evaluated in an opioid blockade study and a randomized, double-blind, placebo-controlled, 24-week, efficacy and safety study in subjects with moderate-to-severe opioid use disorder.[1] In the blockade study, 39 subjects who were stabilized with 8-24 mg/day of sublingual buprenorphine, were challenged with placebo (weeks 1-4), followed by intramuscular 6 mg and 18 mg of hydromorphone (weeks 5-12) after an injection of buprenorphine extended-release injection at the start of weeks 1 and 5. The peak effect of "drug-liking" behavior was assessed based on a 100-point visual analog scale using a noninferiority margin of < 20 (i.e., hydromorphone not substantially more likeable than placebo by this margin). Results indicated noninferiority in "drug liking" between buprenorphine extended-release injection and placebo. Complete blockage was observed throughout the eight weeks of observation after the second injection.

In the efficacy trial, subjects (n = 504) were randomized to six monthly 300 mg injections, two once-monthly 300 mg doses, followed by four once-monthly injections of 100 mg for buprenorphine extended-release, or six once-monthly placebo injections. All subjects were controlled on sublingual buprenorphine/naloxone and received manual-guided, individual psychosocial support at least once a week. Efficacy was assessed over weeks 5-24 based on weekly urine drug screens and self-reported use of illicit opioid use. A "grace period" for weeks 1-4 was allowed for stabilization in treatment. Missing data were counted as positive use. Over 20 weeks, the proportions achieving success (≥ 80% opioid-free weeks) were 28.4%, 29.1%, and 2% for placebo, respectively.

CLINICAL IMPLICATIONS

More than 2.5 million Americans suffer from opioid use disorder.[3] Currently recognized effective medication treatments include buprenorphine, methadone, and extended-release naltrexone. Buprenorphine extended-release injection provides another option to sublingual tablets and subcutaneous implants for opioid dependence. It is only available through a restricted program called the SUBLOCADE REMS program.[1] Healthcare settings and pharmacies that order and dispense the product must be certified and comply with the REMS requirements. Cost was not available at the time of this review. ■

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CME QUESTIONS

1. **These nutrition elements are part of diet to prevent and reverse cognitive decline *except*:**
   a. vegetables.
   b. olive oil.
   c. nuts.
   d. whole wheat.

2. **Which of the following is true about the use of l-methylfolate for depression in people with type 1 bipolar disorder?**
   a. The dose used was 15 milligrams daily.
   b. None of the subjects suffered any side effects.
   c. It seemed to increase MADRS scores after six weeks.
   d. Unfortunately, there was an increase in suicidal ideation in the cohort studied.

Clinical Briefs

By Louis Kuritzky, MD

Diuretic Use in Heart Failure

SOURCE: Ellison DH, Felker GM. Diuretic treatment in heart failure. *N Engl J Med* 2017;337:1964-1975.

Diuretics are employed in heart failure for symptom control, but they are not disease-modifying; that is, in contrast to angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, beta-blockers, aldosterone antagonists, hydralazine/isosorbide, and valsartan/sacubitril, each of which has demonstrated meaningful reductions in mortality in heart failure clinical trials, diuretics are employed solely for improved patient quality of life. Perhaps that helps explain why there is remarkably less clinical trial data specifically focused on diuretic therapies for heart failure.

Two areas in which knowledge about best diuretic use is particularly important are acute decompensated heart failure and the scenario of diuretic resistance. For patients with acute decompensated heart failure, a trial comparing twice-daily furosemide IV boluses vs. continuous infusion (using low-dose and high-dose regimens) did not demonstrate any statistically significant difference for the coprimary endpoint of the patient's global assessment of symptoms. However, secondary endpoint outcomes, which must be regarded as hypothesis-generating rather than definitive since the primary outcome was not achieved, tended to favor high-dose regimens regarding dyspnea, weight change, and net fluid loss.

For diuretic resistance, the authors endorsed continuous diuretic infusion with stepwise dose increases to achieve a 3-5 liter/day urine volume until euvolemia is achieved. The modest amount of clinical trial data to assist clinicians in choosing doses of diuretics, mode of administration, and target fluid losses suggests that much more information is needed. ■

Sexual Dysfunction Among Diabetics

SOURCE: Owiredu WKBA, Alidu H, Amidu N, et al. Sexual dysfunction among diabetics and its impact on the SQoL of their partners. *Int J Impot Research* 2017;29:250-257.

Among diabetic men, the pathophysiologic derangements leading to sexual dysfunction are evident. Neuropathy and vascular disease (microvascular and macrovascular) readily explain the disproportionate incidence of observed sexual dysfunction. Explanations for sexual dysfunction in diabetic women, some of whom also have exhibited a higher incidence of sexual dysfunction than age-matched, non-diabetic comparators, are more difficult to discern.

Of the topics related to sexual health, there is less research on the partner impact of sexual dysfunction. Encouragingly, interventions that restore erectile capacity in men (e.g., phosphodiesterase type 5 inhibitors, intracavernosal injection therapy, and vacuum constriction devices) have been associated with corresponding improvements in partner quality of life, albeit not without occasional partner reports of unwelcome improvements in erectile capacity, sometimes labeled "Viagravation."

In a review of diabetic men (n = 130) and diabetic women (n = 116), evaluations of sexual quality of life in both genders was meaningfully affected by partner sexual dysfunction. Perhaps not surprisingly, age and duration of diabetes were the strongest predictors of sexual dysfunction in diabetic men. The authors opined that insufficient attention has been given to the presence and effect of sexual dysfunction on the quality of life of patients and their partners. ■

When Gastrointestinal Complaints Are *Not* Prominent

SOURCE: Paez MA, Gramelspacher AM, Sinacore J, et al. Delay in diagnosis of celiac disease in patients without gastrointestinal complaints. *Am J Med* 2017:130:1318-1323.

Most clinicians think of celiac disease as primarily a gastrointestinal disorder. Hence, when patients present with typical symptoms (e.g., persistent non-acute abdominal pain, diarrhea) not explained by other disorders, identification of celiac disease by screening for anti-transglutaminase antibodies usually follows. But what about when the gastrointestinal symptom profile of celiac disease is not a prominent part of the picture? Manifestations of celiac disease can be as far reaching as anemia, osteoporosis, abnormal thyroid function tests, and abnormal liver function tests, none of which may produce an immediate prompt to consider celiac disease as the etiology.

Paez et al reviewed data on patients with biopsy-proven celiac disease (n = 101) treated at the Loyola University Medical Center. Patients who presented with gastrointestinal symptoms exhibited a median time to diagnosis of 2.3 months, compared to 42 months for those without gastrointestinal symptoms. While celiac disease certainly is not the most common cause of anemia, osteoporosis, abnormal liver function tests, or abnormal thyroid function tests, these results suggest that clinicians should think of celiac disease earlier in the differential diagnosis process, since the aforementioned consequences are largely remediable through appropriate dietary restrictions. ■

Internal Medicine [ALERT]

ECG Review

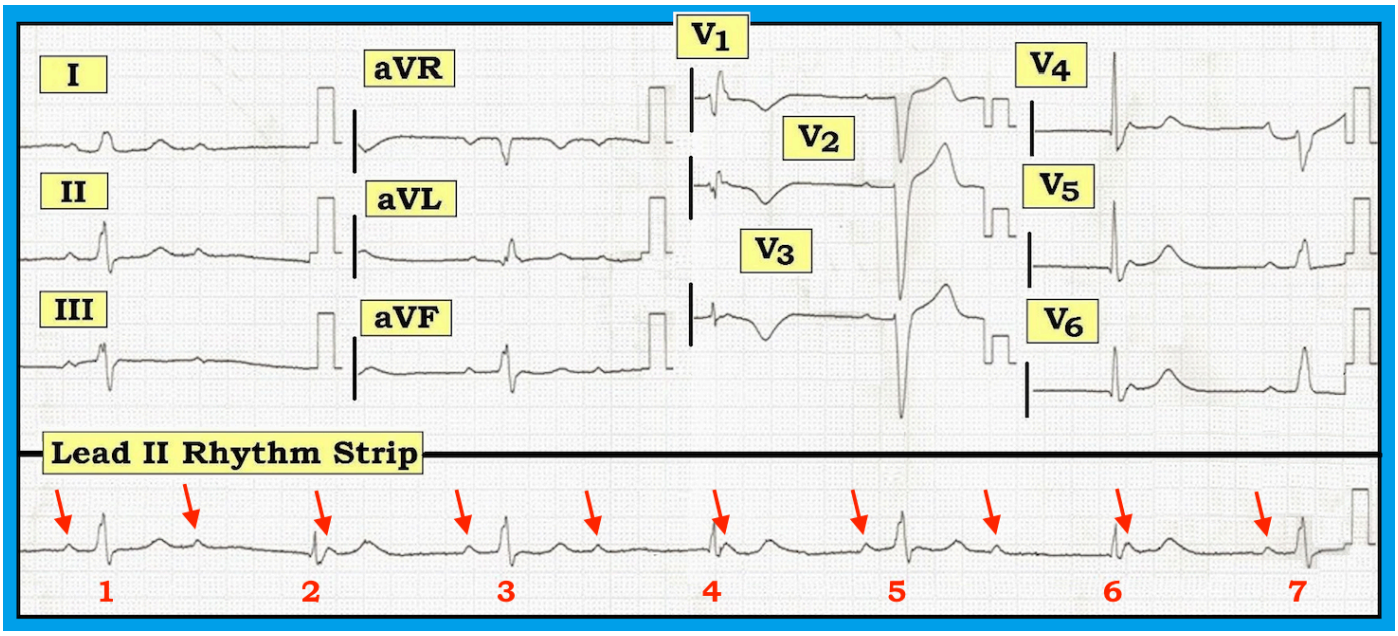
By Ken Grauer, MD

Professor Emeritus in Family Medicine, College of Medicine, University of Florida

Dr. Grauer is the sole proprietor of KG-EKG Press, and publisher of an ECG pocket brain book.

How Many Conduction Defects?

The ECG and long lead II rhythm strip in the figure below was obtained from a 58-year-old man who was admitted to the hospital with chest pain and weakness. How would you interpret this tracing? How many different types of conduction disturbances can you identify?



This is a complex tracing. That said, attention to some basic principles of arrhythmia interpretation go a long way toward deciphering the mechanism of this rhythm. We proceed as follows, focusing first on the long lead II rhythm strip at the bottom of the figure.

It is often easiest to begin by identifying atrial activity. Using calipers greatly facilitates this task. Red arrows in the figure reveal that the underlying atrial rhythm here is quite regular. In contrast, the ventricular rhythm is not regular. Instead, there is a pattern of "group beating," with alternating long-short R-R intervals. Two different shapes of QRS complexes are evident. That is, the QRS complex of beats 1, 3, 5, and 7 looks similar. A different-shaped QRS is evident for beats 2, 4, and 6.

Some P waves are conducting. Note that the PR interval preceding beats 1, 3, 5, and 7 is constant, albeit slightly prolonged (i.e., slightly more than one large box = 0.20 second in duration). Therefore, the P waves preceding beats 1, 3, 5, and 7 are conducting with first-degree AV block. A look at simultaneously recorded lead I (for beat 1), lead V1 (for beat 5), and lead V6 (for beat 7) suggests that in addition to first-degree AV block, these P waves are conducting with left bundle branch block (LBBB). Beats 2, 4, and 6 occur later than expected and are not preceded by P waves. Since the R-R interval preceding each of these QRS complexes is similar and longer than the R-R interval preceding the sinus-conducted beats, this defines beats 2, 4, and 6 as escape beats arising from either the AV node or the bundle of His. A look at simultaneously recorded lead V1 (for beat 4) and lead V6 (for beat 6) suggests that these beats manifest as right bundle branch block (RBBB) morphology. Some form of second-degree AV block is present, because many of the P waves are not conducting. But because some P waves are conducting, this is not complete (i.e., not third-degree) AV block.

It is impossible to be certain from this single tracing whether this form of second-degree AV block tracing represents Mobitz I (i.e., AV Wenckebach) or Mobitz II because we never see two P waves in a row that conduct to the ventricles. Nevertheless, the conduction disturbance seen here is severe since there is first-degree AV block, some form of second-degree AV block, and alternating bundle branch blocks in the form of LBBB for conducting beats and RBBB for escape beats. Additionally, the deep, symmetric T wave inversion that is maximal in lead V3 (see beat 4) is more than one expects to see in lead V3 when there is RBBB. This means ischemia and/or recent infarction probably has occurred. The chances are good that a pacemaker will be needed.

For more information about and further discussion on this case, please visit: http://bit.ly/2z3T6iD.