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INSIDE

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Testing for Influenza

ABSTRACT & COMMENTARY

By Allan J. Wilke, MD

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

Synopsis: *Rapid influenza diagnostic tests have modest sensitivity and high specificity.*

Source: Chartrand C, et al. Accuracy of rapid influenza diagnostic tests: A meta-analysis. *Ann Intern Med* 2012;156:500-511.

THERE ARE THREE MAIN WAYS OF TESTING FOR INFLUENZA: VIRAL CULTURE (VC), reverse transcriptionase polymerase chain reaction (RT-PCR), and immunochromatographic assays. The latter are often called rapid influenza diagnostic tests (RIDTs), which reflects their chief advantage — their results are generally available in 15 to 30 minutes. VC was the original gold standard, but suffers from long delay between acquisition of samples to results, 3 to 10 days. RT-PCR has replaced VC as the gold standard because it has the highest sensitivity and specificity. However, it is also the most expensive, and results are available in hours rather than minutes. Immunofluorescence (IF) and enzyme-linked immunosorbent assays (ELISA) are other less commonly used methods. Of the various types of tests, then, RIDTs would appear to be the most clinically useful, assuming that they are accurate. Chartrand and colleagues performed a meta-analysis to determine RIDTs' accuracy.

Searching PubMed, EMBASE, BIOSIS, and Web of Science, the investigators found 286 articles that met their inclusion criteria: RIDT accuracy compared to VC, RT-PCR, or both. They excluded articles that compared their accuracy to IF or ELISA. After initial review, 119 articles remained and formed the basis for the meta-analysis.

Pooled sensitivity was 62.3% (range, 4.4% to 100%). Pooled specificity was 98.2% (range, 50.5% to 100%). In subgroup analysis, RIDTs were more sensitive in children (66.6%) vs adults (53.9%); there was no difference in specificity. RIDTs were more sensitive in detecting

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influenza A than B (64.6% vs 52.2%, respectively). There was no significant difference in their ability to detect influenza A (H3N2), the usual strain that circulates in North America compared to influenza A (H1N1), the 2009 pandemic strain ("swine flu"). The type of respiratory sample and the type of person collecting it (lab tech vs office personnel) did not influence results. However, the timing of collection did, with a tendency for collection on day 2 or 3 of symptoms to be more sensitive than day 1. Industry-sponsored studies reported higher sensitivities than those without that support (pooled sensitivity 73.3% vs 59.4%). When specific brands were studied, Directigen Flu A® had the highest pooled sensitivity (76.7%). QuickVue Influenza® was second at 69.0%. BinaxNOW,® Directigen Flu A+B®, and QuickVue A+B® were all less sensitive at 57.0%, 57.2%, and 48.8%, respectively. Specificities were all > 95%.

■ COMMENTARY

The influenza-like illness (ILI) case definition used by the Centers for Disease Control and Prevention (CDC) for national surveillance is fever > 100° F (37.8° C) and cough and/or sore throat (in the absence of a known cause other than influenza).[1] Of course, the problem with this definition is that there are many ILIs that present with a fever and cough or sore throat. Some are viral and some are bacterial. The sensitivity and specificity of fever and cough for influenza are 64% and 67%, respectively.[2] The sensitivity of a symptom history then is greater than that for RIDTs. (Reminder: Sensitivity measures the true positive rate, and specificity the true negative rate.) The CDC has published a RIDT algorithm that advises their use in people who present with signs and symptoms consistent with influenza and where "the results of influenza virus testing [will] change clinical care of the patient (especially for hospitalized patients and those with high-risk conditions) or influence clinical practice for other patients."[3]

One of the actions you might consider is prescribing a neuraminidase inhibitor (NI), oral oseltamivir (Tamiflu®), or inhaled zanamivir (Relenza®). However, the efficacy of NIs has been called into question.[4] The best offense though remains a good defense: yearly vaccination.

One could speculate why industry-sponsored studies had better results than independent studies, but I won't. The authors reason that the fact that children carry higher viral loads than adults explains why the sensitivities are higher in them. They invoke similar reasoning to explain the better results on day 2 or 3 vs day 1: we shed more viruses on those days. They caution against reading too much into the differences between brands since no head-to-head studies have been performed.

This has been a strange influenza season with a very late start, low total activity, and already a decrease in activity.[5] While it appears that the season may have already peaked, the CDC does not want us to become complacent and warns, "Sporadic influenza outbreaks continue to occur." ■

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The Changing Paradigm in Estimating the Risk of Cardiovascular Disease

ABSTRACT & COMMENTARY

By Rahul Gupta, MD, MPH, FACP

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

Synopsis: *The lifetime risk of cardiovascular disease is strongly influenced by risk factor burden and may be similar across race and birth cohorts.*

Source: Berry JD, et al. Lifetime risks of cardiovascular disease. *N Engl J Med* 2012;366:321-329.

THE FRAMINGHAM RISK SCORE (FRS) IS OFTEN UTILIZED in clinical practice to estimate an individual's 10-year absolute risk for developing coronary heart disease (CHD).[1] Currently, the identification of risk status in persons without clinically manifest CHD or other forms of atherosclerotic disease is clinically determined by an overall two-step process. First, the number of risk factors, including measuring serum cholesterol, is counted. Second, for persons with multiple risk factors, a 10-year risk assessment is carried out with FRS to identify individuals whose short-term (10-year) risk warrants consideration of intensive treatment. By this method, appropriate persons can be targeted for drug therapy as primary prevention of CHD. However, by focusing on short-term risk, the FRS may inherently underestimate the lifetime cardiovascular risk in certain individuals, such as the younger population, who may feel otherwise falsely comforted in a good score and therefore may either not work to mitigate their existing risk factors or develop new ones. As a result, individuals categorized as low or intermediate 10-year risk for CHD may actually be at greater risk in the longer term.

Estimating lifetime risk rather than short-term risk may communicate the actual progressive cumulative risk of developing a disease during the remainder of an individual's life. In public health policy, lifetime risk estimates are often used to convey risk information about diseases such as cancers. This concept has also been used in the design of public health education campaigns for specific cancers in the general population, leading to early screening and diagnosis. Similar estimates of the lifetime risk of cardiovascular disease in individuals can provide a more comprehensive assessment of the overall burden of disease in population.

In their study, Berry et al utilized existing data from 18 cohort studies involving a total of 257,384 men and women (black and white) whose risk factors for cardiovascular disease were measured at the ages of 45, 55, 65, and 75 years. Their meta-analysis used blood pressure, cholesterol, diabetes, and smoking status to stratify participants according to risk factors into five mutually exclusive categories.

The researchers observed that among men and women who were 55 years of age, the higher burden of risk factors was associated with a much higher lifetime risk of death from cardiovascular disease. Those with an optimal risk-factor profile had a lower (4.7% in men; 6.4% in women) risk of death from cardiovascular disease through the age of 80 years compared to those with two or more major risk factors (29.6% in men; 20.5% in women). Those participants with an optimal risk-factor profile also had a lower (3.6% in men; < 1% in women) risk of fatal CHD or nonfatal myocardial infarction through the age of 80 years compared to those with two or more major risk factors (37.5% in men; 18.3% in women). Parallel trends were also observed for fatal or nonfatal stroke. Additionally, trends were similar among blacks and whites and across different birth cohorts. The authors found that a relatively low burden of these risk factors was associated with significant increases in the long-term risk of cardiovascular disease whereas the absence of such traditional risk factors was associated with a very low lifetime risk.

■ COMMENTARY

When describing the lifetime likelihood of developing cardiovascular disease in an individual, the presence or absence of traditional risk factors may be the most significant determinant. However, currently used tools for assessing such risk (FRS) may not adequately describe the lifetime cardiovascular disease burden in all individuals equitably. For example, individuals with multiple risk factors and an estimated 10-year CHD risk of > 20% are categorized as high risk and typically require drug therapy and therapeutic lifestyle changes to reach an LDL cholesterol goal of < 100 mg/dL.[2] Similarly, individuals with an estimated 10-year CHD risk of 10-20% are categorized as moderately high risk and therapeutic lifestyle changes are recommended with an option for lipid-lowering therapy if LDL cholesterol is > 130 mg/dL. Individuals with an estimated 10-year CHD risk below 10% are considered moderate risk and therapeutic lifestyle changes are recommended with an option for lipid-lowering therapy only if LDL cholesterol is > 160 mg/dL. However, individuals with 0 to 1 risk factors are considered to be in the low-risk category and thus therapeutic lifestyle changes may be the only recommendation for many individuals. Such "low-risk" characterization may mislead such individuals to consider that it is not imperative to modify their risk factors. As a result, these individuals' persisting risk factors would significantly contribute to development of atherosclerosis over their lifetime. This increase in the overall burden of cardiovascular disease has significant clinical and public health implications. It is clear from existing studies that a decline in cardiovascular event rates in the general population is much more attributable to changes in the prevalence of risk factors rather than the effects of treatment.[3,4] Therefore, the lifetime estimations of an individual's risk for cardiovascular disease may allow the development of suitable public health policies that would lead to lifestyle changes resulting in lowering of this burden by not only modification of the existing risk factors (such as cholesterol) but also prevention of the develop-

ment of additional risk factors (diabetes, hypertension, smoking). ■

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Advice Ignored on Acute Mountain Sickness

ABSTRACT & COMMENTARY

By Brian G. Blackburn, MD, and Michele Barry, MD, FACP

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This article originally appeared in the February issue of Travel Medicine Advisor. *At that time it was peer reviewed by Lin Chen, MD, Assistant Clinical Professor, Harvard Medical School; Director, Travel Medicine Center, Mt. Auburn Hospital, Cambridge, Mass. Dr. Chen reports no financial relationships relevant to this field of study.*

Synopsis: *A retrospective survey of 744 Dutch and Belgian travelers who had ventured to 2500 m (8200 feet) or higher revealed that 25% developed acute mountain sickness. Only half of this group had followed pre-travel advice regarding altitude sickness, and few took preventive acetazolamide.*

Source: Croughs M, et al. Acute mountain sickness in travelers who consulted a pre-travel clinic. *J Travel Med* 2011;18:337-343.

ACUTE MOUNTAIN SICKNESS (AMS) IS A SYNDROME THAT CAN affect travelers who are not acclimatized and gain altitude too quickly, usually occurring above 2500 m (8200 feet) elevation. Typical symptoms include headache, nausea, dizziness, sleeplessness, anorexia, and fatigue. Although usually benign, life-threatening high altitude cerebral or pulmonary edema (HACE or HAPE) can result if the syndrome is allowed to progress. Pharmacologic treatment and prophylaxis (e.g., acetazolamide) are efficacious,[1-3] but perhaps the most important preventative measure is halting ascent at the onset of any AMS symptoms. In addition, if symptoms worsen while travelers rest at the same altitude, they must descend. Predeparture counseling regarding the symptoms and risks of AMS is critical for decreasing the risks of this potentially serious illness.

Consensus guidelines have been published regarding the prevention and treatment of altitude sickness.[4,5] These suggest limiting daily ascent to a maximum of 500 m (1600 feet) for activities above 2750 m (9000 feet), adding one acclimatization day for every 1000 m (3300 feet) elevation gained above this altitude, and initiating acetazolamide prophylaxis in certain specific situations.[4,5] The authors undertook a retrospective survey of adult travelers to high altitude that were seen at one of four travel clinics in the Netherlands and Belgium before their trip. These patients were given specific written and oral instructions about AMS during the visit, and written surveys regarding AMS were then mailed to all patients after their return.

Overall, 744 persons that slept > 1 night above 2500 m (8200 feet) were included in the study. The age range was 17-76 years (mean, 36); most traveled to South America (74%) or Asia (18%). The maximum sleeping altitude averaged 3950 m (13,000 feet). Above an altitude of 2500 m (8200 feet), 43% of people climbed more than 500 m (1600 feet) per day.

While 658 respondents (88%) read the information they received about AMS from the travel clinic, 160 (22%) did not understand instructions regarding the use of acetazolamide. Although 541 (72%) brought acetazolamide with them, only 116 (16%) took it for AMS prevention; the median dose among such users was 125 mg twice daily (median course, 4 days). Sixty-six (9%) had suffered from AMS previously, and these individuals took acetazolamide prophylaxis twice as frequently as those who had never suffered from AMS (29% vs 14%).

Overall, 184 respondents (25%) had symptoms during their trip that met the definition of AMS; 76% of these resolved within three days. Eighty-seven (47%) continued climbing despite their AMS symptoms, and one-quarter of these individuals experienced some exacerbation of their symptoms. One-hundred two (55%) symptomatic patients took acetazolamide for treatment of AMS (median 375 mg total daily dose for 3 days). Several travelers reported that they did not think their symptoms were severe enough to warrant acetazolamide, or that they were uncertain regarding when they should begin taking it.

■ COMMENTARY

This retrospective survey of high-altitude travelers who had received advice about AMS from travel clinics before their journey yielded interesting descriptive results. The

overall rate of AMS for travelers to this altitude was generally similar to past studies, despite the advice given by the travel clinics.[6,7] As has been demonstrated in other settings, predictors of AMS included a past history of AMS, a higher maximum altitude, and spending fewer nights acclimatizing. Younger age and female sex were demographic factors associated with a higher risk of AMS; past studies have been mixed on the relationship of these factors to the development of AMS.[6,7]

The troubling finding in this study was the strikingly low compliance rate of travelers with the advice they received about AMS. Despite care at travel clinics specifically geared towards addressing the risks of AMS, 43% of travelers climbed more than 500 m (1600 feet) per day when above 2500 m (8200 feet), and only 16% took acetazolamide for prophylaxis of AMS. Of even greater concern, almost half of patients with symptoms of AMS continued to climb. Although the ambitious, fixed itineraries trekkers and climbers frequently embark upon may mean that compliance with advice regarding AMS will always be problematic, improvement of counseling protocols might help alleviate this.

For example, advice might focus on the risks of developing HACE or HAPE if patients continue to ascend with symptoms of AMS, guidelines for the use of acetazolamide might be made clearer, and patients could be advised to build more flexibility into itineraries, so that travelers with AMS might be more likely to rest and acclimatize rather than continuing to ascend. Although the best means to achieve these goals remains uncertain, advice should probably be communicated both orally and in writing, in a standardized manner for all patients. If it seems that unsafe ascent remains likely in a particular patient despite such advice, recommendations regarding inclusion of at least one companion who is trained in the management of altitude sickness, and who would carry pharmacologic (e.g., dexamethasone) and non-pharmacologic (e.g., a Gamow bag for HACE or HAPE) therapy for AMS and its complications might also be considered.

A surprising finding of this study was the apparent ineffectiveness of acetazolamide prophylaxis. The median dose used (125 mg twice daily) was less than the previously recommended prophylaxis dose (250 mg twice daily), and earlier studies did suggest that higher doses were necessary to effectively prevent AMS.[8] However, more recent randomized studies in multiple settings have demonstrated the efficacy of 125 mg twice daily for preventing AMS,[1-3] and this is now the recommended dose in several consensus guidelines.[4,5] While acetazolamide also appeared ineffective at alleviating symptoms of AMS in this study, the dose used (375 mg total daily dose) was lower than the currently recommended dose (250 mg twice daily) for AMS treatment. Use of acetazolamide for treatment of AMS was also erratic in this cohort, again resulting in selection bias.

While intriguing, the results of this study are insufficient to conclude that a change in the recommendations regarding acetazolamide use for AMS are necessary. The key contribution of this study is to increase awareness among travel medicine practitioners that their advice regarding AMS will not be followed by many high-altitude travelers, and that clinic practices may need to be adapted to this unfortunate reality of caring for such patients. ■

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Pharmacology Update

Sitagliptin and Metformin Extended-Release Tablets (Janumet® XR)

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

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

THE FDA HAS APPROVED AN EXTENDED-RELEASE, ONCE-daily, dipeptidyl-4 (DPP-4) inhibitor in combination with metformin for adults with type 2 diabetes. Janumet XR combines sitagliptin and metformin. The new combination is the second such product joining Kombiglyze XR, which combines saxagliptin and metformin. Janumet XR is marketed by Merck & Co., Inc.

Indications

Sitagliptin and metformin extended-release tablets

(SIT/MET ER) are indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus when treatment with both sitagliptin and extended-release metformin is appropriate.[1]

Dosage

The starting dose of SIT/MET XR should be individualized based on the patient's existing dosages and maintaining the same total daily dose of sitagliptin and metformin.[1] The dose may be titrated up to 100 mg of sitagliptin and 2000 mg of extended-release metformin. The dose should be taken once daily, preferably with the evening meal.

SIT/MET XR is available as 50 mg/500 mg, 50 mg/1000 mg, and 100 mg/1000 mg tablets.

Potential Advantages

SIT/MET XR provides a once-daily formulation involving two drugs with different and complementary mechanisms of action. Fixed-combination medications reduce pill burden and may improve adherence in some patients.[2]

Potential Disadvantages

There have been postmarketing reports of worsening renal function in patients taking sitagliptin with or without metformin as well as reports of acute pancreatitis.[1] The fixed combination limits the flexibility of dose titration.

Comments

As with the combination of saxagliptin and metformin XR, SIT/MET XR was also approved based on bioequivalence of the fixed combinations and coadministration of the individual drugs.[1,3] There were no clinical studies conducted with SIT/MET XR per se. The combination of SIT/MET XR provides greater HbA1c reduction than either agent alone. In a double-blind, placebo-controlled, 24-week study as initial treatment in type 2 diabetics with a mean baseline HbA1c of 8.8%, sitagliptin 100 mg and metformin 2000 mg daily showed a placebo-adjusted reduction of HbA1c of 2.1%, (95% confidence interval [CI], -2.3, -1.8) compared to sitagliptin, -0.8% (CI, -1.1, -0.6) and metformin, -1.3% (CI, -1.5, -1.1).[1,4] The addition of sitagliptin 100 mg to patients inadequately controlled on metformin doses of at least 1500 mg daily produced a placebo-adjusted reduction -0.7% (CI, -0.8, -0.5) in HbA1c.[1]

Clinical Implications

SIT/MET XR is the second extended-release formulation of a DPP-4 inhibitor and metformin. There are no known advantages of the combination over the saxagliptin/metformin XR formulation. The consensus panel of the American Association of Clinical Endocrinologists/American College of Endocrinology stated that these combinations are preferable to sulfonylurea/metformin or thiazolidinedione/metformin in patients at risk for hypoglycemia and/or weight gain.[5] DPP-4/metformin combinations provide benefit similar to sulfonylurea/metformin in lowering postprandial glucose but less benefit in lowering fasting glucose levels.[5] ■

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CME Objectives

Upon completion of this educational activity, participants should be able to:

- describe new findings in the differential diagnosis and treatment of various diseases;
- describe the advantages, disadvantages and controversies surrounding the latest advances in the diagnosis and treatment of disease;
- identify cost-effective treatment regimens;
- explain the advantages and disadvantages of new disease screening procedures.

CME Questions

1. **Which statement is correct regarding rapid influenza diagnostic tests?**
   a. They have greater pooled sensitivity than pooled specificity.
   b. They are more sensitive in children than adults.
   c. They are more sensitive for influenza B than influenza A.
   d. They perform better in the hands of lab techs than office personnel.
   e. They perform better on day 1 than day 2 of symptoms.

2. **In the study by Berry et al, which one of the following statements is *false*?**
   a. Differences in risk-factor burden translate into differences in lifetime risk of cardiovascular disease.
   b. Decline in cardiovascular event rates in the general population depends more on reducing risk factors than effects of treatments.
   c. With similar risk factor profiles, there is higher lifetime cardiovascular mortality in blacks compared to whites.
   d. Lifetime estimates of cardiovascular risk may provide more comprehensive data on disease burden in the general population than short-term risk scores.

Clinical Briefs

By Louis Kuritzky, MD, Clinical Assistant Professor, University of Florida, Gainesville

Dr. Kuritzky is an advisor for Endo, Kowa, Pricara, and Takeda.

Donepezil and Memantine for Moderate-Severe AD

Source: Howard R, et al. *N Engl J Med* 2012;366:893-903.

The choice of if and when to employ pharmacotherapy in the management of Alzheimer's disease (AD) is not an easy one. Early in the disease process (mild-moderate AD) — where clinical trials have demonstrated beneficial outcomes, albeit of debatable clinically relevant magnitude — clinicians and caregivers may be least motivated to treat, since disease status is relatively less problematic and measureable benefits are smaller. In moderate-severe AD, memantine (MEM) has demonstrated beneficial effects. A single, never-replicated trial of the addition of MEM to donepezil (DON) in mild-moderate AD had favorable outcomes. Data on whether cholinesterase inhibitors provide improved outcomes as the disease progresses to the moderate-severe stages have been lacking. Indeed, there is some support for discontinuation of cholinesterase inhibition when AD progresses to the severe stage.

Howard et al randomized patients (n = 295) with moderate-severe AD already on treatment with DON to one of four groups: continued DON alone, MEM alone, continued DON plus MEM, or placebo alone. Patients were followed for 1 year, measuring outcomes by means of the Standardized Mini-Mental State Examination (SMMSE) and Bristol Activities of Daily Living Scale (BADLS). The minimum clinically important difference on these scales is 1.4 points and 3.5 points, respectively.

At 1 year, scores in the group that continued DON were superior to the placebo group as measured by the SMMSE (1.9 points difference); on the BADLS, the score was statistically significantly improved but failed to meet the minimum clinically important difference threshold. Neither substitution of MEM for DON nor addition of MEM to DON provided clinically important improvement.

In moderate-severe AD, these data support continuation of DON, but not substitution or augmentation with MEM. ■

Treating Hyperhidrosis with Systemic Therapy

Source: Walling HW. *J Am Acad Dermatol* 2012;66:387-392.

Even though hyperhidrosis (HHD) has a prevalence almost three times as great as rheumatoid arthritis (± 3% vs ± 1%), clinician awareness and management of this disorder are often suboptimal. Although the palms of the hands and plantar surfaces of the feet are the most commonly involved sites, axillary, craniofacial, and multisite involvement is reported. The HHD disease severity scale describes moderate HHD as "tolerable but sometimes interferes with daily activities," and severe as "barely tolerable to intolerable, that frequently to always interferes with daily activities." HHD is not just a quality-of-life issue; skin infections are more common in HHD sufferers.

The mainstay of HHD treatment for several decades has been topical drying agents, especially with those containing aluminum chloride. Iontophoresis, botulinum toxin, and even sympathectomy have demonstrated some efficacy, but the expense and inconvenience of such interventions is an obstacle.

Walling performed a chart review of HHD patients seen in an academic department of dermatology who had received one of three systemic agents to treat HHD: glycopyrrolate, oxybutynin, or clonidine.

Glycopyrrolate was effective in 30 of 45 patients; among glycopyrrolate treatment failures, six of 15 were nonresponders, and nine had adverse anticholinergic effects (e.g., dry mouth). Clonidine was effective in six of 13 patients; among clonidine treatment failures, three were nonresponders and four experienced hypotension. A single patient responded favorably to oxybutynin (an anticholinergic typically used for overactive bladder).

Because no one treatment for HHD is uniformly effective, clinicians must become aware of alternative therapies. Previous literature has suggested that systemic treatments might not be well tolerated, yet efficacy in this data set was good with no serious adverse effects. Systemic treatments may help patients with HHD. ■

Can Male Pattern Baldness Predict BPH?

Source: Arias-Santiago S, et al. *J Am Acad Dermatol* 2012;66:401-408.

Aside from genetic influences, testosterone (TST) and dihydrotestosterone (d-TST) play an important role in both benign prostatic hyperplasia (BPH) and male pattern baldness (also known as androgenetic alopecia). For BPH, conversion of TST to d-TST by means of 5-alpha-reductase (5-AR) results in stimulus for prostate gland growth. In the prostate, 5-AR of both type 1 and type 2 are operant. 5-AR blockers (e.g., finasteride, dutasteride) have been shown to shrink prostate size.

In the scalp, only 5-AR type 2 is functional. In susceptible individuals, conversion of TST to d-TST in the scalp results in follicular diminution, producing hair loss. Might the same susceptibility to male pattern baldness be reflected in an increased incidence or severity of BPH?

Arias-Santiago et al compared metrics pertinent to BPH in men with and without early-onset male pattern baldness. Although there was no difference between groups in levels of testosterone, prolactin, other gonadal steroids, or testosterone-binding proteins, the men with early male pattern baldness had significantly greater levels of PSA, more lower urinary tract symptoms consistent with BPH, greater prostate gland size as measured by ultrasound, and lower urinary flow rates.

Clinicians may wish to look for BPH-related symptoms in men with early androgenetic alopecia. ■

Why All the P Waves?

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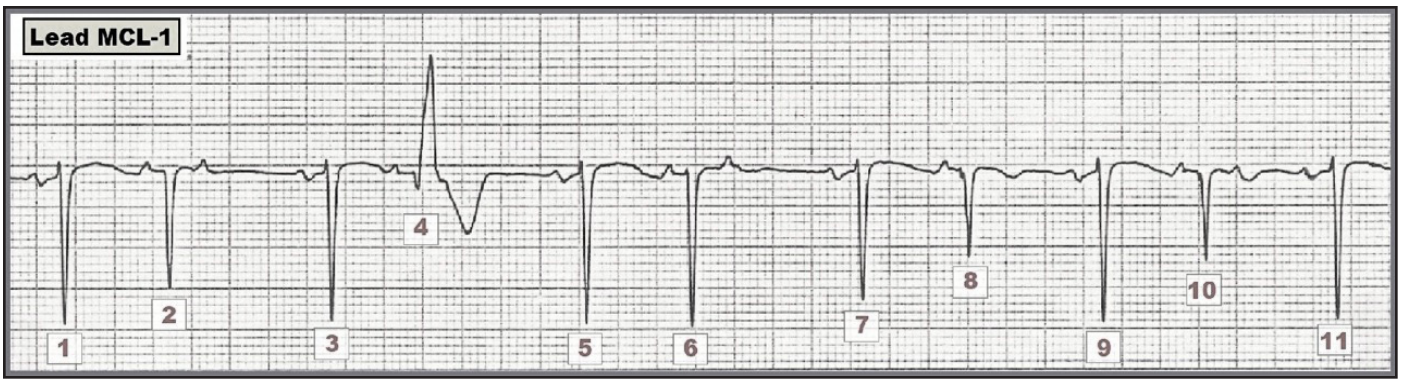

Figure — Right-sided MCL-1 monitoring lead rhythm strip. Can you explain the irregularity?

Scenario: Interpret the lead MCL-1 rhythm strip shown above. Can you explain the irregularity?

Interpretation: The easiest way to approach interpretation of challenging arrhythmias is to start with what is known. Save more difficult parts of the tracing until later. We always look first to see if there is an underlying rhythm. The underlying rhythm in the Figure is sinus, as determined by beats #1, #3, #5, #7, #9, and #11. Each of these beats is preceded by a similar-morphology biphasic P wave with fixed PR interval. All QRS complexes except for beat #4 are narrow. Note the interesting bigeminal periodicity of the rhythm with alternating short-long cycles. Every other QRS complex in this tracing occurs early. Every other QRS complex is a premature atrial contraction (PAC).

The rhythm in the Figure is, therefore, sinus with multiple PACs. We highlight a number of additional interesting points about this rhythm: 1) P wave morphology of each PAC is slightly different in being primarily positive compared to the biphasic P waves of each sinus beat. This is as it should be since PACs by definition originate from a different site in the atria than the sinus node. 2) Not all PACs are conducted. Note that no QRS complex follows the PACs that occur just after beats #2, #6, and #10. These PACs are "blocked" (nonconducted) because they arise so early in the cycle as to occur during the absolute refractory period when conduction to the ventricles from an impulse arriving early at the AV node is not possible. 3) The widened QRS complex (beat #4) is not a premature ventricular contraction. Instead, it too is a PAC conducted with aberration. Note that beat #4 is also preceded by a "telltale" premature P wave which confirms that this beat is an aberrantly conducted PAC. 4) In fact, beats #2, #4, #8 and #10 are all aberrantly conducted PACs! Normally, QRS morphology of PACs will be virtually identical to QRS morphology of sinus beats. PACs merely arrive earlier than anticipated at the AV node — but once there, they typically conduct to the ventricles in normal fashion. It is only when PACs arrive especially early (or when the relative refractory period is for some reason prolonged) that PACs may manifest aberrant conduction. 5) Beats #2, #4, #8, and #10 are all PACs that manifest different degrees of aberrancy. Of these beats, it is beat #4 that manifests the greatest degree of aberrant conduction (in the form of a complete right bundle branch block pattern). This makes sense because the coupling interval of the PAC preceding beat #4 (distance between this P wave and beat #3) is shorter than the coupling interval for the other PACs. The P wave preceding beat #4 therefore arrives earlier at the AV node at a time when it is more likely to encounter the conduction system in a relatively refractory state. In contrast, the coupling intervals of the P waves following beats #2, #6, and #10 are even shorter. Physiologically, the P waves following beats #2, #6 and #10 are presumably occurring during the absolute refractory period, which is why these PACs are "blocked." In summary, our interpretation of this lead MCL-1 rhythm strip is that it shows underlying sinus rhythm with multiple PACs that are either blocked or conducted with varying degrees of aberration. ■

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