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'Cardiac syndrome X' and coronary microvascular dysfunction

Revisiting the 'great masquerader'

The importance of serial ECGs

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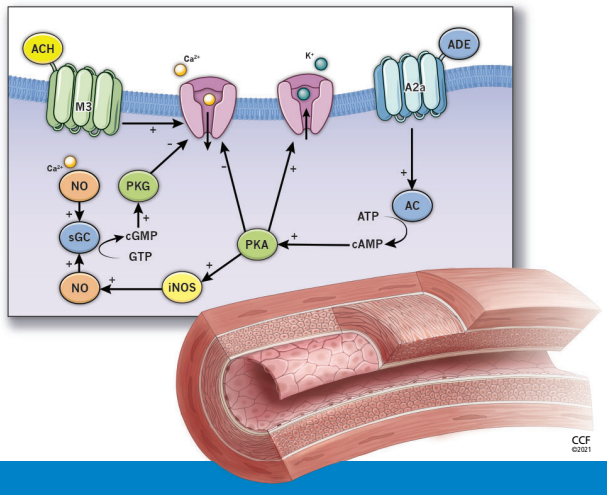
Rapid cognitive decline and myoclonus

Coronary microvascular dysfunction: Diagnosis and management



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We have a greater understanding of 'cardiac syndrome X,' but questions remain

There was a time when diagnosing coronary artery disease and managing its clinical expression of angina and myocardial infarction focused almost entirely on the lumens of the major coronary vessels. Culprit stenoses needed to be recognized and rectified, mainly via bypass or an endovascular procedure. Medical therapy was adjunctive or preventative. Improved understanding of the biologic nature of the stenosing plaque and proliferating and remodeling vascular tissue led to the implementation of still-evolving approaches directed at plaque stabilization and shrinkage, as well as antithrombotic and antiproliferative therapies. We also saw that some patients experienced classic angina with imaging or electrocardiographic evidence of myocardial ischemia and sometimes infarction in the absence of significant epicardial coronary artery obstructive lesions. The pathogenesis was unclear, and these patients were thus diagnosed as having "cardiac syndrome X." In current parlance, they have ischemia and no obstructive coronary artery disease (INOCA). Greater understanding of this condition, which can clinically mirror obstructive coronary artery disease (CAD) until coronary angiography is performed, has led to the recognition that many of these patients have coronary microvascular dysfunction (CMD).[1]

As discussed by Tjoe et al[2] in this issue of the *Journal*, INOCA-related syndromes are most commonly precipitated by coronary spasm or by CMD. Definitive diagnosis requires accurate epicardial coronary imaging to exclude significant obstruction and epicardial coronary spasm, and then physiologic assessment of the coronary microvasculature. Physiologic assessment, as Tjoe et al describe in detail, includes measurement of coronary flow reserve and interventional evaluation of endothelial function. These procedures may not be available in all catheterization laboratories.

CMD seems to be more common in women than men and is not benign, as it is associated with the presence or future development of atherosclerotic obstructive CAD. But even in the absence of coexistent obstructive CAD, there is an association with heart failure with preserved ejection fraction, with acute coronary syndromes, and with several comorbidities including diabetes, chronic kidney disease, and hypertension, and perhaps with some systemic inflammatory and autoimmune diseases.

As I was thinking through these associations and the independent role that CMD might play in clinical outcomes, I wondered if its more common presence in women (for reasons I do not fully understand) might contribute to the variably described protective effects of aspirin in women vs men, assuming a nonthrombotic pathophysiology for CMD. Perhaps CMD could also explain some of the increased cardiovascular risk, incompletely accounted for by traditional cardiac risk factors, attributed to autoimmune disorders such as rheumatoid arthritis and systemic lupus erythematosus—perhaps as a result of the effect of inflammatory cytokines or activated cells on regulatory control of the coronary microvasculature, in addition to the underlying biologic effects attributable to the female host. (Recall that these 2 conditions occur more commonly in women.)

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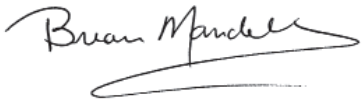
Another interesting observation regarding patients with CMD is that patients (66% female) initially screened for participation in the CIAO-ISCHEMIA trial[3] who had angina with ischemia but no coronary obstruction on angiography were followed over a year's time and underwent repeat stress echocardiographic testing along with angina questionnaires. The patients received medical treatment at the discretion of their physicians. After 1 year, the stress echo was normal in approximately half of the patients, and angina had improved in 43% and worsened in 14%, but the changes in imaging did not correlate with the changes in angina.[4] Apparently, we still have a lot to learn about the nature and expression of pain, even in a pain syndrome like angina, which we think we understand.



Brian F. Mandell, MD, PhD
Editor in Chief

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CME MOC

2021

OCTOBER

VIRTUAL NEPHROLOGY UPDATE
October 1
Live stream

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October 1
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2022

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Revisiting the 'great masquerader'

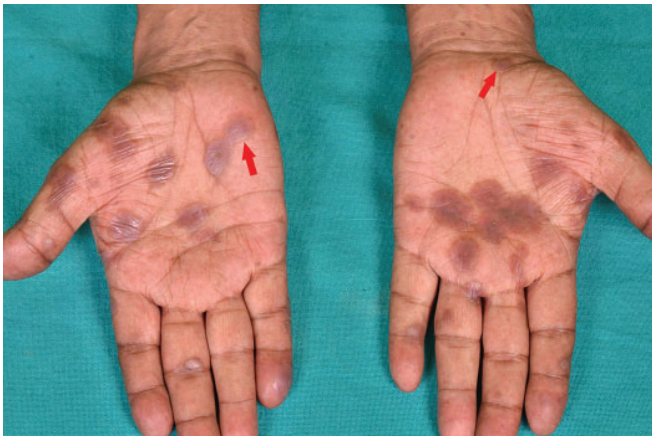

Figure 1. Well-defined dusky, discoid patches and plaques with peripheral collarette of scales (red arrows) on the palms.

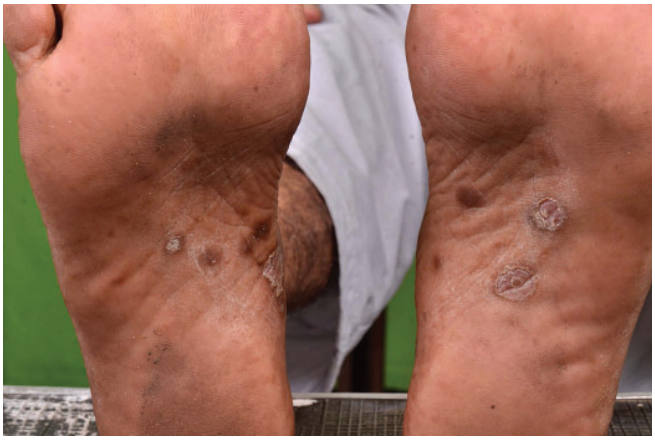

Figure 2. Well-defined dusky, discoid plaques with peripheral desquamative scaling on the instep of the patient's soles. Some of the lesions appear psoriasiform.

A 51-year-old man presented with a 3-month history of reddish-brown lesions on his body and scaly brown lesions on the palms and soles and a 1-month history of mildly painful oral erosions. He had also noticed a buzzing sound in the right ear for the past 20 days.

Review of his medical record showed that he had engaged in unprotected sexual contact with a commercial sex worker 1 year earlier. He had human immunodeficiency virus (HIV) infection and had been taking antiretroviral therapy consisting of zidovudine, lamivudine, and nevirapine for the last 10 years, and his CD4 cell count was 706/µL.

Cutaneous examination revealed well-defined dusky to erythematous papules and plaques on his face, neck, back, and hands. There were well-defined ulcers on the tip of the tongue and split papules on both angles of the mouth. There were discoid plaques with peripheral scales on the palms (**Figure 1**) and soles (**Figure 2**). Other mucosae were normal, as were the results of the nervous system and ophthalmologic examinations.

Skin biopsy of a cutaneous papule revealed dermis with periadnexal and perivascular plasma-cell-rich inflammatory infiltrate. Immunostain for *Treponema* further revealed helically coiled spirochetes present diffusely in the dermis (**Figure 3**).

A Venereal Disease Research Laboratory test (titres of 1:64) and *Treponema pallidum* hemagglutination assay were positive (titres of 1:80). Cerebrospinal fluid analysis was normal. However, tympanometry revealed a type C tympanogram with minimal sensorineural hearing loss in the right ear.

Based on these findings and the patient's history, otosyphilis accompanying secondary syphilis was suspected. Owing to the unavailability of crystalline penicillin and procaine penicillin, intravenous ceftriaxone 2 g daily was administered for 14 days, which led to clearance of the mucocutaneous lesions and

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improvement in the tinnitus. A subsequent audiogram showed improvement in his hearing loss after 3 months.

DIFFERENTIAL DIAGNOSIS

The differential diagnosis for palmoplantar lesions of secondary syphilis includes palmoplantar psoriasis and pustulosis, palmoplantar eczema, keratoderma blennorrhagicum, tinea manuum, and pityriasis rosea. The presence of a peripheral rim of scale (Biett sign, Biett collarette) and pain caused by blunt pressure on these lesions (Buschke-Ollendorff sign) helps differentiate them from other conditions. Biett collarette may also be seen with lesions of porokeratosis and pityriasis rosea when they occur on the palms. However, porokeratosis generally causes scales that are rough and uneven, and pityriasis rosea produces multiple fine scales with an undefined direction.[1] Palmoplantar lesions may have a configuration resembling erythema multiforme[2] and rarely present as interdigital papules (condyloma lata) or erosions.[3]

Incidence rates of syphilis are known to be substantially higher in the HIV-positive population,[4] and the secondary incubation period of syphilis is usually shortened in these patients. However, in our patient, manifestations of secondary syphilis were delayed by 9 months after exposure.

Incidence rates of otosyphilis in the HIV population are not well known. In a recent case series of 12 patients with otosyphilis, 8 (67%) were positive for HIV.[5]

Otosyphilis is often a presumptive diagnosis based on positive serology in patients with cochleovestibular symptoms with no other likely causes. It may present differently depending on the stage of syphilis. Sensorineural hearing loss (often bilateral and rapidly progressing) and tinnitus are the most common complaints in secondary syphilis. The presence of cerebrospinal fluid findings with otosyphilis ranges from 5.6% to 67%.[5,6]

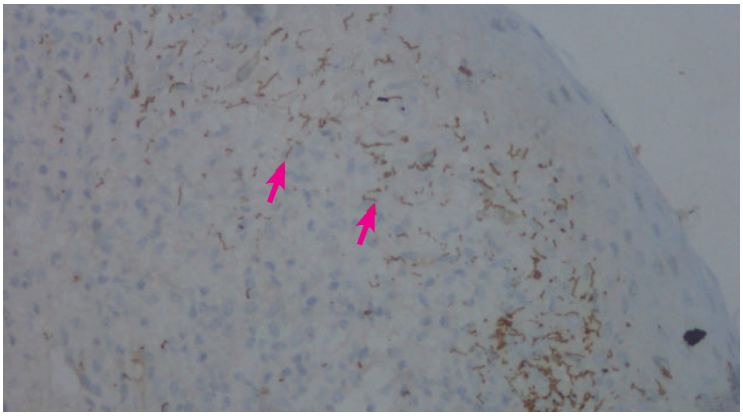

Figure 3. Immunostain for *Treponema* showed helically coiled spirochetes, stained brown (red arrows), scattered throughout the dermis (magnification × 40).

The presentation of secondary syphilis is highly variable, including its dermatologic manifestations, earning it the name of the "great masquerader." However, the presence of copper-colored patches and plaques on the palms and soles necessitates that syphilis be ruled out before considering other diagnoses.

It is imperative to ask any patient with syphilis about symptoms of ocular, otologic, and central nervous system involvement and to evaluate accordingly, thus saving the patient from considerable morbidity. ■

In our patient, manifestations of secondary syphilis were delayed by 9 months after exposure

DISCLOSURES

The authors report no relevant financial relationships which, in the context of their contributions, could be perceived as a potential conflict of interest.

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Chest pain: The importance of serial ECGs

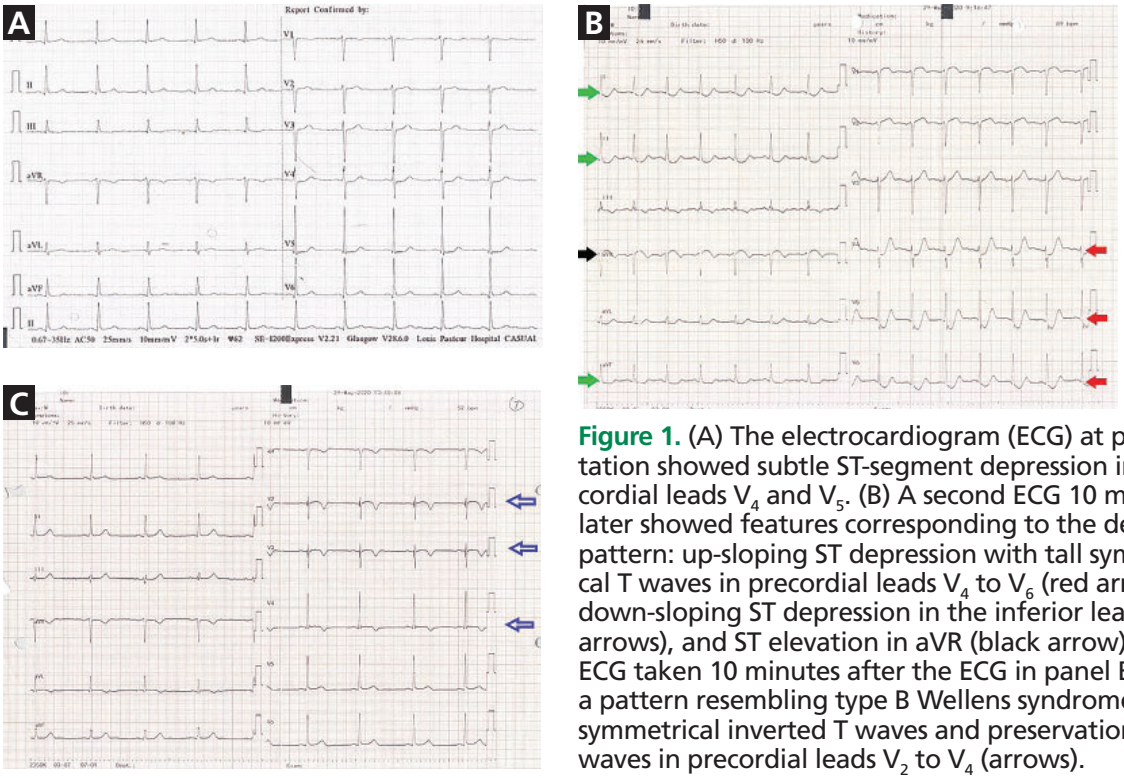

Figure 1. (A) The electrocardiogram (ECG) at presentation showed subtle ST-segment depression in precordial leads V_4 and V_5. (B) A second ECG 10 minutes later showed features corresponding to the de Winter pattern: up-sloping ST depression with tall symmetrical T waves in precordial leads V_4 to V_6 (red arrows), down-sloping ST depression in the inferior leads (green arrows), and ST elevation in aVR (black arrow). (C) An ECG taken 10 minutes after the ECG in panel B showed a pattern resembling type B Wellens syndrome, with symmetrical inverted T waves and preservation of R waves in precordial leads V_2 to V_4 (arrows).

A 44-YEAR-OLD MAN, previously well, presented to the emergency department with severe hypertension and a 4-hour history of typical angina-like chest pain with associated diaphoresis. He had dyslipidemia, a 5-pack-year history of smoking, and, likely, undiagnosed hypertension.

On arrival, his blood pressure was 200/110 mm Hg, representing a hypertensive emergency. A clinical examination was unremarkable. A blood sample was sent for troponin analysis, and a nitroglycerin infusion was started.

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An initial ECG showed minimal ST-segment changes in the precordial leads (**Figure 1a**). However, the patient's typical chest pain prompted a second ECG (**Figure 1b**) 10 minutes later, which showed features corresponding to a de Winter ECG pattern including the following features:

- Up-sloping ST-segment depression at the J point, with tall symmetrical T waves in precordial leads V_4 to V_6
- Down-sloping ST-segment depression in the inferior leads
- ST-segment elevation in aVR.

The de Winter ECG pattern is highly

predictive of acute proximal left anterior descending artery (LAD) occlusion.[1]

A third ECG (**Figure 1c**) taken 10 minutes after the second ECG showed a pattern resembling that in type B Wellens syndrome, ie, symmetrical inverted T waves with preservation of R waves in precordial leads V_2 to V_4. Wellens syndrome is also associated with transient proximal LAD occlusion or critical LAD stenosis.[2] Our patient likely experienced reperfusion after the ECG that showed the de Winter pattern.

Taken together, the serial ECGs demonstrated progression seen during acute myocardial infarction.

HYPERTENSIVE EMERGENCY AND ECG PATTERNS

A hypertensive emergency may present with T-wave inversion, ST-segment displacement, or even asymmetrical tall T waves, indicative of cardiac injury that necessitates prompt intervention. Hypertensive emergency causes a sudden increase in afterload, which increases myocardial oxygen demand and workload, resulting in myocardial ischemia.

Changes on ECG related to hypertensive emergency usually revert to baseline once the blood pressure is controlled. In hypertensive crisis with associated chest pain, it is important to look for ischemic triggers and actively exclude target-organ damage. Serial ECGs can help identify myocardial ischemia and monitor response to blood pressure treatment.[3]

The de Winter syndrome

The de Winter syndrome is reported in 2% of patients with anterior myocardial infarction and should not be missed.[1] In initial reports in the literature, the ECG changes noted in de Winter syndrome were static and did not progress to ST-segment elevation. However, the evolution of the de Winter ECG pattern to an ST-segment elevation myocardial infarction (STEMI) pattern has been well documented.[4] The electrophysiologic mechanism to explain the absence of ST elevation remains unclear, and multiple hypotheses have been postulated.[1,5,6]

Wellens syndrome

Wellens syndrome is associated with a critical stenosis of the proximal LAD. It is classified as type A or type B. Type A is characterized by biphasic T waves in precordial leads V_2 to V_3. Type B is classified by deep symmetrical T waves in the anterior precordial leads.[2]

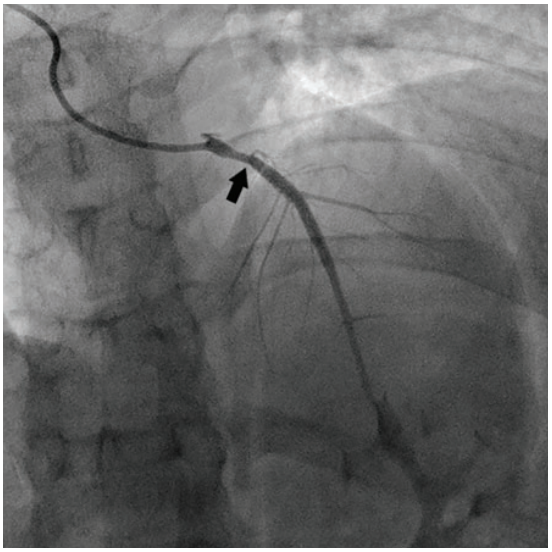

Figure 2. Coronary angiography confirmed significant stenosis of the proximal left anterior descending artery (arrow).

The role of serial electrocardiography

The ECGs in our patient highlight the importance of serial ECGs in a patient presenting with ongoing chest pain and a normal or inconclusive initial ECG. They demonstrate progression to 2 high-risk ECG patterns hinting at critical coronary stenosis or occlusion, often referred to as STEMI-equivalents. Measurement of troponins is of the utmost importance in the diagnosis of myocardial infarction, but not in STEMI. Awaiting a troponin result in this patient would have led to a costly delay of urgent revascularization.[7]

Taken together, the serial ECGs demonstrated progression seen during acute myocardial infarction

MANAGEMENT

Current American Heart Association/American College of Cardiology and European Society of Cardiology guidelines do not specifically address the management of acute coronary syndrome in patients with the de Winter ECG pattern. They do however suggest percutaneous coronary intervention in patients with possible ongoing myocardial ischemia and an early invasive strategy in high-risk patients.[8–10] The proximal LAD occlusion associated with this ECG pattern means it can be treated as an STEMI-equivalent.

Good reperfusion success rates have been reported with initial thrombolytic therapy.[4,11] In a setting with limited resources or during the current pandemic, when access to many procedures may be limited, initial thrombolytic therapy coupled with early angiography (within 2 to 24 hours) as part of a pharmacoinvasive approach should be considered in patients with de Winter ECG pattern.

OUR PATIENT'S TREATMENT

The patient received guideline-directed medical therapy.[10] In STEMI, a presenting blood pressure of 200/110 mm Hg is a relative contraindication to thrombolytic therapy, but he responded well to nitroglycerin infusion.[7] His initial troponin I level was 230 ng/L (rule-in value for acute coronary syndrome > 300 ng/L) and went up to 14,139 ng/L.

He underwent urgent coronary angiography, which confirmed critical stenosis of the proximal LAD (**Figure 2**). A drug-eluting stent was placed. He was discharged 2 days later on dual antiplatelet therapy (lifelong aspirin and 12 months of clopidogrel) and lifelong atorvastatin, enalapril, and atenolol.

TAKEAWAYS

- The de Winter and the Wellens ECG patterns carry a life-threatening prognosis, yet they are underrecognized by clinicians. Awareness of these high-risk patterns and STEMI-equivalents can lead to earlier diagnosis and treatment, which may improve clinical outcomes and prognosis.
- Serial ECGs can help identify dynamic ECG changes when the initial ECG is normal, and can help diagnose life-threatening ischemia and acute coronary syndrome, allowing early intervention and prevention of complications.
- Primary percutaneous coronary intervention or initial thrombolytic therapy coupled with early angiography (within the first 2 to 24 hours) as part of a pharmacoinvasive approach should be initiated as soon as possible when a patient presents with a de Winter pattern on ECG.

DISCLOSURES

The authors report no relevant financial relationships which, in the context of their contributions, could be perceived as a potential conflict of interest.

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EDITORIAL

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Fungus among us: A poster child for diagnostic stewardship

In this issue of *Cleveland Clinic Journal of Medicine*, El-Baba et al address the clinical significance of *Aspergillus* species isolated from respiratory cultures.[1] The authors elegantly and succinctly summarize the clinical classification and diagnostic approach to *Aspergillus*-related lung disease.

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Interpretation of diagnostic studies, including microbiologic tests, should always be predicated on the clinical indication for testing.[2] So before interpreting the clinical significance of isolation of *Aspergillus* species from respiratory cultures, we should first ask whether the culture was clinically indicated, or whether this was an incidental finding.

Aspergillus species are ubiquitous in the water environments of the home and of healthcare facilities.[3] Therefore, while *Aspergillus* species can cause several forms of lung disease, some of which are life-threatening, incidental growth of this organism should be expected due to contamination or colonization. Contamination refers to the transient presence of this organism in the airways without causing illness, or its accidental addition to inanimate objects in the process of collection, transport, or processing in the laboratory. Colonization refers to the persistent presence of the organism in the airways, again without causing illness, but it can be one step away from resulting in clinical disease. These concepts apply to other human organ systems, including the skin and the urinary tract.[4]

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EVOLVING DEFINITIONS OF FUNGAL INFECTIONS

Clinicians have struggled to define fungal infections at the bedside for several decades. The first international consensus defining opportunistic invasive fungal infections in immunocompromised patients with cancer and hematopoietic stem cell transplants was published in 2002.[5] Diagnostic and management approaches to invasive fungal infections evolved rapidly over the last 2 decades, necessitating consecutive updates in 2008[6] and 2020.[7]

These consensus definitions were intended to harmonize research studies but nevertheless have been widely adopted for clinical practice. With each update, the definition of the "probable" category expanded, while the scope of the category "possible" was contracted. The International Society for Heart and Lung Transplantation published its own standardized definitions pertaining to lung and heart transplant recipients.[8]

NEEDED: DIAGNOSTIC STEWARDSHIP

El-Baba et al[1] describe the diagnostic accuracy of the available imaging and laboratory tests, their limitations, and the risks associated with invasive bronchoscopic and surgical procedures necessary for histopathologic confirmation.

Our antifungal drug options are limited, and most agents have significant adverse effects and drug interactions and are expensive, further complicating management decisions. Practice guidelines by the Infectious Diseases Society of America,[9] the American Society of Transplantation,[10] and the American Society of Transplantation and Cellular Therapy[11] provide excellent guidance in these patient populations.

Interpretation of diagnostic studies, including microbiologic tests, should always be predicated on the clinical indication for testing

If all patients in whom *Aspergillus* species grow from respiratory cultures were to be treated, the risks would outweigh the benefits. In making these decisions, clinicians should apply the principles of diagnostic stewardship[2] before applying the principles of antimicrobial stewardship.[12] El-Baba et al provide a clinically driven, systematic approach to applying these principles.

DISCLOSURES

The author reports no relevant financial relationships which, in the context of his contributions, could be perceived as a potential conflict of interest.

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ONE MINUTE CONSULT

BRIEF ANSWERS TO SPECIFIC CLINICAL QUESTIONS

Q: Is *Aspergillus* isolated from respiratory cultures clinically significant?

A: It depends on the patient's symptoms, underlying lung condition, immune status, and radiologic findings.

Because *Aspergillus* is ubiquitous, many patients have false-positive findings on respiratory culture and need no additional workup or treatment. But positive respiratory cultures may also indicate underlying serious lung disease. A thorough history to detect symptoms, underlying chronic lung disease, or an immunocompromising state followed by targeted laboratory tests and radiologic evaluation are adequate to ascertain the significance of this finding in the vast majority of patients.

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THREE MAJOR GROUPS OF DISEASE

Aspergillus is an environmentally ubiquitous and easily aerosolized mold encountered through daily exposure.[1] Broadly, *Aspergillus*-related lung diseases can be categorized into 3 major groups (**Figure 1**).

Allergic bronchopulmonary aspergillosis (ABPA) is an inflammatory lung condition caused by hypersensitivity reaction to *Aspergillus* antigens that almost exclusively occurs in patients with asthma or cystic fibrosis.[2] Allergic reactions that do not fulfill the criteria for ABPA include *Aspergillus* sensitization and severe asthma with fungal sensitization.

Invasive pulmonary aspergillosis (IPA). IPA, unlike ABPA and chronic aspergillosis, is a severe, life-threatening, and often systemic disease process caused by *Aspergillus* species invading blood vessels, classically presenting in severely immunocompromised hosts and critically ill patients.[3] A rare form of IPA is invasive *Aspergillus* tracheobronchitis.

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Chronic pulmonary aspergillosis is an umbrella term for a spectrum of disease patterns typically occurring in immunocompetent hosts with underlying lung diseases such as tuberculosis, chronic obstructive pulmonary disease, sarcoidosis, lung cancer, and lung radiation exposure and presenting with cavitary lesions that may progress slowly over time.[4]

WHEN IS A POSITIVE CULTURE CLINICALLY SIGNIFICANT?

Aspergillus infections, most commonly with A *fumigatus* and A *flavus*, account for approximately 15,000 hospitalizations and an estimated $1.2 billion in hospital costs annually across the United States.[5] Therefore, it is not uncommon for physicians to encounter an *Aspergillus*-positive respiratory culture in the clinical setting. This begets the question, Is the finding clinically significant?

In an adult patient without significant medical history, isolation of *Aspergillus* species in respiratory culture is likely a false-positive finding due to contamination or colonization of the respiratory flora by these ubiquitous fungal organisms. In hospitalized patients who undergo routine respiratory cultures, 80% to 90% of those with positive *Aspergillus* findings do not have significant aspergillosis lung disease.[6,7] Even in patients with proven *Aspergillus* pulmonary infection, respiratory cultures are positive in 20% to 50% of patients, and as such the isolation of *Aspergillus* in respiratory cultures is neither sensitive nor specific in the diagnosis of most fungal respiratory infections and is not an integral part of the diagnostic criteria for *Aspergillus*-related lung diseases.[8] Under these circumstances, in a patient who has no underlying lung disease and no immunocompromised state, we recommend obser-

Because *Aspergillus* is ubiquitous, many patients will have false-positive findings on respiratory culture

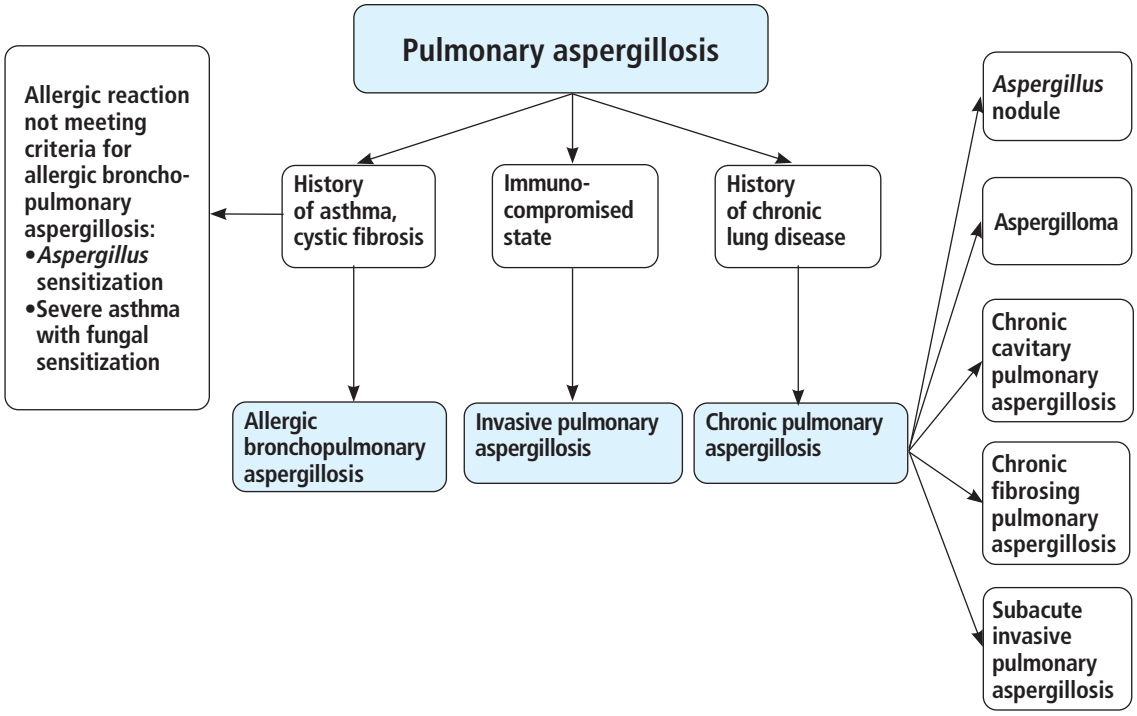

Figure 1. Pulmonary aspergillosis types, based on the patient's medical history.

vation and no further diagnostic or therapeutic intervention.

On the other hand, in a patient with respiratory symptoms, critical illness, underlying chronic lung disease, or an immunocompromising condition, detection of *Aspergillus* in respiratory culture may indicate underlying *Aspergillus* lung disease.[3] In these situations, we recommend additional workup, and if the *Aspergillus* is proven to be the causative agent, then appropriate treatment should be started.

Invasive pulmonary aspergillosis is a severe, life-threatening, and often systemic disease process

THE HISTORY AND PHYSICAL

It is imperative to assess the patient's history to quickly identify risk factors for pulmonary aspergillosis. We recommend first obtaining a thorough history and physical examination for all patients.

Key factors to consider include symptoms such as hemoptysis, chest pain, fever, and recent respiratory illness. Carefully assess for underlying chronic lung conditions including asthma, cystic fibrosis, chronic obstructive pulmonary disease, tuberculosis, lung surgery, radiation, pneumoconiosis, or sarcoidosis. In addition, a thorough evaluation should be done for conditions that may affect the immune system including leukemia, hematopoietic stem cell or solid-organ transplant, immunosuppressive therapy, and chronic corticosteroid therapy.[3,5–10] In immunocompromised patients who present with sepsis and demonstrate tachypnea, tachycardia, fever, hypotension, and hypoxia, IPA should be considered, and rapid identification and treatment of the causative agent are crucial, as the mortality rate is high.

LABORATORY TESTS AND IMAGING

In patients with clinical presentations suggestive of aspergillosis, we suggest pairing a basic laboratory assessment (ie, a complete blood cell count) with radiographic imaging. Initial laboratory findings may narrow the differential diagnosis by identifying eosinophilia, which suggests ABPA, or severe neutropenia, which suggests IPA.

For imaging, we recommend high-resolution computed tomography (CT) of the chest rather than chest radiography to evaluate for *Aspergillus*-related lung disease, as it has superior ability to identify nodules, consolidation, cavitary lesions, and bronchiectasis. The finding of a cavitary lesion with or without intra-

cavitary radiopacity suggests chronic aspergillosis, whereas the "halo" sign or "air crescent" sign suggests IPA (**Figure 2**), and bronchiectasis is seen in patients with ABPA.[11] In evaluating chest CT findings, it is always useful to compare against previous imaging results and to consider other conditions that may coexist with positive *Aspergillus* in the respiratory sample.

Galactomannan and beta-D-glucan

In patients with risk factors and suspicious imaging findings, we recommend next testing for the serologic markers galactomannan and beta-D-glucan.

The specificity and sensitivity of these tests in the diagnosis of IPA depend on the host and cutoff value. When a cutoff assay index of 0.5 is used, the combined sensitivity for serum galactomannan has been calculated as 74% (95% confidence interval [CI] 64–82) and its sensitivity as 85% (95% CI 77–90). Serum beta-D-glucan had a sensitivity of 81% (95% CI 73–87) and specificity of 61% (95% CI 46–75).[10]

The detection of galactomannan in bronchoalveolar lavage fluid is more sensitive and specific in the diagnosis of IPA, with a combined sensitivity of 79% (95% CI 65–88) and specificity of 84% (95% CI 74–91). The procedure is relatively safe and should be considered in patients who have risk factors or have significant radiologic findings that suggest *Aspergillus* lung disease.

If the clinical or radiologic picture suggests ABPA, measuring serum total and *Aspergillus*-specific immunoglobulin E levels is needed to confirm the diagnosis.

Biopsy is the gold standard but rarely needed

The gold standard for diagnosis of most cases of *Aspergillus*-related lung disease is surgical biopsy and histopathologic confirmation. Unfortunately, biopsy often cannot be done owing to concomitant pulmonary comorbidities, severe immunocompromise, or critical illness with respiratory failure. Innovations in bronchoscopic procedures for microbiologic and pathologic samples, coupled with advances in radiology and *Aspergillus* biomarkers, have significantly reduced the need for surgical lung biopsy in these patients.

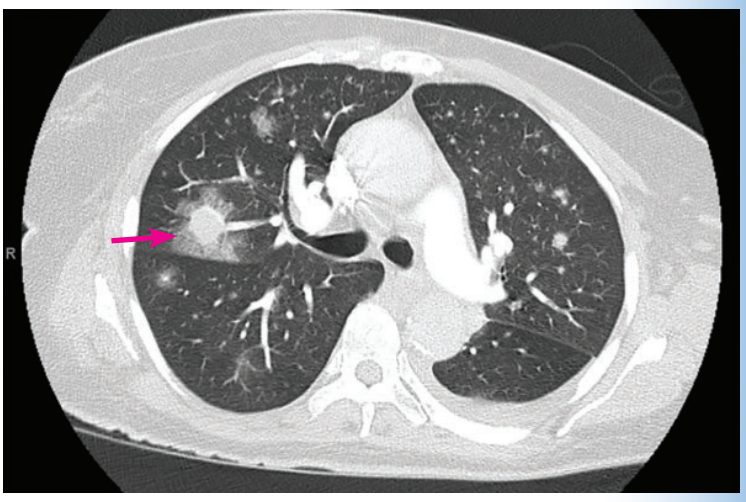

Figure 2. Computed tomography shows multiple pulmonary nodules, some surrounded by ground-glass changes consistent with the "halo" sign (arrow) in a patient with invasive pulmonary aspergillosis.

MANAGEMENT

Management depends on the *Aspergillus*-related diagnosis and the patient's clinical status. When considering conditions such as ABPA or chronic aspergillosis, we suggest waiting until the diagnosis is confirmed before initiating treatment.

However, IPA is more rapidly progressive and has a high mortality rate. Therefore, if clinical suspicion is high, therapy should not be delayed for the establishment of the diagnosis of proven or probable disease. In these situations, we suggest starting empiric therapy with a triazole agent while waiting for the results of cultures and biomarkers.

ALWAYS CONSIDER THE CLINICAL PICTURE

Due to the ubiquity of *Aspergillus*, many patients have false-positive findings on respiratory culture and require no additional workup or treatment. However, *Aspergillus*-positive respiratory cultures may be an indication of underlying serious *Aspergillus* lung disease. A thorough history to detect symptoms, underlying chronic lung disease, or immunocompromising state, followed by targeted laboratory tests and radiologic evaluation, is adequate to ascertain the significance of this finding in most patients. ■

DISCLOSURES

The authors report no relevant financial relationships which, in the context of their contributions, could be perceived as a potential conflict of interest.

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REVIEW

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Ketogenic diets in the management of type 1 diabetes: Safe or safety concern?

ABSTRACT

The jury is still out on whether a low-carbohydrate, ketosis-inducing diet is an effective and safe adjunctive therapy to insulin in type 1 diabetes. The limited published literature reports an association with weight loss and improved glycemic control and may, over the long-term, lead to reduced macrovascular and microvascular harm. However, the attendant increased risk of dyslipidemia, diabetic ketoacidosis, and hypoglycemia warrant caution, close monitoring of patients who embark on the diet, and further research.

KEY POINTS

Ketogenic diets are high in fat, moderate in protein, and low in carbohydrate; they should be well formulated for maximal nutritional benefit and well-being.

Ketogenic diets have been reported to improve hemoglobin A1c and glycemic variability in patients with type 1 diabetes and may improve biochemical and physical markers of cardiovascular risk.

Key safety concerns include the risk of dyslipidemia, diabetic ketoacidosis, and hypoglycemia.

Insulin therapy usually requires adjustment when starting a ketogenic diet, and patients should be closely monitored.

Sodium-glucose cotransporter 2 inhibitors should be discontinued when following a ketosis-inducing diet, but metformin is considered safe. Glucagon-like peptide 1 receptor agonists can be continued with close monitoring.

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A 31-year-old man with a 14-year history of type 1 diabetes presented for routine follow-up. He had been on hybrid closed-loop insulin pump therapy for 6 months. Before using this system, he used multiple daily injections of insulin, with hemoglobin A1c (HbA1c) levels ranging from 7.5% to 9.0% (target range < 7%). Glycemic control improved on insulin pump therapy but was still subpar (HbA1c 7.7%) and highly variable. He self-initiated a very-low-carbohydrate, ketosis-inducing diet (< 30 g of carbohydrates per day), self-adjusted his insulin pump settings, and subsequently reported that his glucose control improved with minimal hypoglycemia.

His HbA1c was 5.7%, and he weighed 18 lbs less than at his previous visit (pre-diet body mass index [BMI] 30.4 kg/m^2). Glucose levels were reported as within the desired range (3.9–10.0 mmol/L [70–180 mg/dL]) 97% of the time, with very few boluses of insulin required. The patient inquired if this dieting program was safe in patients with type 1 diabetes.

KETOGENIC DIET AND DIABETES TYPE

Ketogenic diets have risen in popularity in recent years as a strategy for weight loss and treatment of a variety of diseases. For patients with type 2 diabetes mellitus, the diet can lead to clinical improvement, including better glycemic control, lower cholesterol, and weight reduction.[1–3]

The diet is also becoming popular among patients with type 1 diabetes, but its clinical impact remains unclear, as much of the literature consists of retrospective case reports and series. The subject has not been well investigated, likely because of concern about induc-

ing ketoacidosis and hypoglycemia in patients already at high risk for these complications.

This article reviews potential risks and benefits of a ketogenic diet for managing type 1 diabetes based on available evidence.

KETOGENIC DIET PARAMETERS

Ketogenic diets are generally high in fat (60%–85%), moderate in protein (15%–30%), and low in carbohydrates (5%–10%).[4] This leads to the body using fat as its principal energy source.

Total caloric needs and preferred macronutrient distribution can be calculated using one of a variety of formulas (eg, Mifflin-St. Jeor).[5] Unfortunately, the literature of ketogenic and very-low carbohydrate diets varies in defining diet composition. Feinman et al[6] define a very-low carbohydrate ketogenic diet as containing 20 to 50 g of carbohydrate in a 2,000 calorie diet, or less than 10% of total energy intake.

Common misconceptions about ketogenic diets are that followers can consume few vegetables and must eat excessive amounts of meat. But a well-formulated diet can incorporate a variety of protein-containing foods, including fish, cheese, and Greek-style yogurt. The diet may also include 4 or 5 servings of vegetables daily, which contain about 20 to 30 grams of carbohydrate in total; hence, the low amount of allowable carbohydrate may be obtained entirely from vegetables. Fat calories can also come from plants and fish that are on the Mediterranean diet, such as olives, olive oil, nuts, seeds, avocado, tuna, and salmon.

Ketogenic diets are becoming popular for type 1 diabetes, but the clinical impact remains unclear

A long-term ketogenic diet should be designed to meet all nutritional needs. Using a hypothetical case study design, Zinn et al[7] demonstrated that a low-carbohydrate, high-fat diet (10% of calories from carbohydrate) could be formulated to be micronutrient replete. Further, nutrition counseling and attention to hydration can ensure that appropriate amounts of electrolytes such as sodium, potassium, and magnesium are achieved.

BIOCHEMISTRY OF KETOSIS

Under normal physiologic circumstances, glucose is the main substrate for glycolysis, resulting in the production of adenosine triphosphate (ATP), the body's main energy source. Under circumstances of starvation or dietary carbohydrate restriction, the body breaks down glycogen (ie, the storage form of glucose) in the liver to provide the body with glucose.

In a prolonged fasting or carbohydrate-restricted state (> 48–72 hours), liver glycogen stores become depleted. Without glucose as a substrate for ATP production, the liver breaks down triglycerides to make ketone bodies that travel to target tissues (eg, brain, muscles) and ultimately generate ATP.[8,9] This process of ketogenesis is regulated by insulin; low carbohydrate intake leads to low insulin levels, promoting ketosis.[10]

MONITORING KETONES

For patients with type 1 diabetes, monitoring ketones is important to identify and prevent diabetic ketoacidosis (DKA). Three types of ketone bodies, resulting from the liver metabolizing fatty acids, are measured in different ways, each with advantages and disadvantages: acetone, acetoacetic acid, and beta-hydroxybutyrate.[11]

Acetone is measured with a breath test. Breath analyzers are painless, convenient, and noninvasive. Although they can cost more than blood ketone meters, breath analyzers typically do not have recurring costs. However, research on the accuracy of breath analyzers is limited, and several available devices are not approved by the US Food and Drug Administration.

Acetoacetic acid is measured in urine. Urine ketone tests are painless, inexpensive, and noninvasive. However, they are not ideal for early detection of DKA, as results provide an average of urine ketone concentration since the last void rather than reflect current ketone levels.

Beta-hydroxybutyrate is measured in capillary blood. Blood ketone measurements provide timely identification of DKA, as they measure the current plasma concentration of beta-hydroxybutyrate, the ketone body that appears earliest in DKA. They also are more sensitive and specific than urine tests. However, blood tests are invasive, and the cost includes the initial purchase of a meter in addition to the recurring expense for disposable test strips and lancets.

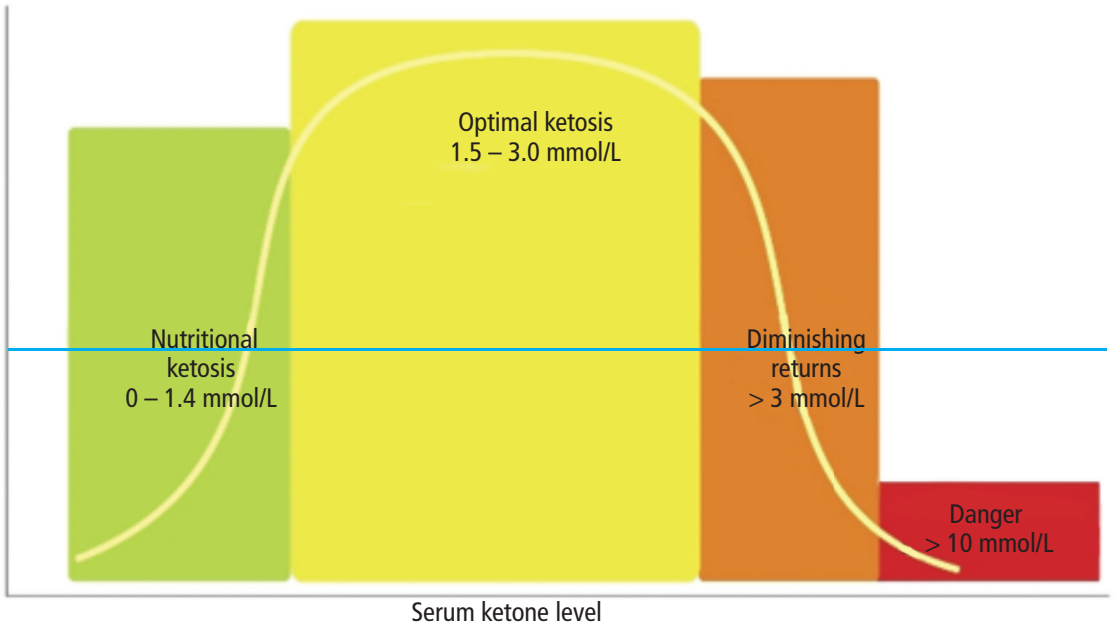

Figure 1. Safety ranges of serum ketone levels.

Based on data from reference 12.

DKA OR DESIRED KETOSIS?

Differentiating DKA from desired nutritional ketosis for a patient following a ketogenic diet poses a challenge when interpreting monitored test results. According to Volek and Phinney,[12] blood ketone levels ranging from 0.5 to 3.0 mmol/L are expected in nutritional ketosis, with the upper end (1.5–3.0 mmol/L) being optimal (**Figure 1**).[12] Although such levels are not high enough to indicate DKA, they can be a warning sign. As such, the clinical picture should be considered. Patients should be educated regarding symptoms of DKA, including nausea, vomiting, and difficulty breathing.

Diligent and more frequent blood glucose monitoring should be a mainstay in patients with diabetes on a ketogenic diet. Although euglycemic DKA is possible while following a ketogenic diet, blood glucose levels above 250 mg/dL may be seen and are a sign of potential DKA.

Glucose monitoring can also be helpful for preventing hypoglycemia, a potential consequence of reduced carbohydrate intake. Clinical studies indicate that a continuous glucose monitor (CGM) can be a useful tool in reducing hypoglycemia.[13,14]

ADJUSTING DIABETES THERAPIES

Little has been published on how to adjust medications in people with type 1 diabetes who follow a ketogenic diet.

Insulin requirements change

Ranjan et al[15] conducted a small, randomized crossover study of a high-carbohydrate vs low-carbohydrate diet in patients with type 1 diabetes. All patients used an insulin pump with a CGM. Insulin pump settings were optimized in a 2- to 3-week period before the diet. The diets resulted in similar basal insulin requirements, but the total bolus dosage was lower in the low-carbohydrate diet group (defined as ≤50 g carbohydrates per day), with the total daily insulin dose reduced by 44.3%. This is similar to that observed in clinical trials in patients with type 2 diabetes starting a low-carbohydrate diet, in which insulin dosages are typically decreased by 50%.[1,16,17] A key difference is that people with type 2 diabetes on a low-carbohydrate diet can usually completely stop bolus doses in addition to reducing basal insulin.[18]

In clinical practice, it is not uncommon to escalate basal insulin rather than add or increase bolus doses, thus allowing the long-acting insulin to cover some or all of a patient's

A low-carbohydrate, high-fat diet can be formulated to be micronutrient-replete

post-meal insulin needs. In such cases, excessive basal coverage can increase the risk of hypoglycemia when a patient reduces mealtime carbohydrate intake when starting a ketogenic diet. Furthermore, many people with type 1 diabetes have an elevated BMI, and insulin resistance is expected to improve and insulin requirements decrease as weight is lost on a ketogenic diet.

How to adjust insulin

Insulin dosages usually need to be reduced after starting a ketogenic diet; in type 1 diabetes, this usually entails decreasing the amount of insulin received per gram of carbohydrate. The following strategy can be used:

- If a patient's HbA1c is near target, the daily dosage of basal insulin may need to be decreased by 10% to 20%
- If the HbA1c is elevated, no adjustments may be required
- It is often safest to adjust insulin with the aim of reducing the risk of hypoglycemia; the patient can be instructed to take additional correction doses of short-acting insulin to address hyperglycemia
- Insulin dosages often need to be adjusted weekly in the initial stages as weight loss and adherence to the ketogenic diet will impact the necessary insulin adjustments, and these factors are highly individual.

Monitoring ketones is important to identify and prevent diabetic ketoacidosis

Other diabetes medications

Usually with the aim of weight loss, many patients with type 1 diabetes also take medications off-label that are approved by the US Food and Drug Administration for type 2 diabetes, including metformin, sodium-glucose cotransporter 2 (SGLT-2) inhibitors, and glucagon-like peptide 1 (GLP-1) receptor agonists.

SGLT-2 inhibitors are associated with an increased risk of euglycemic DKA, particularly in type 1 diabetes. This may occur through multiple mechanisms, including reduction in insulin-mediated suppression of lipolysis and ketogenesis, volume contraction, promotion of glucagon secretion, and decrease in renal clearance of ketone bodies.[19] Accordingly, SGLT-2 inhibitors should be stopped before starting a ketogenic diet owing to the risk of DKA that often presents as euglycemic, making it difficult to recognize.[20]

GLP-1 receptor agonists, when used in type 1 diabetes, may increase the risk of hypoglycemia and DKA.[21,22] They can be continued with close monitoring in patients following a ketogenic diet, although some providers prefer to stop them.

Metformin is generally considered safe to continue.[23]

BLOOD GLUCOSE CONTROL: A BALANCING ACT

Optimizing glycemic control in type 1 diabetes can be extremely challenging but is essential to prevent life-threatening, short-term complications such as DKA. Long-term glycemic control is also important to reduce the risk of microvascular complications (neuropathy, retinopathy, and nephropathy) and perhaps macrovascular complications (stroke, coronary artery disease, and peripheral vascular disease). However, preventing hyperglycemia comes with the risk of inducing frequent or severe hypoglycemia, which can lead to lower quality of life, hospitalization, coma, and death.

Much of the challenge in maintaining euglycemia in patients with diabetes lies in the difficulty in matching carbohydrate intake with insulin administration, owing to errors in estimating the carbohydrate content in meals, variable insulin absorption, timing of insulin administration, and gastroparesis. Given these complicating factors, it is plausible that low carbohydrate intake and resulting lower prandial insulin bolus requirements may lead to better glycemic control, less blood glucose variability, and improved quality of life.[24]

EFFICACY AND SAFETY

Before the adoption of insulin as the gold standard treatment for type 1 diabetes, diet was one of the few therapy options available. In the early 20th century, the use of a very low-calorie, low-carbohydrate diet was used experimentally to manage it.[9]

The existing literature regarding the use of the ketogenic diet in type 1 diabetes is limited and has yielded mixed results. Many of the publications are case reports, and the majority are from the pediatric population for the treatment of medication-refractory epilepsy. The few studies are mostly observational and

vary considerably in terms of the dietary macronutrient composition, making it difficult to generalize their results. Data on long-term cardiometabolic effects are also limited.

Diet lowers blood glucose, sometimes dangerously

Leow et al[25] investigated the effects of a ketogenic diet (< 55 g of carbohydrates per day and fasting beta-hydroxybutyrate ≥ 0.4 mmol/L) in 11 adults with type 1 diabetes who self-initiated the diet before study recruitment. Mean HbA1c of study participants was excellent at 5.3%, and participants spent an impressive average of 74% of time within target range. However, many had a disproportionately high frequency and duration of hypoglycemic episodes.

Lennerz et al[26] evaluated the effect of a very low carbohydrate diet on 316 patients with type 1 diabetes, using an online survey of a social media group. Average carbohydrate intake was 36 ± 15 g of carbohydrates per day for an average duration of 2.2 ± 2.9 years. Patients achieved good glucose control (average HbA1c 5.7% ± 0.66%, average blood glucose by CGM 104 ± 16 mg/dL) and reported high satisfaction. The rate of severe adverse events was low and included 7 patients (2%) with diabetes-related hospitalizations and 4 (1%) with DKA.

In their small, randomized crossover study, Ranjan et al[15] compared 1 week each on a low-carbohydrate diet (≤ 50 g carbohydrates per day) and a high-carbohydrate diet (≥ 250 g carbohydrates per day) in patients with type 1 diabetes using insulin pump therapy. The low-carbohydrate diet group had significantly lower average daily blood glucose levels (122 mg/dL vs 140 mg/dL, $P = .02$), longer time in euglycemia (defined as 3.9–10.0 mmol/L [70–180 mg/dL]; 83% vs 72%, $P = .004$), less glycemic variability (1.9 vs 2.6 mmol/L, $P = .02$), lower total daily insulin dose (22 vs 39 units, $P = .0001$), and fewer daily units of bolus insulin administered (6.6 vs 23, $P = .0001$).[15]

Weight loss possible but not well studied

Another potential benefit of the ketogenic diet is weight loss. Obesity in patients with type 1 diabetes is a common problem that has worsened in recent decades. This may be in part due to the use of long-term insulin, an anabolic hormone that promotes weight gain. Obesity in type 1 diabetes can lead to metabolic syndrome and insulin resistance, as well as increased risk for microvascular complications.[27–30]

The ketogenic diet has been suggested as a tool for weight loss in overweight or obese patients with type 1 diabetes, although it has not been well studied in this population. In a well-designed crossover study, Rosenfalck et al[31] looked at insulin sensitivity and BMI and found no significant change in weight or BMI after 3 months of a ketogenic diet in 10 patients with type 1 diabetes.

Animal studies have mixed results

A few animal studies have examined the effect of a ketogenic diet in type 1 diabetes, but their significance in humans is unclear. Poplawski et al[32] examined the effects of an 8-week ketogenic diet (5% carbohydrate, 8% protein, 87% fat) vs a high carbohydrate diet (64% carbohydrate, 23% protein, 11% fat) in rat models of type 1 diabetes with nephropathy. The ketogenic diet group had a drastically improved albumin-creatinine ratio, indicating reversal of diabetic nephropathy.

Al-Khalifa et al[33] placed 42 rats on either a normal diet, low carbohydrate diet, or high carbohydrate diet, all ad libitum, for 8 weeks. Half of each group was injected with streptozotocin to induce diabetes. Blood glucose levels and food and water intake increased with the normal and high-carbohydrate diets but not in the low-carbohydrate group ($P < .01$). Weight gain was also significantly lower in the low-carbohydrate group ($P < .05$). In the low-carbohydrate group, the number of beta cells did not differ between the control group and the group with the streptozotocin injection, while the other diet groups had a significant decrease in beta-cell mass in the streptozotocin groups vs controls. These results suggest that a low-carbohydrate diet may attenuate or prevent the development of diabetes.

Differentiating diabetic ketoacidosis from desired nutritional ketosis poses a challenge

However, other rodent studies suggest potential harm. Kanikarla-Marie and Jain[34] found that hyperketonemia in type 1 diabetes rat models induced macrophage-mediated damage and oxidative stress on hepatocytes, suggesting that a high ketone state may lead to liver damage. Grandl et al[35] reported that

mice fed a low-carbohydrate, high-fat ketogenic diet had a decrease in glucose tolerance due to blunted insulin-dependent hepatic glucose production during the fasting state.

Effects on lipids mixed

Concerns have been raised regarding the ketogenic diet and adverse lipid profile changes, but the literature is inconsistent, and few publications have assessed the issue specifically in type 1 diabetes. Effects of ketogenic diets such as decreased total cholesterol, low-density lipoprotein cholesterol, and triglyceride levels and increased high-density lipoprotein cholesterol levels have been reported.[36–40]

Yancy et al,[41] compared a low-carbohydrate diet to a low-fat diet in a randomized control trial of 120 overweight patients with hyperlipidemia. The low-carbohydrate diet led to greater decreases in serum triglyceride levels compared with patients on a low-fat diet (−74.2 vs −27.9 mg/dL, P = .004) and greater increases in high-density lipoprotein levels (5.5 vs −1.6 mg/dL, P < .001), but no significant differences were seen in low-density lipoprotein levels (P = .2).

Patients should be educated regarding symptoms of diabetic ketoacidosis

Using an online survey of a social media group for children and adults with type 1 diabetes who were following a very low carbohydrate diet, Lennerz et al[26] found that 51 of 316 respondents (16.1%) reported having a diagnosis of dyslipidemia (triglyceride level > 130 mg/dL, low-density lipoprotein level > 130 mg/dL, or high-density lipoprotein level < 35 mg/dL).

In a retrospective chart review of 30 patients with either type 1 or type 2 diabetes on a low-carbohydrate diet (< 30 g daily), O'Neill[40] reported that low-density lipoprotein levels decreased by 17%, from 155 to 130 mg/dL (P = .004), and triglyceride levels decreased by 31%, from 107 to 74 mg/dL (P < .05).

Cardiac effects uncertain

Although multiple studies have examined the effect of a ketogenic diet on clinical markers of cardiovascular risk (eg, BMI, blood pressure, lipids), the literature is limited and inconclusive regarding direct impacts on cardiac health. A ketogenic diet is known to cause electrolyte disturbances, increasing the risk of cardiac arrhythmias, and some studies have suggested that it may increase risk for a prolonged QT interval, atrial fibrillation, and other arrhythmias.[42] A case series reported the de novo development of a long QT interval in 3 of 20 children following a ketogenic diet for seizure disorder.[43] Long-term data of cardiac risk in the adult population are lacking.

Blood pressure evidence scant

Data regarding the impact of a ketogenic diet on blood pressure have been inconsistent, and little exists specifically in the setting of type 1 diabetes. Several studies demonstrated no significant reduction in blood pressure with a ketogenic diet, while others suggested a mild benefit.[37,44–46] A long-term study on the cardiovascular impact of a ketogenic diet on 10 children with glut-1 deficiency over the course of 10 years found no change in systolic or diastolic blood pressures compared with healthy controls (P = .11 and P = .37, respectively).[36]

Possible microvascular benefit

Very little research has been conducted on the impact of a ketogenic diet on microvascular complications in patients with diabetes. Studies on rats have found that a ketogenic diet improved or reversed diabetic nephropathy[32] and reduced reactive oxygen species in peripheral nerve mitochondria, suggesting a positive impact on peripheral neuropathy.[47]

SAFETY IN PEDIATRIC PATIENTS

There is a lack of observational and prospective studies in children following a ketogenic diet, but several case reports have discussed its benefits in children with type 1 diabetes.[2,3,48–52] They have found reductions in glycemia and glycemic variability and improvements in HbA1c level, growth rate, and lipid profiles, and many have been without severe adverse effects, like DKA and hypoglycemia.

Henwood et al[48] described a 4-year-old girl with pyruvate dehydrogenase deficiency, seizure disorder, and type 1 diabetes who was treated with a ketogenic diet. During 28 months follow-up, she had improved activity, better glycemic control, significant developmental advances, and an increase in linear growth from less than 5th percentile to 50th percentile. However, the diet was discontinued when she developed severe DKA.

Other case reports have revealed concerns about the diet's safety in children with and without diabetes. de Bock et al[38] described 6 children with type 1 diabetes who were treated with carbohydrate-restrictive diets for epilepsy (diets varied from 20–90 grams per day in some, with others using a percentage-based formula ranging from 6% to 40% of the total daily calorie intake). Some children experienced weight loss and growth delay. Commonly observed effects were fatigue, reduced enjoyment in physical sports, and eating disorders. Ultimately, most families opted to return to a more liberal carbohydrate-containing diet.

Other reported long-term adverse effects are hyperlipidemia, kidney stones, vitamin and mineral deficiencies, electrolyte abnormalities, hypertriglyceridemia, gallstones, and elevated liver function tests.[53,54] Short-term risks, including hypoglycemia, DKA, dehydration, anorexia, gastroesophageal reflux disease, vomiting, diarrhea, and abdominal pain have also been reported. However, many of the complications seen in children have not been well described in adults.

CASE CONCLUSION

Two years after starting the ketogenic diet, the patient reported that his blood glucose control remained significantly improved. His HbA1c level has remained in the desired range for the past 2 years; most recently it was 5.5%. He lost 35 lbs with BMI improved from 30.4 to 25.5 kg/m^2. His total average daily basal insulin requirement decreased from 48 to 30 units per day, and he reported that he rarely requires prandial or correctional insulin boluses (before the diet, he averaged 33 units per day). According to his pump and CGM download, his bolus insulin requirements comprised only 3% of his total daily insulin dose (average of 1 unit per day). His blood glucose level remained within the goal range (3.9–10.0 mmol/L [70–180 mg/dL]) 98% of the time. He reported episodes of hypoglycemia 2 to 3 times every 2 weeks, but these have been mild and easily manageable. He has not had any episodes of DKA or severe hypoglycemia since starting the diet, but also admitted he would not feel safe following the diet without the safety afforded by CGM. He experienced an increase in low-density lipoprotein level up to 221 mg/dL, requiring starting high-dose atorvastatin, which may be due to a high proportion of saturated animal fats in his diet. He responded well to statin therapy and his low-density lipoprotein level decreased to 104 mg/dL, which has been maintained on the therapy.

THE BOTTOM LINE

Further research is needed on the efficacy and safety of the ketogenic diet in patients with type 1 diabetes. The diet may be appropriate for select patients, but only after a thorough discussion between patient and care team about the risks and benefits. A registered dietitian and specialists in diabetes care, education, endocrinology, and pharmacy should be part of any discussion. For patients on the diet, extra monitoring is critical, preferably with a CGM. ■

A continuous glucose monitor can be useful for reducing hypoglycemia

DISCLOSURES

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Risk-based guidelines: Redefining management of abnormal cervical cancer screening results

ABSTRACT

In making the 2019 guidelines for risk-based management of patients with abnormal cervical cancer screening tests and cancer precursors, the guidelines committee shifted from results-based to risk-based management recommendations, based on the patient's immediate and 5-year risks of grade 3 or higher cervical intraepithelial neoplasia (CIN 3+). The risk is determined by current and prior screening results (human papillomavirus infection, cytology testing) and the clinical history including age. An immediate 4% or higher risk of CIN 3+ was established as the dividing line between higher and lower risks, and the corresponding management recommendations. This article reviews the changes and their evidence base and discusses clinical implications of the revised guidelines.

KEY POINTS

Management of patients with abnormal cervical cancer screening results is based on their risk of cervical cancer rather than only on the results of Papanicolaou and human papillomavirus tests.

For individuals at higher risk (ie, immediate CIN 3+ risk of 4% or higher), more frequent surveillance via colposcopy and earlier treatment is recommended.

For those at lower risk (ie, immediate CIN 3+ risk below 4%), colposcopy surveillance can be deferred.

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The 2019 American Society for Colposcopy and Cervical Pathology (ASCCP) risk-based management consensus guidelines for abnormal cervical cancer screening tests and cancer precursors, published in April 2020,[1] represent a shift away from results-based management and toward risk-based management. Management of patients with abnormal cervical cancer screening results is now based on their risk of cervical cancer rather than only on results of Papanicolaou (Pap) and human papillomavirus (HPV) tests. Risk is determined based on clinical factors (including age), prior and current HPV infection (including genotyping results, if known), and cytology (Pap test) results. Calculation of risk is quite complicated and requires use of a smartphone application or a computer.[2]

Specifically, management is based on a patient's immediate and 5-year risks of cervical intraepithelial neoplasia grade 3 or higher (CIN 3+), determined by current and prior screening results as well as the clinical history, including age and past testing results. Thus, patients with the same current Pap and HPV test results may have different management recommendations based on their individual medical history.

WHO WROTE THE GUIDELINES?

A guidelines committee of 19 organizations under the direction of the ASCCP compiled the guidelines. The committee included medical societies, federal agencies, and patient advocacy organizations including the American Academy of Family Physicians, American

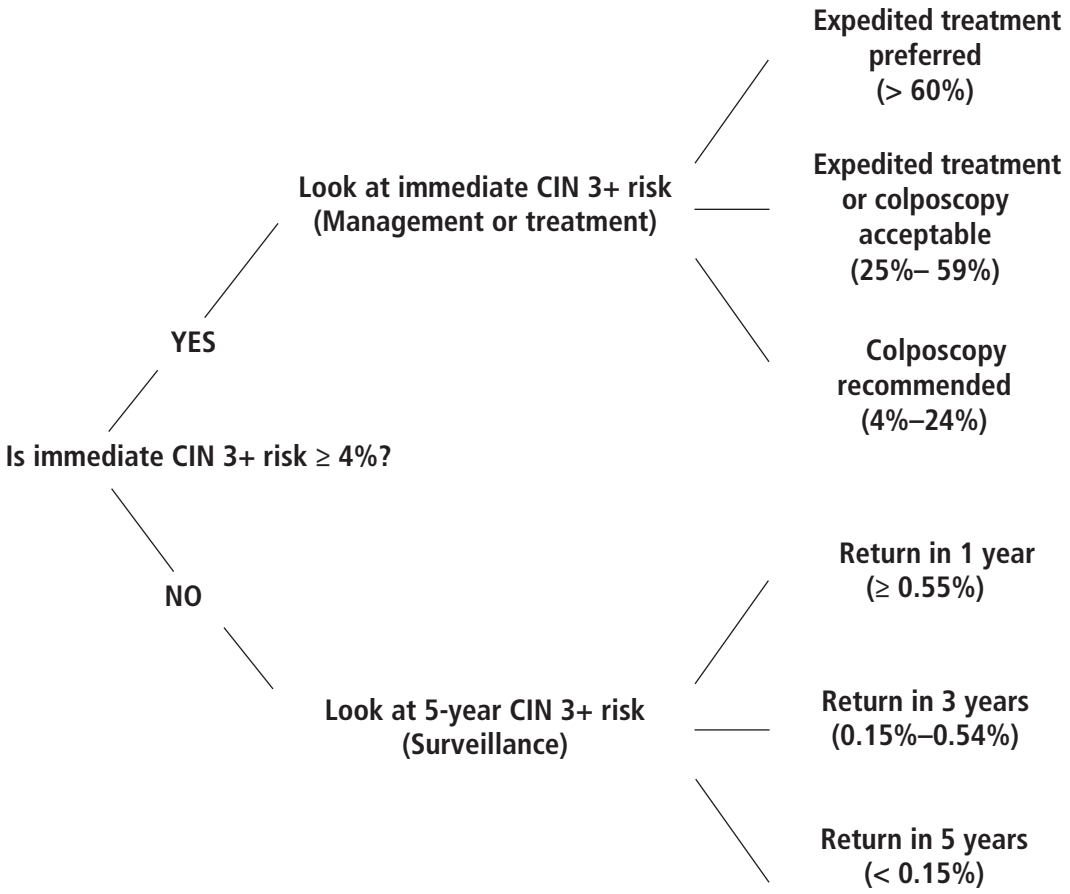

Figure 1. An example of patient risk evaluation.

CIN 3+ = cervical intraepithelial neoplasm grade 3 or higher

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College of Obstetrics and Gynecology, US Centers for Disease Control and Prevention, and the National Cancer Institute.

WHAT ARE THE MAIN RECOMMENDATIONS?

The updated guidelines provide a more personalized management strategy based on the patient's CIN 3+ risk (**Figure 1**), using a 4% or higher risk of CIN 3+ as the threshold for referral for colposcopy and expedited treatment.[1] For individuals at higher risk (ie, immediate CIN 3+ risk 4% or higher), more frequent surveillance with colposcopy and earlier treatment are recommended. For those at lower risk (ie, immediate CIN 3+ risk below 4%), surveillance with colposcopy can be deferred, and follow-up is recommended at longer intervals, ie, 1 to 5 years.

The guidelines designate CIN 3+, which encompasses CIN 3, adenocarcinoma in situ, and cervical cancer, as a cancer precursor because of the infrequent incidence of cervical cancer in the United States and because treatment of this precursor can drastically reduce cervical cancer risk. In addition, CIN 3+ provides a more consistent pathological diagnosis than cervical intraepithelial neoplasia grade 2 or higher (CIN 2+).[1]

Recommendations for when to conduct continued surveillance (Pap and HPV testing) remain at 1-, 3-, and 5-year intervals, consistent with the previous guidelines,[3] which are

familiar to clinicians. Additionally, the new guidelines review best practices for performing and reporting on colposcopy results, to help ensure standardization among those who perform the procedure.[4]

TREATMENT RECOMMENDATIONS

In patients at highest risk (ie, those with immediate CIN 3+ risk higher than 60%), expedited treatment is recommended.[1] Expedited treatment, an option in previous guidelines, is further defined, with guidance based on risk stratification. Excisional treatment is preferred to ablative therapies such as cryotherapy and laser therapy for both expedited treatment and treatment indicated by colposcopy.[5] Postexcisional treatment surveillance now includes HPV-based testing for at least 25 years at 3-year intervals.[1] This recommendation is based on evidence showing that after treatment for histologic high-grade squamous intraepithelial lesions (CIN 2, CIN 3, or adenocarcinoma in situ) a patient's risk does not return to the range in the general population.[1,6]

PATHOLOGY TEST RECOMMENDATIONS

The goals of the new recommendations are to increase accuracy for treatment and to reduce complexity for providers and patients

The guidelines also recommend that laboratories should report high-grade squamous intraepithelial lesions as either CIN 2 or CIN 3 in histopathology reports, based on recommendations from the Lower Anogenital Squamous Terminology Standardization Project work group[7] and the World Health Organization.[8] This distinction can help with management strategies when considering the patient's reproductive goals. The concept of reproductive goals replaces the term "young women," which was used in previous guidelines. Specifically, patients with CIN 2 histopathology who also desire to maintain their fertility may be followed with close surveillance. In contrast, patients with CIN 3 histopathology should undergo excisional treatment, which could pose an increased risk of complications during a future pregnancy.

Cervical cancer screening by cytology alone is acceptable only when HPV testing is not available.[1] Also acceptable is primary HPV screening (HPV alone) without cytology. The US Food and Drug Administration (FDA) has approved 2 assays for primary HPV screening—cobas HPV (Roche)[9] and Onclarity HPV (Becton, Dickinson, and Company)[10]—and they should be used only according to their regulatory approval.[11] All positive primary HPV screening tests should include reflex triage testing (cytology) on that same specimen.[12]

WHAT IS DIFFERENT FROM PRIOR GUIDELINES?

The goals of the new recommendations are to increase accuracy for treatment and reduce complexity for providers and patients compared with the 2012 guidelines. The underlying concept is "equal management for equal risks" based on results of history and testing, as opposed to algorithms based on test results alone. The new recommendations introduce the concept of "clinical action thresholds," which are management scenarios that include current and past test result combinations to determine an individual's risk profile. Thresholds are based on an estimated risk of CIN 3+ at the time of the abnormal cervical cancer screening result. As noted above, an immediate risk of CIN 3+ of 4% or higher leads to a management recommendation of colposcopy or expedited treatment. If the immediate risk is calculated as less than this 4% threshold, surveillance recommendation is then based on the specific 5-year risk of CIN 3+.[1]

Current screening results and medical history are used to determine the CIN 3+ risk estimate for each individual, as derived from calculated data tables.[2] As further research provides nuanced understanding of the natural history of HPV and cervical carcinogenesis, it is clear that persistent HPV infection is necessary for the progression to cervical precancer and cancer.[13–16] Research has also provided data on how an HPV-negative history affects the clinical meaning of current test results and an individual's risk of CIN 3+.[17] As our understanding of cervical cancer risk and prevention continues to evolve, including the long-term impact of HPV vaccination, updated risk calculations can be more easily incorporated into guideline updates to ensure equal management for equal risks.

Another noteworthy change is guidance on the timing of surveillance after treatment

of high-grade squamous intraepithelial lesions or higher-grade lesions. HPV screening is recommended in 6 months regardless of the status of the postexcision margin. If HPV screening is positive, referral for colposcopy is indicated. If HPV screening is negative, annual follow-up with primary HPV or cotesting for 3 years is indicated. If consecutive tests are negative, continued surveillance every 3 years for at least 25 years up to age 65 (or older if the patient is in good health), is now the standard.[1,17]

EVIDENCE BASE FOR RISK ESTIMATES

The formulation of risk estimates is based primarily on a Kaiser Permanente Northern California database of more than 1.5 million women who underwent routine cotesting from 2003 to 2017, including HPV genotyping for 19,000 patients.[18] The data analysis was conducted at the National Cancer Institute by statisticians using updated methods to produce the risk tables. These risk estimates and tables underlie the guidelines.[17]

These data are the largest and the longest real-world clinical experience with HPV-based screening and provide risk-based evidence for most of the common decision points of screening. Although the database has been criticized for limited inclusion of diverse socioeconomic cohorts in the context of a population with cervical cancer risk that is lower than the national average, comparison of risks and risk-based management to that of other large cohorts or clinical trials has validated the data used in the guidelines.[1,6,18,19] The updated guidelines accommodate the 3 cervical screening strategies available in the United States: primary HPV screening, cotesting with HPV testing and cervical cytology, and cervical cytology alone.[1,20]

WHAT IS THE EXPECTED CLINICAL IMPACT?

The new guidelines provide a framework for triaging high-risk individuals to treatment while avoiding unnecessary procedures and tests for lower-risk individuals, thus achieving a better balance of benefits to harm for cervical cancer screening. It is estimated that the number of patients referred for colposcopy will be reduced from 9.8% to 8.3% over 2 rounds of screening with the transition to risk-based vs results-based interventions.[1]

The guidelines are designed to be enduring. Integral to the data and risk-estimate analysis is the ability to include new technologies. When a new screening strategy is devised or a new test is FDA-approved, it can be considered for inclusion in the guidelines, assuming that sufficient data are available. Likewise, as HPV vaccinations decrease the prevalence of HPV infections and the risk of cervical carcinoma, management recommendations will incorporate these data. It is hoped that a longer interval will transpire before the next guideline revision is needed, leading to more stable clinical management for providers.

HOW WILL THIS CHANGE DAILY PRACTICE?

Because of the complexities involved in calculating the CIN 3+ risk estimates for each patient, it will be nearly impossible for clinicians to memorize the algorithms. Risk estimations now require use of computerized technology. The extensive risk table compiled by the National Cancer Institute is accessible on the National Institutes of Health website, https://CervixCa.nlm.nih.gov/RiskTables.[2] A smartphone application that calculates the risk is available for purchase from the ASCCP.[21] Clinicians should acquaint themselves with use of the risk calculator, which will allow them to competently guide the management of this patient population.

The guidelines provide a framework for triaging high-risk individuals to treatment while avoiding unnecessary procedures and tests for those at lower risk

Most scenarios commonly encountered in clinical practice can be easily managed by calculating the risk estimates and applying them to the guidelines. The detailed management protocols will allow primary care providers who do or do not manage abnormal cervical cancer screening tests to be able to accurately guide patient management and avoid unnecessary referrals or procedures. In settings where resources are limited, the protocols will enable clinicians to confidently refer for treatment patients who are at high risk and would benefit from immediate treatment.

WHEN DO THE GUIDELINES NOT APPLY?

Guidelines apply to average-risk, asymptomatic individuals with an intact cervix, based on screening management data for patients

ages 25 to 65. The guidelines separately address management of special populations, ie, those who are under age 25 or over age 65, are pregnant, are receiving immunosuppressive therapy, or have had a hysterectomy.[1] Notably, an accurate risk estimation for patients under age 25 is challenging. This is due primarily to a changing influence of HPV vaccination on cervical cancer risks for this population, as well as a higher rate of regression of histologic high-grade dysplasia and a lower incidence and progression risk of invasive cervical cancer. Pregnancy necessitates management and treatment options that consider the risk of a missed cancer diagnosis to both the fetus and the patient.

Also, some cytologic and HPV results have been found to be disproportionately important for the risk of invasive cancer. Specifically, results showing the genotype HPV 18, HPV-negative atypical glandular cells, and atypical squamous cells cannot exclude high-grade atypical squamous cells. These patients are recommended for colposcopy even though they do not meet the 4% immediate CIN 3+ risk threshold. For safety reasons, this recommendation considers absolute risk of cancer in addition to risk of precancer.[1]

DISCLOSURES

The authors report no relevant financial relationships which, in the context of their contributions, could be perceived as a potential conflict of interest.

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Coronary microvascular dysfunction: Considerations for diagnosis and treatment

ABSTRACT

Ischemia and no obstructive coronary artery disease (INOCA) is an increasingly recognized cause of angina, and it is more commonly diagnosed in women. Coronary microvascular dysfunction (CMD), or the abnormal dilation and constriction of the small vessels of the heart, is the underlying cause of INOCA in one-half of cases. This review discusses coronary microvascular pathophysiology, considerations for invasive coronary function testing and noninvasive diagnostic modalities, implications for management, and remaining knowledge gaps.

KEY POINTS

- Women presenting with signs and symptoms of myocardial ischemia are more likely than men to have no obstructive coronary artery disease.
- CMD should be considered in patients presenting with persistent angina, evidence of ischemia, and no obstructive coronary artery disease.
- CMD is associated with considerable risk of major adverse cardiac events including heart failure, myocardial infarction, stroke, and death.

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From one-half to two-thirds of women with angina symptoms who undergo coronary angiography for suspected ischemic heart disease have no obstructive coronary artery disease (CAD), according to some estimates.[1–3] This condition, characterized by signs and symptoms of ischemia in the setting of nonobstructive CAD (defined as < 50% stenosis on diagnostic angiography),[4] is termed "ischemia and no obstructive coronary artery disease" (INOCA).[5] Recent studies have estimated that there are at least 3 to 4 million patients with stable INOCA in the United States,[6] and it is more prevalent in women than in men.[7] The overall prevalence of INOCA has been increasing as clinical recognition grows, along with expanded use of diagnostic tests to assess microvascular dysfunction.

Coronary microvascular dysfunction (CMD) and vasospasm of the epicardial arteries are the 2 most common causes of INOCA.[8] In studies, nearly 50% of patients with INOCA have been found to have abnormal vasomotor behavior of the coronary microvasculature.[9] Although CMD occurs in both men and women, it is more prevalent in women, with a 2015 study showing that 66% of females and 60% of males with nonobstructive CAD had CMD on invasive testing.[10]

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Historically, patients with INOCA were thought to have a good prognosis and relatively low incidence of a major adverse cardiac event (MACE). However, this understanding has since been refuted by studies showing that patients with INOCA have elevated risk for cardiovascular events including acute coronary syndrome, heart failure hospitalization, stroke, and death.[6] The Women's Ischemia Syndrome Evaluation (WISE) study, started in 1996, has followed more than 900 women with signs and symptoms of myocardial ischemia who had undergone clinically indicated coronary angiography. Of these women, nearly two-thirds were found to have no obstructive CAD.[11] An analysis of this cohort found that INOCA was associated with a higher rate of MACE than in patients with normal coronary arteries, with a 2.5% rate of death, nonfatal myocardial infarction, nonfatal stroke, and heart failure hospitalization at the 5-year follow-up.[5]

Hospitalizations for angina were found to have occurred at relatively constant rates during a 9.1-year follow-up study.[11] Furthermore, women with stable INOCA and nonobstructive CAD had 10-year all-cause mortality and cardiac mortality rates of 17% and 11%, respectively, compared with 10% and 6% in women with normal coronary arteries.[12] The WISE study has also shown that females with INOCA are at increased risk for progression to obstructive CAD.[13]

From 3 to 4 million Americans may have stable INOCA

In addition to adverse clinical outcomes, CMD and persistent anginal symptoms affect patients' quality of life, limit their exercise capacity, and may contribute to unnecessary testing, costs, and more frequent healthcare visits.[14] Thus, early diagnosis and intervention are crucial to improving outcomes.

At present, invasive coronary function testing (CFT) is the technical standard for diagnosing CMD and coronary vasospasm. It can identify those at higher risk of MACE and help facilitate medical management. This review will discuss coronary microvasculature physiology, CFT, noninvasive diagnostic modalities, and treatment options, as well as knowledge gaps and future directions regarding CMD.

TINY VESSELS, BIG EFFECTS

The coronary microvasculature consists of the smaller cardiac vessels including the pre-arterioles (diameter 100–500 µm) and intracardiac arterioles (< 100 µm).[15] These arterioles are regulated by different mechanisms (**Figure 1**) that work in tandem to modulate cardiac blood flow, as follows:

- Larger proximal arterioles use endothelial-dependent vasodilatory mechanisms by which an increase in coronary blood flow leads to vasodilation and a decrease in blood flow leads to vasoconstriction
- Medium-sized arterioles have vascular smooth muscle cell stretch receptors to detect intraluminal pressure
- The smallest distal arterioles are regulated by local metabolic activity.[15]

The endothelium, or the layer of cells lining the arteries and arterioles, plays a vital role in regulating blood flow to the myocardium.[16] A healthy endothelium promotes vasodilation, antioxidant effects, inhibition of smooth muscle cell proliferation, and anticoagulant effects. Furthermore, endothelial cells act to regulate inflammation and serve as a barrier to potentially toxic materials.[17] An imbalance of nitric oxide consumption is thought to be the primary driver of dysfunction, leading to the inability to properly dilate and to subsequent ischemia.[18] Endothelium dysfunction is a principal contributor to both macro- and microvascular coronary dysfunction and is thought to be a key player in the development of plaque progression and atherosclerosis.[16]

CMD may be characterized by heightened sensitivity of the small vessels to vasoconstrictor stimuli and decreased microvascular vasodilator capacity.[19] In healthy vessels, adenosine, acetylcholine, and nitroglycerin induce vasodilation.[20] However, in patients with CMD, the microvasculature may exhibit a blunted vasodilatory response to these agents. Coronary flow reserve (CFR)—the ratio of coronary blood flow at maximal dilation in response to intracoronary adenosine from baseline—is impaired in patients with CMD. In the setting of endothelial dysfunction, acetylcholine may induce paradoxical vasoconstriction and micro- or macrovascular vasospasm in compromised vessels. Nitroglyc-

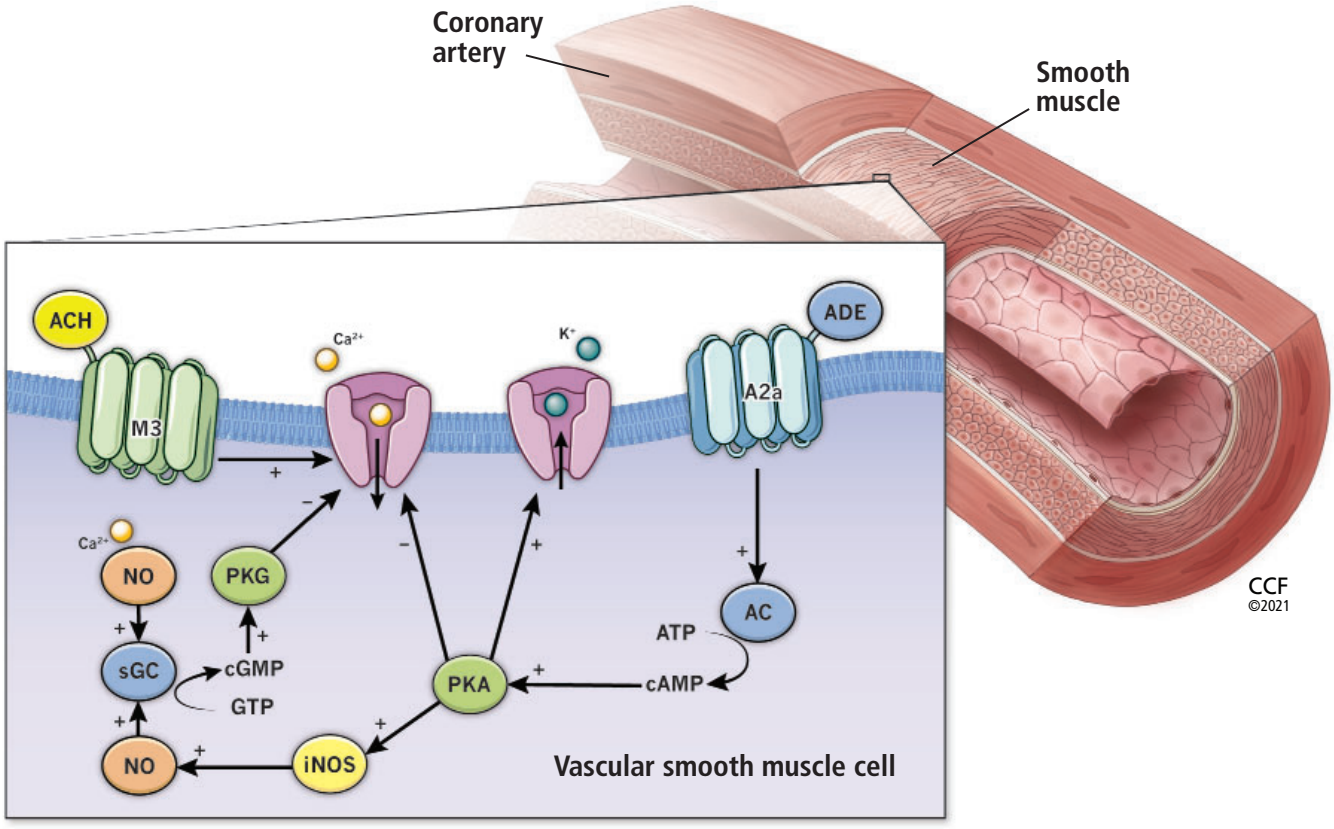

Figure 1. The effects of acetylcholine (ACH) and adenosine (ADE) on the smooth muscle of the coronary vasculature. ACH binds to the muscarinic receptor (M3), stimulating the release of calcium (Ca^{2+}) into the vascular smooth muscle cell, which drives nitric oxide (NO) formation for vasodilation and also drives contraction for vasoconstriction. ADE stimulates the conversion of adenosine triphosphate (ATP) to cyclic adenosine monophosphate (cAMP), leading to inhibition of calcium influx and induction of nitric oxide formation, both of which result in vasodilation.

A2a = adenosine receptor; AC = adenylate cyclase; ACh = acetylcholine; ADE = adenosine; ATP = adenosine triphosphate; Ca^{2+} = calcium; cAMP = cyclic adenosine monophosphate; cGMP = cyclic guanosine monophosphate; eNOS = endothelial nitric oxide synthase; GTP = guanosine triphosphate; iNOS = inducible nitric oxide synthase; M3 = muscarinic receptor; NO = nitric oxide; PKA = protein kinase activation; PKG = guanosine monophosphate-dependent protein kinase; sGC = soluble guanylate-cyclase

erin response is used to evaluate for nonendothelial-dependent macrovascular function.

RISK FACTORS AND CLINICAL PRESENTATION OF MICROVASCULAR DYSFUNCTION

Traditional cardiovascular risk factors, including hypertension, hyperlipidemia, advanced age, obesity, smoking, and diabetes, have been found to be associated with CMD.[19,21] Aging is associated with an increase in arterial wall stiffness, medial thickening, and lumen enlargement that results in an increase in pulse pressure and hypertrophy of arteries, ultimately contributing to endothelial dysfunction.[22] Studies have found that CFR is reduced in patients with diabetes, which is thought to be a consequence of the microvascular inflammation that also leads to diabetic retinopathy and nephropathy.[23] Additionally, smokers and patients with chronic inflammatory conditions such as rheumatoid arthritis and systemic lupus erythematosus often have lower CFR, with a 21% reduction observed in smokers.[24]

Coronary function testing: Protocol and methods

Several protocols exist for coronary function testing for the purposes of evaluating for coronary microvascular dysfunction (CMD) and coronary vasospasm. At our institution, we utilize the following methods:

Patient preparation. Patients fast for 12 hours before the scheduled procedure.[30] To avoid confounding of results, patients are asked to discontinue caffeine, long-acting nitrates, short-acting calcium channel blockers, alpha- and beta-blockers, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, renin and aldosterone inhibitors, ranolazine, diuretics, angiotensin-neprilysin inhibitors, ticagrelor, and aspirin-dipyridamole for 24 hours before the procedure. Long-acting calcium channel blockers are withheld for 48 hours, and sublingual nitroglycerin and nicotine are held for 4 hours prior to testing.

Vasoactive agent preparation. Two concentrations of acetylcholine (0.182 µg/mL and 18.2 µg/mL) are premixed by the hospital pharmacy, within 3 hours of the scheduled procedure.[30] Two doses of adenosine (18 µg and 100 µg) and 200 µg of nitroglycerin are prepared by the catheterization laboratory nursing staff. Of note, the precise agent dosages used may vary by institution.

Angiography to confirm nonobstructive disease. Coronary angiography is performed to assess for atherosclerosis, myocardial bridging, anomalies, and slow flow. Any catheter-induced spasm or chest pain observed during contrast administration or catheter manipulation is also documented. Left ventricular end-diastolic pressure is measured. Fractional flow reserve should be measured to rule out hemodynamically significant stenoses. Any obstructive disease or spontaneous spasm observed at this time may obviate the need for further testing.

Intracoronary vasoactive agent infusions. Patients are given body-weight-adjusted heparin to achieve activated clotting time above 250 seconds.[30] A 0.014-inch Doppler guidewire is placed into the proximal to mid left anterior descending artery until an adequate Doppler signal is obtained. Prior to each infusion, a baseline heart rate, blood pressure, and average peak velocity of blood flow are recorded. At specified time intervals, the peak heart rate, blood pressure, and average peak velocity are documented. The line is flushed, and return to baseline average peak velocity is permitted before infusion of subsequent dosages and agents. Any symptoms, ischemic changes on electrocardiography, or arrhythmias during infusions are noted. Cine images are taken at 2 time points: when the baseline average peak velocity is measured, and immediately after the peak average peak velocity is measured. This allows quantitative coronary angiography measurement of the vessel diameter 5 mm distal to the tip of the Doppler guidewire.

Assessment of mechanistic pathways and significance. This assessment is most often performed to completion in the following order to assess for the simultaneous presence of multiple pathways of coronary artery dysfunction. If the patient experiences a complication at any time, the procedure may be aborted.

1. Nonendothelial dependent microvascular function: First, 18-µg and 100-µg dosages of adenosine are consecutively delivered via intracoronary bolus to induce maximal hyperemia.[30] Coronary flow reserve is calculated as the ratio of the peak to baseline average peak velocities.[30,31] A peak flow reserve < 2.5 is considered abnormal.

2. Endothelial-dependent macrovascular function: Next, the 0.182-µg/mL and 18.2-µg/mL concentrations of acetylcholine are administered via infusion pump at a rate of 2 to 3 mL over 3 minutes. The change in vessel diameter is then calculated by quantitative coronary angiography. An increase in mean lumen diameter of $\leq 5\%$ suggests dysfunction. Of note, the infusion rate may vary according to institutional protocol. Coronary angiography is performed after each dosage of acetylcholine to evaluate for epicardial vasospasm. It is important to withdraw the contents of the guide catheter prior to angiography in order to avoid inadvertently delivering a bolus of any acetylcholine that may be left in the guide catheter after the slow infusion.

3. Endothelial-dependent microvascular function: The aforementioned infusion of the 18.2-µg/mL concentration of acetylcholine is used to calculate coronary blood flow, with 2 to 3 mL infused over 3 minutes. Coronary angiography is performed after each dose of acetylcholine to evaluate for epicardial vasospasm. Again, it is important to withdraw the contents of the guide catheter prior to angiography. A $< 50\%$ increase in coronary blood flow is considered abnormal. As described above, the infusion rate may vary according to institutional protocol.

4. Vasospasm: As the graded 0.182-µg/mL and 18.2-µg/mL dose infusions of acetylcholine are given, the operator assesses for signs of vasospasm. If no spasm is exhibited, a higher concentration of acetylcholine is infused at a rate of 2 mL per minute for 3 minutes. If spasm is provoked, subsequent higher acetylcholine dose testing is withheld, and nitroglycerin is administered immediately. Epicardial vasospasm is defined as a diameter reduction $> 90\%$ associated with chest pain or ischemic ST-segment changes, or both. Microvascular coronary spasm is suggested by chest pain and ischemic ST-segment changes without significant epicardial artery vasoconstriction.

5. Nonendothelial-dependent macrovascular function: After acetylcholine infusion, nitroglycerin (150–200 µg) is given, and quantitative coronary angiography is performed after 30 seconds. Dilation $< 20\%$ is considered abnormal. This measurement allows for assessment of the macrovascular responsiveness to treatment with nitrates.

6. Nociceptive abnormality: Heightened pain sensitivity at any point in the procedure, demonstrated by chest pain during catheter manipulation or contrast administration, is suggestive of nociceptive abnormality.

There is also evidence that women with a history of an adverse pregnancy outcome such as preeclampsia, gestational hypertension, or diabetes may have an increased risk of CMD.[13]

Symptoms include chest discomfort, dyspnea, and reduced exercise tolerance, with some patients having angina that persists after cessation of exertion.[25] Because nitroglycerin acts preferentially to dilate larger vessels of the heart and has little effect on the smaller arterioles, it may not provide symptom relief to patients with CMD.[26] Objective clinical evidence of myocardial ischemia can include elevated troponin levels and ST-segment electrocardiographic or imaging abnormalities at rest or with stress.[27]

CORONARY FUNCTION TESTING

When is it appropriate?

Testing for CMD should be considered for patients with persistent symptoms and objective signs of myocardial ischemia despite absence of obstructive CAD (< 50% coronary artery diameter reduction).[28] But before invasive testing, patients should be evaluated for other diagnoses, including hyperthyroidism, anemia, hypertensive urgency, and substance abuse.

For patients with persistent symptoms but angiographically normal coronary arteries or nonobstructive CAD, the 2019 European Society of Cardiology guidelines recommend "consideration" (ie, the weight of evidence favors efficacy, but it is not well established) of guidewire-based CFR measurements and intracoronary acetylcholine for assessment of spasm.[29] These guidelines also recommend consideration of noninvasive transthoracic Doppler of the left anterior descending artery, cardiac magnetic resonance imaging, and positron emission tomography for CFR measurement.[29]

The decision to proceed with invasive CFT depends on a variety of factors including local hospital practices, patient preference, goals, and availability of CFT and noninvasive diagnostic modalities. Discussion with the patient includes a comprehensive individualized evaluation to determine whether there is more benefit than risk. In patients with prior myocardial infarction or high suspicion for vasospasm, invasive CFT with acetylcholine provocation testing is preferable based on its ability to delineate pathways and elicit spasm.

For a detailed description of the CFT protocol used at our institution, see "**Coronary function testing: Protocol and methods**."[30,31]

Procedure

CFT is an angiographic procedure to evaluate both endothelial-dependent and nonendothelial-dependent macrovascular and microvascular response to vasoactive agents in patients with INOCA (**Table 1**). After diagnostic angiography to exclude obstructive epicardial disease, myocardial bridging, and other coronary anomalies, the drugs adenosine, acetylcholine, and nitroglycerin are administered sequentially to evaluate for microvascular function, vasospasm, and smooth muscle response.[32,33]

Functional testing involves inserting a guiding catheter and positioning a Doppler wire into the coronary artery to be studied. Typically, this evaluation is done in the left anterior descending artery, but it can also be performed in the left circumflex and right coronary arteries.

Adenosine. First, an intracoronary injection of adenosine is given to assess nonendothelial-dependent dysfunction. Flow reserves are measured before and after adenosine administration. Graded doses are used to achieve maximum hyperemia. A CFR below 2.5 is diagnostic for nonendothelial-dependent microvascular dysfunction. When interpreting CFR results, it is important to note that this measurement has been shown to be a continuous predictor of MACE, similar to blood pressure and low-density lipoprotein cholesterol levels.[5] It has also been shown that patients with stable INOCA and a CFR below 2.0 experience higher MACE rates (in females and males).[34] In the WISE study, it was shown that a CFR below 2.32 best predicted adverse outcomes in women.[5]

Coronary microvascular dysfunction is more prevalent in women

Acetylcholine. Next, acetylcholine is administered to assess for endothelial-dependent dysfunction. It is given in increasing concentrations to stimulate the release of nitric oxide. An increase in coronary blood flow less than 50% is diagnostic of endothelial-dependent microvascular dysfunction. Vessel diameter response is measured, and a change of less than 5% is diagnostic for endothelial-dependent macrovascular dysfunction. A

TABLE 1

Invasive coronary function testing in patients with INOCA: Three medications

Drug administered	Results	Diagnosis
1. Adenosine	Coronary flow reserve < 2.5	Nonendothelial-dependent microvascular dysfunction
2. Acetylcholine	< 50% increase in coronary blood flow	Endothelial-dependent microvascular dysfunction
	< 5% increase in coronary artery diameter	Endothelial-dependent macrovascular dysfunction
	> 90% decrease in coronary artery diameter Chest pain and ischemic ST-segment changes on electrocardiography	Epicardial coronary spasm
	Chest pain and ischemic ST-segment changes on electrocardiography in the absence of significant epicardial coronary vasoconstriction	Microvascular coronary spasm
3. Nitroglycerin	< 20% increase in coronary artery diameter	Nonendothelial-dependent macrovascular dysfunction

INOCA = ischemia and no obstructive coronary artery disease (ie, < 50% stenosis)

Endothelial dysfunction contributes to macro- and microvascular coronary dysfunction

higher dose of acetylcholine is given to assess for coronary spasm. Coronary vasospasm is defined as more than a 90% diameter reduction with chest pain and ischemic ST-segment changes on electrocardiography.

Nitroglycerin. The last drug administered is nitroglycerin to test macrovascular function. A change in diameter of less than 20% indicates abnormal smooth muscle reactivity and nonendothelial-dependent macrovascular dysfunction.

If the patient experiences chest pain during catheter manipulation or contrast administration, it suggests nociceptive abnormality. This is thought to be associated with altered afferent neuronal pathways, change in cerebral cortical activation, or reduced endogenous opioid release.[28]

CFT has been shown to be safe and effective overall, with the WISE study reporting a low rate of serious adverse events (0.7%),[32] although these rates were observed at healthcare centers of excellence. A prospective multicenter study has reported cases of coronary artery dissection, ST-elevation myocardial infarction associated with vasospasm, transient air microembolism, and deep vein thrombosis, but the overall rate of periprocedural adverse events was low at 1.4%.[32] As the reactivity testing prolongs the length of angiography, precautions must be taken for those at higher risk of contrast-induced nephropathy.[35] Adenosine should be avoided or used with caution in patients with a history of asthma, as it may contribute to bronchospasm.

OTHER DIAGNOSTIC APPROACHES

Pharmacologic stress testing using noninvasive diagnostic modalities—positron emission tomography, cardiac magnetic resonance imaging, and transthoracic Doppler echocardiography—and an empiric approach to therapy

can also be used to assess for CMD. These may provide a suitable approach for patients who are hesitant to proceed with invasive testing.

Positron emission tomography utilizes various radioactive tracers, in patients both at rest and with vasodilator-induced stress, to quantify absolute myocardial blood flow and detect regional variations suggestive of CMD. Computed tomography can also be performed to determine the coronary artery calcium score for risk stratification.[33]

Cardiac magnetic resonance imaging is a tool with high diagnostic accuracy, low ionizing radiation, and high spatial resolution. It can be used to quantify the myocardial perfusion reserve index and assess for late gadolinium enhancement, a signal of myocardial damage and scar associated with vasomotor dysfunction.[36] The presence of scar is useful for risk stratification. This modality is more widely available than invasive CFT.

Doppler echocardiography of the left anterior descending artery can be used to quantify coronary blood flow. CFR calculated by this procedure has been shown to correlate well with measurements obtained through positron emission tomography and invasive techniques.[30] This method is less expensive and more accessible than other techniques and lacks ionizing radiation, but limits evaluation to that of the left anterior descending artery.

Empiric therapy is an approach that assesses the cardiac response to an empiric trial of drug therapy. For example, in patients with sporadic angina responsive to nitrates suggestive of vasospasm, providers can implement and monitor symptomatic response to a trial of calcium channel blockers. For those with comorbid hyperlipidemia and hypertension and high pretest probability of endothelial dysfunction and CMD, the anginal response to statins and angiotensin-converting enzyme (ACE) inhibitors can be monitored. This approach may be suitable for patients with contraindications or allergies precluding diagnostic procedures.

DRUG AND NONDRUG THERAPIES

Using CFT to identify affected pathways helps guide selection of the best targeted therapies (**Table 2**). It is important to note that treatment strategies are not clear or standardized, largely because of a lack of evidence-based guidelines, but there is some evidence to follow.

TABLE 2

Treatments for coronary microvascular dysfunction based on the pathway identified by invasive coronary function testing

Endothelial dysfunction
Angiotensin-converting enzyme inhibitor
Angiotensin receptor blocker
Statin
L-arginine
Cardiac rehabilitation
Enhanced external counterpulsation
Nonendothelial dysfunction
Angiotensin-converting enzyme inhibitor
Beta-blocker
Alpha-/beta-blocker
Ranolazine
Ivabradine
Phosphodiesterase-5 inhibitor
Vasospasm
Calcium channel blocker
Nitrate
Nociceptive abnormality
Tricyclic antidepressant
Spinal cord stimulation
Cognitive behavior therapy

Nonendothelial-dependent dysfunction

Nonendothelial CMD is treated with drugs targeting ischemia. Beta-blockers and beta-blockers with alpha-blocking activity reduce the frequency and severity of angina and improve CFR.[37] They act by reducing myocardial oxygen consumption and increasing diastolic filling time. Both short-acting and long-acting nitrates help angina by promoting vasodilation and reducing preload.[37] Ranolazine and ivabradine can be considered in patients with

Consider coronary function testing when myocardial ischemia is suspected in the presence of nonobstructive CAD

refractory angina and contraindications to traditional antianginal drugs as they have less hemodynamic effect. More recently, phosphodiesterase-5 inhibitors have been used to drive vasodilation in CMD.

Endothelial dysfunction

Treatment options aimed at both macro- and microvascular dysfunction are similar to those targeting atherosclerotic disease, including ACE inhibitors, angiotensin receptor blockers, statins, and low-dose aspirin. High-dose quinapril has been associated with reduced angina in women with CMD, likely by reducing vascular inflammation.[38] Statins have been shown to improve exercise tolerance and reduce angina due to their anti-inflammatory effects on endothelial function.[39] Aspirin is recommended based on the observation that even if no significant plaque burden is seen on angiography, most patients with CMD have coronary atherosclerosis when evaluated by intravascular ultrasonography.[40] L-arginine, a precursor of nitric oxide, has been shown to improve coronary blood flow.[41]

Vasospasm

Pharmacologic stress testing with noninvasive diagnostic modalities is an alternative to invasive testing

Calcium channel blockers and nitrates are preferred in the setting of vasospastic angina.[29] The calcium channel blockers recommended are amlodipine, diltiazem, verapamil, and long-acting nifedipine. A randomized trial of patients with angina, small coronary arteries, and limited vasodilator reserve showed that patients on verapamil and nifedipine had fewer episodes of angina, consumed fewer nitroglycerin tablets, and had greater exercise tolerance than patients on placebo.[42] Tachyphylaxis is a known risk with long-term nitrate use and, thus, drug-free intervals (12 hours daily) are recommended. Unopposed beta-blockade should be avoided as it may contribute to coronary artery spasm.[43] If beta-blockers are indicated in patients with vasospasm, a combined alpha-beta agent such as carvedilol is favored.

Nociceptive abnormality

For nociceptive abnormality identified by CFT, low-dose tricyclic antidepressants reduce the frequency of angina. In refractory cases, spinal cord stimulation, cognitive behavior therapy, and biofeedback can be considered.[37]

Nonpharmacologic treatments

Several nonpharmacologic approaches are available for CMD. Cardiac rehabilitation has been shown to improve diastolic resting blood pressure, body mass index, and exercise capacity. These programs also improve overall quality of life and psychological morbidity.[37,44] Enhanced external counterpulsation, a therapy consisting of pneumatic stockings on the lower extremities electronically timed to inflate during diastole and deflate during systole, can also improve CMD symptoms.[37] This therapy promotes collateral coronary flow and improves endothelial function by reducing afterload and increasing preload. Therapeutic lifestyle recommendations include smoking cessation, nutrition counseling, weight reduction, and regular, moderate-intensity physical therapy.

KNOWLEDGE GAPS REMAIN

Despite considerable evidence regarding MACE and long-term adverse event prognosis associated with INOCA, neither the American College of Cardiology nor the American Heart Association has guidelines for therapy. As a result, internists and cardiologists may lack confidence in the recognition, diagnosis, and management of this phenotype of ischemic heart disease. In 2017, the American College of Cardiology convened a group to review the current knowledge and provide next steps for evidence-based management.[5] In 2019, the European Society of Cardiology published guidelines for chronic coronary syndromes that include a discussion and recommendation for evaluation of vasospastic and microvascular disease.[29]

At present, no standardized diagnostic algorithm exists. Decisions regarding testing may depend on patient risk stratification (ie, history of prior myocardial infarction), the impact of anginal symptoms on quality of life, and local availability of testing modalities. Compared with noninvasive methods, functional reactivity testing has the benefit of identifying the specific mechanism of dysfunction (ie, nonendothelial-dependent vs endothelial-dependent, presence of spasm, and nociceptive abnormality) to better direct therapy. However, this approach is invasive,

can be time-consuming, and requires specially trained cardiac interventionalists.[27] Ongoing investigations are evaluating how functional testing may be implemented following standard diagnostic angiography when no obstructive lesions are found. A streamlined and abbreviated protocol of adenosine for CFR measurement followed by acetylcholine to observe angiographically for vasospasm can be easily used by interventionalists.

In addition, differences of INOCA in males vs females remain evident and require further investigation. One hypothesis is that women may have a greater ability to widen and narrow arteries perhaps as a result of the need to control blood flow during pregnancy. Additionally, women have been shown to have more pain sensation than men and, thus, may have more perceived pain and anginal symptoms.[45] With regard to outcomes, females with INOCA have been shown to have higher rates of cardiac events than males. One study of 13,695 patients with INOCA found a 3-fold higher MACE rate in women compared with men in the first year.[46] A significant knowledge gap remains on this matter.

FUTURE DIRECTIONS

Recent studies have suggested that cardiomyocyte injury and myocardial stiffness caused by CMD play a role in the pathophysiology of patients with heart failure and preserved ejection fraction (HFpEF).[47] It is hypothesized that microvascular endothelial dysfunction, decreased nitric oxide bioavailability, and increased cytokine signaling may contribute to the increased microvascular inflammation and myocardial fibrosis observed in these patients.[48,49] Clinically, decreased CFR has been found to be associated with diastolic dysfunction and with a 5-fold increased rate of hospitalizations for HFpEF.[47] Clinical studies also suggest a higher prevalence of HFpEF in women than in men.[50] The association between CMD and HFpEF needs further investigation, specifically with regard to sex differences.

To better target prevention and treatment, practitioners need to understand the risk factors. While traditional comorbid risk factors such as hypertension, hyperlipidemia, and diabetes have been implicated, less is known about autoimmune conditions and adverse pregnancy outcomes. Additionally, much remains to be studied about novel risk markers including high-sensitivity C-reactive protein, lipoproteins, interleukins, and other inflammatory markers.

Regarding treatment, more randomized trials are needed to guide an evidence-based approach. The Women's Ischemia Trial to Reduce Events in Nonobstructive CAD (WARRIOR), an ongoing multicenter, prospective, randomized, and blinded outcome trial, is designed to explore the long-term outcomes of intensive statin, ACE inhibitor, and aspirin therapy vs usual care in symptomatic women with INOCA.[51] This trial aims to enroll 4,442 participants. Randomized stem cell trials are also under way to further evaluate the effectiveness of coronary CD34+ infusions in improving CFR in patients with CMD and persistent refractory angina after a trial showed that this treatment effectively reduced hospitalizations, cardiac procedures, and healthcare expenditures in patients with refractory angina.[52]

HOPE FOR STRONG GUIDELINES LIES IN ONGOING CLINICAL TRIALS

In patients who present with angina symptoms but who have no evidence of obstructive coronary artery disease, it is important to consider the diagnoses of INOCA and CMD given the substantial morbidity associated with this condition. At present, there is no uniform comprehensive diagnostic and therapeutic strategy or algorithm, but several options exist. Both noninvasive and invasive tests are available to establish the diagnosis. CFT is currently the therapeutic standard, providing a means to determine the mechanistic pathways for CMD that, in turn, guide targeted therapeutic options with the goal of preventing future adverse cardiac events. Our evolving knowledge of CMD and its management relies on ongoing investigations and outcomes of clinical trials.

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Dr. Wei has disclosed membership on advisory committees or review panels for Abbott Vascular. Dr. Bairey Merz has disclosed consulting for Abbott Diagnostic and Sanofi and board membership for iRhythm. The other authors report no relevant financial relationships which, in the context of their contributions, could be perceived as a potential conflict of interest.

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Rapid cognitive decline and myoclonus in a 52-year-old woman

Her symptoms included confusion, blank staring, blurred vision, incoordination of the extremities, difficulty following commands, and decreased verbal communication

A 52-year-old woman presented to the emergency department in Las Vegas, NV, with progressively worsening altered mental status for the past 2 weeks. A history of symptoms was obtained from the patient's sister, with whom she was staying. The sister reported that during the week before presentation, the patient had episodes of confusion, intermittent blank staring, blurred vision, bilateral incoordination of the upper and lower extremities, difficulty following commands, and decreased verbal communication. The patient had also been holding her left hand in a fist. Two days before presentation, the patient experienced a significant decline in mentation and had multiple episodes of urinary incontinence, which she never had before. During a period of lucidity in the emergency department, the patient denied having fever, chills, nausea, vomiting, chest pain, shortness of breath, abdominal pain, dysuria, or headache.

The patient had a history of major depressive disorder treated with fluoxetine until 8 days before presentation, when she was switched to escitalopram by an outpatient psychiatrist owing to onset of the psychomotor symptoms. The patient had no prior blood transfusions or surgeries and no known drug allergies.

The patient was from California and spoke only Spanish. She was employed by a shoe store, was single, lived alone, and had no children. She had been fully independent in activities of daily living, maintained full-time employment, and was financially stable, but did not have health insurance. She did not smoke, drink alcohol in excess, or use recreational drugs.

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On physical examination, the patient was in moderate distress and exhibited waxing and waning alertness. She was consistently arousable with painful stimulation. She was aware that she was in a hospital that was not in California but was otherwise disoriented. Her Glasgow Coma Scale score was 14 out of 15, ie, responsive (range 3–15, with 3 being completely unresponsive). Her blood pressure was 148/76 mm Hg, heart rate 89 beats per minute, body temperature 36.7°C (98.0°F), and respiratory rate 20 breaths per minute, and the oxygen saturation level was 97% on room air. Body mass index was 30 kg/m^2.

Cardiovascular, pulmonary, and abdominal examinations were normal. The head was normocephalic and atraumatic, with anicteric sclera and moist mucous membranes. Pupils were equal, round, and reactive to light, and extraocular muscles were grossly intact.

On neuropsychiatric examination, the patient had poor concentration and difficulty participating. She had frequent episodes of staring into space with periods of rhythmic jerking of the eyes, head, and bilateral upper extremities (opsoclonus and myoclonus). During lucid intervals, she demonstrated intact cranial nerves II to XII and did not show facial asymmetry, gaze preference, inappropriate saccades, nystagmus, or dysarthria. A Babinski reflex test revealed downgoing toes bilaterally. However, significant spasticity and resistance to range of movements were noted, along with 5 to 7 beats of ankle clonus bilaterally after passive dorsiflexion.

Cerebellar and gait examinations were deferred because of the patient's inability to follow commands. Also, we could not perform a Mini-Mental State Examination or Montreal

Cognitive Assessment. The patient was admitted for further evaluation.

1 Which of the following would be an atypical cause of this patient's rapidly progressive cognitive decline?

- ☐ Stroke
- ☐ Toxic metabolic encephalopathy
- ☐ Infectious encephalomyelitis
- ☐ Psychosis
- ☐ Alzheimer disease
- ☐ Malignancy

DIFFERENTIAL DIAGNOSIS: DISEASES, CONDITIONS TO RULE OUT

The initial differential diagnosis for rapidly progressive cognitive decline includes vasculopathy, toxic metabolic encephalopathy, infectious encephalomyelitis, malignancy, and neurodegenerative and psychiatric causes.

Although this patient's myoclonus, progressive encephalopathy, and waxing and waning alertness would be an atypical presentation for stroke, this should be ruled out first because of the potential for rapid, irreversible ischemia to neural tissue. If diagnosed correctly and early enough, acute stroke can be treated either with antiplatelet therapy for ischemic stroke or with surgical or endovascular management for hemorrhagic stroke.

Drug-induced encephalopathies due to lithium, amitriptyline, and baclofen, heavy metal intoxication (eg, bismuth subsalicylate, manganese), and metabolic encephalopathies such as Wernicke-Korsakoff syndrome and vitamin B_{12} deficiency are all possible causes of rapidly progressive dementia. Given the patient's abrupt transition off fluoxetine before admission, serotonin syndrome is also a consideration.

There are several infectious causes of rapid cognitive decline. These include Whipple disease (subacute dementia, ataxia, and myoclonus), human immunodeficiency virus (HIV) encephalitis, tuberculosis, herpes simplex encephalitis, and subacute sclerosing panencephalitis.[1,2] While not strictly caused by infectious pathogens, spongiform encephalopathies (also called prion diseases) such as fatal familial insomnia, kuru, and Creutzfeldt-Jakob disease (CJD) can present with rapid cognitive decline. Autoimmune etiologies should also be considered, including antibodies to both extracellular antigens such as *N*-methyl-D-aspartate receptor and intracellular antigens such as Hu antigens.

Common causes of chronic cognitive decline include neurodegenerative diseases such as Alzheimer disease and frontotemporal dementia (Pick disease), and dementia associated with movement disorders, such as Parkinson disease, Lewy body dementia, and Huntington disease. Although cognitive decline typically occurs over years in these diseases, atypical presentations can lead to rapidly progressive dementia in 15% to 25% of cases and thus should be considered in such cases.[3]

Vascular dementia (eg, multi-infarct dementia, subcortical arteriosclerotic encephalopathy) should be considered in patients with a history of or risk factors for atherosclerotic vascular disease such as diabetes mellitus and hypertension, and risk factors for thromboembolism such as atrial fibrillation and endocarditis. Additional vascular causes could be autoimmune or inflammatory in nature, including primary central nervous system vasculitis or Susac syndrome. Processes that result in mass-effect central nervous system changes can facilitate acute or chronic cognitive decline. These include tumor and cyst, and disorders of cerebrospinal fluid (CSF) production or outflow, such as normal pressure hydrocephalus.

Initial diagnostic workup

In patients with rapid cognitive decline, the initial workup includes a variety of imaging and laboratory testing. Imaging should include urgent computed tomography (CT) of the head without contrast to assess for hemorrhage and mass effect, magnetic resonance imaging (MRI) of the brain, vascular imaging of the head and neck (options include magnetic resonance angiography, CT angiography, and ultrasonography), and echocardiography. Initial laboratory tests should include complete blood cell count, serum thyroid-stimulating hormone, electrolytes (including sodium, calcium, blood urea nitrogen, and creatinine), liver enzyme tests, and toxicology screening. If imaging or the history does not indicate stroke, additional testing can include thiamine and vitamin B_{12} (cobalamin) levels, serologic testing for HIV, hepatitis, and syphilis, and CSF studies, including glucose,

Infectious causes of rapid cognitive decline include Whipple disease, HIV encephalitis, tuberculosis, herpes simplex encephalitis

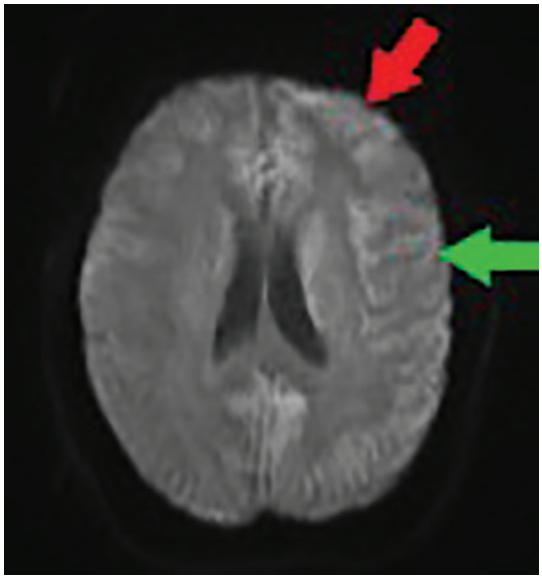

Figure 1. Diffusion-weighted magnetic resonance imaging at admission shows cortical bifrontal (red arrow) and parietal (green arrow) diffusion (cortical ribboning), with greater intensity on the left. No thalamic hyperintensity was seen. Note that the quality of this image was affected by patient movement during the procedure, in spite of attempts to sedate her.

Serotonin syndrome was unlikely as her symptoms were progressive in onset (> 24 hours) and began before switching to escitalopram

protein, gram stain, and culture. These tests can rule out most reversible causes of rapidly progressive dementia, such as infection or metabolic abnormalities.[4]

The most common first-line test for vitamin B_{12} deficiency is the serum vitamin B_{12} level, which has reasonable sensitivity and is widely available and relatively inexpensive. The serum methylmalonic acid level, the standard confirmatory test, has both higher sensitivity and specificity than serum vitamin B_{12} and can be used to track treatment response, but it is less widely available and more expensive. In practice, it is not unreasonable to order both tests at once if resources allow and if pretest probability for vitamin B_{12} deficiency is moderate or high.[5,6]

CASE CONTINUED

Based on the patient's presentation, several potential diagnoses were ruled out. Serotonin syndrome was determined to be unlikely because her symptoms were more progressive in onset (> 24 hours) and began before switching to escitalopram. This was further supported by lack of spontaneous clonus, diaphoresis, agitation, hyperreflexia, or body temperature above 38°C (100.4°F).

The complete blood cell count results showed no leukocytosis, a mean cellular volume of 89.7 fL (reference range 80.1–98.4), and a hemoglobin of 14.8 g/dL (11.0–14.9). An electrolyte panel was normal except for hypokalemia, with a level of 2.9 mmol/L (3.5–5.0). Phosphate and magnesium levels were normal. Results from tests for thyroid function, liver function, vitamin B_{12}, thiamine, and vitamin E were all within normal limits. A urine toxicology screen was negative. Microbiological screening assay results were negative for HIV-1 and HIV-2, viral hepatitis, syphilis, and Lyme disease.

In the likely absence of other infectious causes, fungal infection was considered. However, a beta-D-glucan assay for invasive or disseminated fungal infections was negative.

Imaging studies

CT of the head without contrast was negative for edema, herniation, hemorrhage, and ventriculomegaly, effectively ruling out mass effect or normal pressure hydrocephalus.

Brain MRI showed cortical bifrontal and parietal diffusion restriction on diffusion-weighted imaging—a finding also called cortical ribboning (**Figure 1**). No thalamic hyperintensity was noted. No multiple infarcts suggestive of progressive vascular dementia were seen; these are typically seen with primary angiitis of the central nervous system or uncontrolled hypertension or diabetes.

CT angiography of the head and neck to further assess for vascular causes (ie, primary central nervous system vasculitis) noted no vascular abnormality. Echocardiography to investigate a source of possible embolus showed normal left ventricular function and no valvular pathology or thrombus. Electrocardiography showed normal sinus rhythm.

Additional laboratory testing

CSF testing showed clear, colorless fluid, glucose within normal limits, white blood cell count of 3×10^9/L (reference range 5–10), and red blood cell count of 19×10^{12}/L (4.2–6.1). No oligoclonal bands or organisms were seen, and CSF cultures were negative. Results from

a CSF Venereal Disease Research Laboratory test and 14-pathogen meningitis polymerase chain reaction panel were also negative. (The meningitis panel detects 14 bacterial, viral, and fungal pathogens: *Escherichia coli* K1, *Haemophilus influenzae*, *Listeria monocytogenes*, *Streptococcus agalactiae*, *Streptococcus pneumoniae*, cytomegalovirus, enterovirus, herpes simplex virus 1 and 2, human herpesvirus 6, human parechovirus, varicella zoster virus, and *Cryptococcus neoformans/gatti*.)

Both the CSF protein and myelin basic protein were mildly elevated: CSF protein 65 mg/dL (14–40), myelin basic protein 6.7 ng/mL (0.0–1.2). While these CSF findings can be suggestive of multiple sclerosis,[7,8] the clinical presentation and MRI findings did not suggest multiple sclerosis and oligoclonal bands were negative, effectively ruling out this diagnosis. As imaging findings were not consistent with progressive multifocal luekoencephalopathy and there was no history of immunosuppression, the John Cunningham viral polymerase chain reaction test was not performed on the CSF sample. A CSF analysis for diagnostic markers of Alzheimer disease, including CSF total amyloid, hyperphosphorylated tau (p-tau), and tau-tau ratio, also was not conducted during the initial evaluation, since rapidly progressive Alzheimer disease typically takes months to years to evolve, as opposed to our patient's 2-week decline.[9,10]

The bottom line

The patient's initial radiologic and laboratory results were largely unremarkable, except for mild CSF protein elevation and cortical ribboning on brain MRI, significant progressive cognitive decline, and myoclonus. Therefore, our focus shifted to less common causes of altered mental status, including antibody-mediated encephalitis (50–80 cases per million people per year, according to a prospective study in England),[11,12] paraneoplastic syndrome, and prion diseases including CJD (1–1.5 cases per million population per year).[13]

AUTOANTIBODY ENCEPHALITIS: WHAT TO LOOK FOR

Antibody-mediated encephalitis

Antibody-mediated (or autoimmune) encephalitis is a class of disorders caused by antibodies typically directed against cell-surface antigens located on various components of the central nervous system. They are characterized by a wide range of neuropsychiatric symptoms, including behavioral changes, seizures, and abnormal movements. Autoantibody encephalitis can occur at all ages.

Cases typically resolve partially or completely with appropriate diagnosis and treatment. Treatment is focused on removal of any identifiable triggers (eg, tumor) and immunosuppression with systemic glucocorticoids, intravenous immunoglobulin, or plasmapheresis.

While there are more than 15 antibody-associated encephalitides that have been identified, the most common subtypes are anti-*N*-methyl-D-aspartate receptor antibody encephalitis (incidence of 1.5 cases per million per year) and leucine-rich glioma-inactivated 1 autoantibody encephalitis (0.8 cases per million per year according to a retrospective Dutch study).[12,14]

Paraneoplastic syndromes

Paraneoplastic syndromes are the result of immune-mediated damage from malignancy-associated antibodies directed against intracellular proteins. Commonly implicated antibodies in paraneoplastic encephalitis include anti-Hu, anti-Yo, and anti-Ma antibodies.

Signs and symptoms depend on the affected component of the nervous system and may include confusion, myoclonus, and ataxia. It is not uncommon for patients to initially seek medical care for paraneoplastic symptoms resulting from an undiagnosed malignancy.[15]

As with the antibody-mediated encephalitides, treatment is focused on removing the underlying trigger (in this case, malignancy), and immunosuppression. Immunosuppression therapies include systemic glucocorticoids, intravenous immunoglobulin, and plasmapheresis; medications such as mycophenolate mofetil and tacrolimus are options if there is concern for a T-cell mediated process.[15]

Prion diseases

Prion diseases (spongiform encephalopathy) are a class of neurodegenerative diseases caused by cerebral deposition of misfolded protein and characterized by long incubation periods followed by rapid progression once clinical symptoms present.[16] Sporadic CJD (sCJD) is by far the most common prion dis-

Include sCJD in the differential diagnosis in any patient presenting with a history of rapidly progressive dementia and myoclonus

ease, accounting for 90% of all cases.[17]

The classic clinical manifestations of sCJD are mental deterioration and myoclonus.[18] Most patients are 50 to 70 years old and demonstrate rapidly progressive cognitive impairment and confusion, sometimes with cortical visual disturbances and ataxia. The cognitive syndrome of sCJD is the most commonly reported early symptom (40%), but it can be preceded by mild psychiatric symptoms such as malaise, anxiety, mood changes, and decreased ability to concentrate.[19]

Sleep disturbances, especially hypersomnia, are also common and may be a presenting sign of sCJD.[20] Visual disturbances and oculomotor dysfunction are rarely an early symptom (7%)[19] but frequently occur (42%) during the clinical course.[21] On neurologic examination, dementia patterns may include apraxia, aphasia, inappropriate jocularity, inability to follow commands, and inattention.[22] Involuntary movements can include myoclonus, chorea, dystonia, and tremor. In fact, myoclonus is present in more than 90% of patients with sCJD at some point during their illness.[23] Thus, sCJD should be included in the differential diagnosis in any patient presenting with a history of rapidly progressive dementia and myoclonus.

EEG is an important component in the clinical diagnosis of Creutzfeld-Jakob disease

CASE CONTINUED

After ruling out the more common causes of the patient's worsening altered mental status, diagnostic laboratory testing was pursued for antibody-mediated and paraneoplastic encephalitis and prion disease.

On day 3 of her hospitalization, results from an autoantibody panel were negative, including serum and CSF testing for anti-*N*-methyl-D-aspartate immunoglobulin G. On this same day, a CSF sample was sent to an outside facility for prion disease biomarker testing. Several days later, blood samples were sent to an outside facility for testing with a paraneoplastic antibody panel. Results would not be available for several weeks.

In the interim, CT of the abdomen, pelvis, and chest was done for possible malignancy. The results were normal.

In the absence of CT findings, positron emission tomography to evaluate for malignancy would have been ideal, given its increased sensitivity and specificity for malignancy of the chest, head, and neck[24] but was unavailable at our hospital. Transferring the patient to have the test at a different facility was not possible due to health insurance coverage restrictions.

Therefore, we started empiric treatment for autoimmune and paraneoplastic encephalitis with 5 days of methylprednisolone 1 g, followed by 5 days of 0.2 g/kg of intravenous immunoglobulin, and then 5 days of plasmapheresis.

This treatment has been shown to improve neurologic symptoms (eg, behavior, cognition, speech, memory, seizures) in about half of patients within the first 4 weeks of first-line therapy.[25]

Her clinical condition continued to deteriorate. Although the paraneoplastic antibody panel testing was still in process at that time, the absence of an identifiable malignancy and lack of improvement with empiric treatment with corticosteroids, intravenous immunoglobulin, and plasmapheresis argued against autoimmune and paraneoplastic encephalitis, increasing our clinical suspicion for prion disease.

NEXT STEP: ADDITIONAL IMAGING

While the diagnostic workup and therapeutic efforts were being pursued, several electroencephalography (EEG) recordings were obtained.

2 What is the most typical EEG finding in a patient with spontaneous CJD?

- ☐ Sporadic delta-wave activity
- ☐ Triphasic sharp-wave complexes
- ☐ K-complexes
- ☐ Beta-wave activity

Electroencephalography

EEG is an important component in the clinical diagnosis of CJD. A typical pattern of generalized, periodic, biphasic, or triphasic sharp-wave complexes of 1 to 2 Hz is reported in 65% of patients with sCJD.[26,27] Periodic sharp waves have also been reported in cases of familial CJD. These EEG changes may not appear until later in the course of the disease, but if nonspecific findings are present on EEG, then frequent serial EEG is recommended.

It is important to recognize that EEG patterns in sCJD are nonspecific and can be observed in other causes of dementia. It should

TABLE 1

Diagnostic tests for Creutzfeldt-Jakob disease: Sensitivity and specificity

Testing	Sensitivity	Specificity	Diagnostic criteria	Notes
Magnetic resonance imaging				
DWI or FLAIR[30]	83%	83%	At least 2 cortical regions affected (parietal–temporal–occipital) or both putamen and nucleus caudatum affected	Retrospective evaluation of pathology-proven CJD
DWI and FLAIR[31]	91%	95%	2005 UCSF MRI criteria for CJD[31]	Retrospective evaluation of clinically diagnosed prion disease, majority spontaneous CJD (83%); excellent interreader reliability (kappa 0.96)
DWI and FLAIR[32]	96%	93%	2005 UCSF MRI criteria for CJD[31]	Retrospective evaluation of clinically diagnosed prion disease, majority spontaneous CJD (79%)
DWI[33]	92%	94%	High-intensity lesions in the striatum (caudate or putamen, or both), lesions in the thalamus including the pulvinar, and/or lesions along the cortical ribbon (cerebral or cerebellar)	Retrospective evaluation of clinically diagnosed prion disease, majority spontaneous CJD (78%)
Electroencephalography[32]				
	64%	91%	1996 Steinhoff criteria[27]	Retrospective evaluation of pathology-proven CJD
Cerebrospinal fluid studies[34]				
14-3-3 protein	83%	63%	Positive test	Retrospective analysis of 111 neuropathologically confirmed sCJD cases
Total tau protein	91%	46%	Positive test	
RT-QuIC	92%	99%	Positive test	

CJD = Creutzfeldt-Jakob disease; DWI = diffusion-weighted imaging; FLAIR = fluid-attenuated inversion recovery; RT-QuIC = real-time quaking-induced conversion; sCJD = sporadic Creutzfeldt-Jakob disease; UCSF = University of California, San Francisco

also be noted that variant CJD, a different CJD subtype, does not have the same pattern on EEG as sCJD. Instead, it shows nonspecific slow wave activity without periodic triphasic complexes. Sporadic delta waves are characteristic of physiologic stage N2 and N3 sleep, and K-complexes are characteristic of stage N2 sleep. Beta-wave activity on EEG is characteristic in wakefulness and rapid-eye- movement sleep.[28]

Magnetic resonance imaging

MRI is a useful diagnostic tool in the context of suspected CJD. In sCJD, T2-weighted MRI with fluid-attenuated inversion recovery (FLAIR) will often show hyperintensity of the putamen and the head of the caudate (sensitivity 67%, specificity 93%), although numerous etiologies, including toxic, metabolic, hypoxic, and vascular, can cause hyperintensity within the basal ganglia.[29] In 90% of cases of variant CJD, T2-weighted MRI demonstrates hyperintensity of the posterior (pulvinar sign) (sensitivity 92%, specificity 95%) and dorsomedial thalamus (hockey-stick sign).[23] **Table 1** lists the sensitivity and specificity of diagnostic tests for CJD.[26,27,30–34]

In both sCJD and variant CJD, diffusion-weighted imaging on MRI in particular has been shown to detect disease with high sensitivity (96%) and specificity (93%). Cortical diffusion restriction (cortical ribboning) is a characteristic feature of sCJD

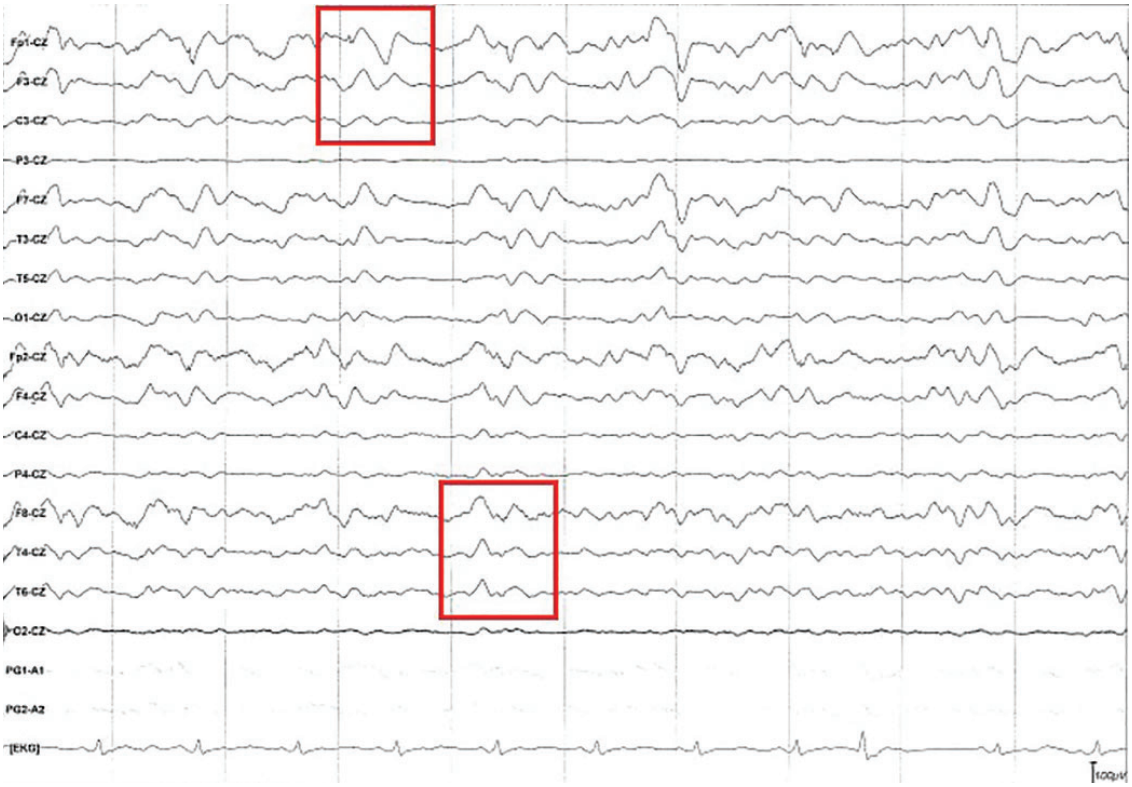

Figure 2. Electroencephalography showed continuous triphasic waves (red boxes) and diffuse cortical slowing. Diffuse slowing is seen throughout the recording, as the background frequency consists mostly of theta waves (frequency 4–7 Hz) despite provoking maneuvers and the patient not being on sedating medications.

Although CT is often one of the first tests ordered in the ER to assess altered mental status, it is not associated with distinct findings for Creutzfeldt-Jakob disease

but can also be seen in the acute phase of viral encephalitis and focal status epilepticus. Further, cortical ribboning decreases in late stages of sCJD.[35]

That said, hyperintensity that is more pronounced on diffusion-weighted imaging than on FLAIR has been determined to be crucial when differentiating sCJD from non-prion causes of rapidly progressive dementia, as was seen in all 48 cases in a cohort of sCJD patients.[32] Based on these findings, neuroradiologists at the University of California, San Francisco, proposed MRI criteria for the diagnosis of definite CJD, including diffusion-weighted imaging and FLAIR hyperintensity within the cortex (> 1 gyrus) and striatum or only in the cortex (> 3 gyri).[32]

Although CT is often one of the first tests ordered in the emergency department for assessment of altered mental status, it is not associated with distinct findings for CJD.[23]

CASE CONTINUED

To investigate acute cognitive decline with myoclonus, EEG performed following admission and again on hospital day 11 showed diffuse cortical slowing, with triphasic wave morphology present throughout the tracing (**Figure 2**). No seizures were observed during the studies, effectively ruling out status epilepticus.

However, after multiple episodes of seizure-like activity and decline in mentation, the patient was upgraded to critical care on day 14. On day 17, EEG again showed diffuse slow waves with triphasic morphology but no seizure activity, despite the presence of posturing movement during the study. The interpreting neurologist noted that the findings on EEG might be associated with CJD. Repeat MRI on day 20 showed resolution of cortical diffusion restriction and continued paucity of thalamic hyperintensity. These findings were also suspicious for sCJD, as the cortical ribboning seen on MRI in sCJD often fades late in the disease course.[35]

On day 18, due to our patient's continued decline in respiratory and neurologic function (her Glasgow Coma Scale score had dropped to 8), she was intubated and started on enteral tube feedings. This decision was based on doubts about the diagnosis (although there was growing concern for prion disease at this point) and the next of kin's wishes that full medical interventions be pursued until additional family could visit the patient. In cases of likely or definite diagnosis of CJD and other end-of-life scenarios, intubation and enteral feeding are not recommended.

On day 20, the paraneoplastic panel returned negative results for all tested antibodies, including anti-Ma and anti-Hu antibodies. Carotid artery angiography to assess for vasculitis was also negative. The patient experienced several seizure-like events, and decorticate posturing was noted on day 22.

At this point, diagnostic testing had been either negative or yielded only nonspecific findings, and attempted treatments had failed to stall or improve the patient's neurologic decline. The only pending test result was for CSF prion disease biomarkers, which had been sent out on day 3.

3 Which of the following is the most helpful CSF test to order if you suspect prion disease?

- ☐ Myelin basic protein
- ☐ Oligoclonal bands
- ☐ Amyloid beta 1-42
- ☐ 14-3-3 protein
- ☐ Real-time quaking-induced conversion (RT-QuIC)
- ☐ Neuron-specific enolase

WHY TEST FOR PRION DISEASE?

CSF analysis can provide additional data if the diagnosis of CJD is uncertain. RT-QuIC monitors for formation of amyloid in real time after adding disease-associated prion protein (PrPSc) from the patient (if present) to recombinant prion protein. The mixture is shaken vigorously, exploiting the ability of PrPSc to induce misfolding of recombinant prion protein, forming aggregates. The formation of the aggregates is monitored in real time using a fluorescent dye, thioflavin T.[36] Currently, the National Prion Disease Pathology Surveillance Center at Case Western Reserve University in Cleveland, OH, is the only facility in the United States that performs the RT-QuIC assay.[37]

The 14-3-3 protein is believed to be a marker of massive neuronal disruption and leakage of brain proteins into the CSF.[38] The protein biomarker total tau (t-tau), another marker of neuronal death, has been found to be elevated in CSF in patients with sCJD, with 1 study showing it to be a more specific but less sensitive test than the 14-3-3 protein assay.[39]

The American Academy of Neurology previously recommended CSF testing for the 14-3-3 protein to decrease uncertainty of diagnosis in patients with rapidly progressive dementia and strong suggestion of sCJD.[40] However, RT-QuIC has been shown to be a much more powerful diagnostic assay. The American Academy of Neurology has not up-

TABLE 2

Criteria for probable diagnosis of sporadic CJD

1. Neuropsychiatric disorder plus positive RT-QuIC in cerebrospinal fluid or other tissues

   OR

2. All 3 of the following subcriteria:

   2a. Rapidly progressive dementia and at least 2 of these 4 clinical features:
   - Myoclonus
   - Visual or cerebellar disturbances
   - Pyramidal or extrapyramidal dysfunction
   - Akinetic mutism

   2b. A positive result on at least 1 of the following laboratory tests:
   - Typical electroencephalogram (periodic sharp-wave complexes) during an illness of any duration
   - Positive 14-3-3 protein cerebrospinal fluid assay in patient with a disease duration of less than 2 years
   - High signal in caudate and/or putamen on MRI, or in at least 2 cortical regions (temporal, parietal, occipital) on DWI or FLAIR

   2c. No routine investigation indicates an alternative diagnosis

CJD = Creutzfeldt-Jakob disease DWI = diffusion-weighted imaging; FLAIR = fluid-attenuated inversion recovery; MRI = magnetic resonance imaging; RT-QuIC = real-time quaking-induced conversion;

From US Centers for Disease Control and Prevention, reference 41.

dated its recommendation for testing for sCJD since 2012, around the same time that studies showing the favorable test characterstics of RT-QuIC began to be published. A retrospective analysis of 111 pathologically confirmed sCJD cases found that RT-QuIC had superior sensitivity and specificity in the diagnosis of sCJD when compared with 14-3-3 protein or t-tau (**Table 1**).[34] A prospective analysis of these data showed similar results.[34]

Making a probable diagnosis

As such, a positive RT-QuIC assay is a highly weighted component of the scoring systems used to make the probable diagnosis of sCJD (**Table 2**).[41] However, RT-QuIC can be less sensitive in some molecular subtypes of sCJD, so a negative test does not necessarily rule out the disease. In those cases, 14-3-3 protein results, clinical presentation, and characteristic findings on MRI and EEG can aid the diagnosis.[34]

It should be noted that the most recent World Health Organization guidelines for diagnosis of CJD (released in 2003)[23] do not take RT-QuIC into account, and thus it may be considered out of date.

The results of off-site CSF analysis were nearly 100% specific for sporadic Creutzfeldt-Jakob disease

High levels of myelin basic protein and oligoclonal Ig G bands are CSF findings useful to diagnose demyelinating disorders such as multiple sclerosis.[42] Amyloid beta (along with t-tau, p-tau, and tau-tau ratio)[9] is a protein essential to the pathogenesis of Alzheimer disease, implicated in free radical-induced oxidative stress.[43] Neuron-specific enolase is a marker that has great utility in the evaluation of both small cell and non-small cell lung cancers, stroke and brain injury, neuroendocrine tumors, and neuroblastoma.[44]

CASE CONTINUED

On day 26, the off-site CSF analysis returned positive results for RT-QuIC, 14-3-3 protein, and t-tau protein. In combination, these results are nearly 100% specific for sCJD and make other causes of dementia, such as Alzheimer disease, frontotemporal dementia, or Lewy body dementia, unlikely. The poor prognosis of CJD was discussed with the patient's sister, but further action was deferred.

The patient was noted to have continued posturing and no longer withdrew from painful stimuli or tracked objects. When the patient's brother arrived on day 31, the family requested palliative care only. The patient was extubated and prescribed midazolam and fentanyl. She exhibited labored breathing with substernal retractions and died on hospital day 37.

EPIDEMIOLOGY OF PRION DISEASES

As noted earlier, prion diseases are neurodegenerative diseases with long incubation periods but with rapid progression once symptoms emerge. There are 5 recognized prion diseases: kuru, CJD, variant CJD, Gerstmann-Straussler-Scheinker syndrome, and fatal familial insomnia. Of these, CJD accounts for more than 90% of prion disease cases.[17] However, the low incidence of CJD—about 1 case per 1 million individuals per year[16]—can present diagnostic challenges to practitioners unfamiliar with the disease.

Sporadic, familial, iatrogenic, and variant forms of CJD are all recognized (variant CJD is sometimes categorized separately because of its distinct clinical and pathological findings).[45] The vast majority of CJD cases (85% to 95%) are sporadic. Familial CJD accounts for 5% to 15% of cases but is much less common, accounting for fewer than 1 case per 10 million people.[18,23] However, a single autosomal dominant trait (PRNP E200K–129M) accounts for 70% of familial CJD cases, which are clustered among populations in Chile, Italy, Japan, and Slovakia, and in Jews from Libya.[46] Variant CJD is the disease type transmitted from bovine spongiform encephalopathy. As of February 2020, only 235 cases of variant CJD had been reported since 1980.[47]

What are the risk factors for CJD?

Several studies have attempted to identify risk factors for sCJD. A review of 3 case-control studies published in 1996 showed that a family history of CJD (odds ratio [OR] 19.1) and a medical history of psychosis (OR 9.9) were the only factors significantly associated with the disease.[48] A study conducted in Australia found that living or working on a farm for more than 10 years was associated with a significantly increased risk for sCJD (OR 2.61, 95% CI 1.34–3.41).[49] A systematic review

published in 2017 reported, based on very low-quality evidence, that sCJD was associated with heart (OR 1.96) and vascular (OR 2.13) surgery.[50] However, the low incidence of the disease makes it difficult to assess predisposing factors.

PATHOLOGY DRIVES PRECAUTIONS

Classic neuropathologic findings in CJD are marked neuronal loss, spongiform change, and astrogliosis. However, immunohistochemical staining for prion protein is considered the technical standard for diagnosing CJD (**Figure 3**).[51]

4 What precautions are required if CJD is suspected or diagnosed?

- ☐ Strict isolation with hazardous material suit
- ☐ Contact precautions with gloves and gowns
- ☐ Droplet precautions
- ☐ Airborne precautions
- ☐ Strict universal precautions, special attention to instrument-, body fluid-, and tissue-handling, and transport

Prion diseases are transmitted through contaminated instruments and infected tissues, with different tissues being categorized as having high or low infectivity. High-infectivity tissues include brain, spinal cord, eye tissues, spinal ganglia, and trigeminal ganglia. Low-infectivity tissues include CSF, peripheral nerves, blood, kidney, liver, lung, lymph nodes and spleen, and placenta.[52] There have been only 4 cases of variant CJD transmitted via blood transfusion.[53] No person-to-person transmission has been reported through usual contact. If a patient is suspected to have CJD, the following measures should be taken to prevent iatrogenic or nosocomial exposure to prion disease:

- Screen donor sources of dura and cornea
- Label all reusable instruments that have contacted low- or high-infectivity tissue as "biohazard," place them in a robust, leakproof container, and transport them to sterilization as soon as possible after use
- Incinerate all disposable instruments and treat heat-resistant instruments with sodium hydroxide
- Treat CSF as if it were highly infective tissue
- Take World Health Organization precautions for high- and low-infectivity tissues from patients with known or suspected CJD.[23]

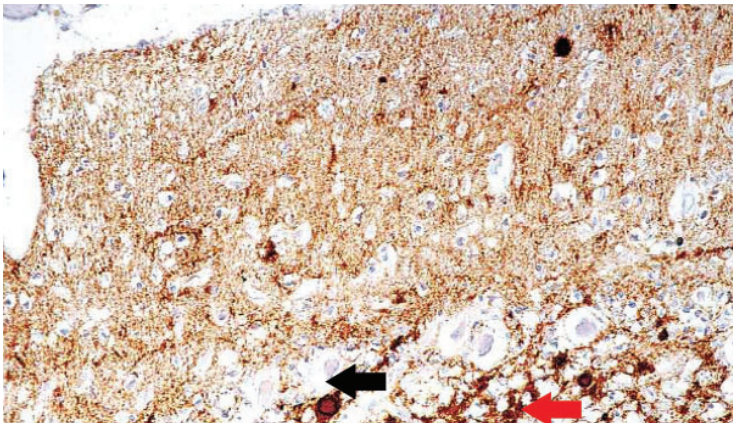

Figure 3. Immunohistochemical staining shows fine prion protein deposits in the molecular layer, coarser deposits in the granular layer, and plaques in both layers of the cerebellum (magnification × 600). Fine deposits in the upper portion (molecular layer) of the image appear as numerous dark deposits. The red arrow points to coarse deposits in the granular layer, and the black arrow points to plaque.

From Kovács GG, Head MW, Hegyi I, et al. Immunohistochemistry for the prion protein: comparison of different monoclonal antibodies in human prion disease subtypes. Brain Pathol 2002; 12(1):1–11. doi:10.1111/j.1750-3639.2002.tb00417.x. Copyright John Wiley and Sons, Inc. Reprinted with permission..

TREATMENT AND PROGNOSIS

Unfortunately, there is no curative treatment for the underlying disease process of CJD. Attempts at treatment of myoclonus using clonazepam or valproate may be helpful for palliation.[23]

Prognostically, CJD is characterized by a rapidly deteriorating course. Death usually occurs within 1 to 2 years of symptom onset, most often from aspiration pneumonia.[22,23] However, the time from presentation to death can vary among the subtypes of CJD. Based on a systematic review of more than 9,000 patients, sCJD and familial CJD have the most rapid clinical deterioration (median mortality 6 months), iatrogenic CJD has a slightly longer course (median mortality 9 months), and variant CJD and inherited prion disease have the longest course (median mortality 14 months).[23]

Within sCJD, there are various molecular subtypes characterized by the presence of a valine or methionine allele at codon 129 of the prion protein gene, as well as the type of PrPSc (type 1 vs type 2), that can also affect the prognosis. For example, homozygosity for methionine at codon 129 and expression of PrPSc type 1 is the most common subtype and has the shortest duration from symptom onset to death (mean 3.9 months). Meanwhile, me-

Immunohistochemical staining for prion protein is considered the technical standard for diagnosing Creutzfeldt-Jakob disease

thionine-valine heterozygosity and expression of PrPSc type 2 has a more prolonged course (mean 17.1 months).[54]

Genetic testing for prion protein gene allelic mutations is available for patients with a family history of CJD. A diagnosis of familial CJD can be confirmed with a recognized prion protein mutation (of which there are at least 41 from unrelated families) and a definite or probable transmissible spongiform encephalopathy in a first-degree relative.

The National CJD Research & Surveillance Unit (based at the University of Edinburgh, Scotland, UK) recommends genetic analysis for prion protein codon mutations to exclude the possibility of genetic disease.[55] All patients who die with suspected or probable sporadic or variant CJD should have brain tissue frozen and sectioned postmortem to confirm the presence of PrPSc and make the definitive diagnosis.

TAKE-HOME MESSAGES

There are many possible infectious and neurodegenerative causes of dementia, making the differential diagnosis broad. Given our patient's lack of risk factors for CJD (eg, no family history of psychosis or CJD), it was low on the initial list of diagnostic considerations. However, through a systematic approach and diagnostic workup, the relatively common causes were quickly ruled out, thus increasing suspicion for CJD.

Practitioners can rely on the patient's medical history and a thorough neuropsychiatric assessment to guide clinical suspicions. If support is lacking for more common diagnoses, the clinician can reach a probable diagnosis of sCJD through CSF assay and commonly ordered imaging studies.

Although prompt diagnosis does not alter the prognosis, it does provide benefits in 2 important ways. First and foremost, it helps to prevent the family from developing unrealistic expectations of patient recovery, informs decision-making on goals of care, and allows them to appropriately grieve for their loved one. Second, it serves as an educational opportunity for all healthcare professionals involved, encouraging them to widen their differential diagnosis, consider uncommon investigations, and communicate complex ideas to both colleagues and patients.

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