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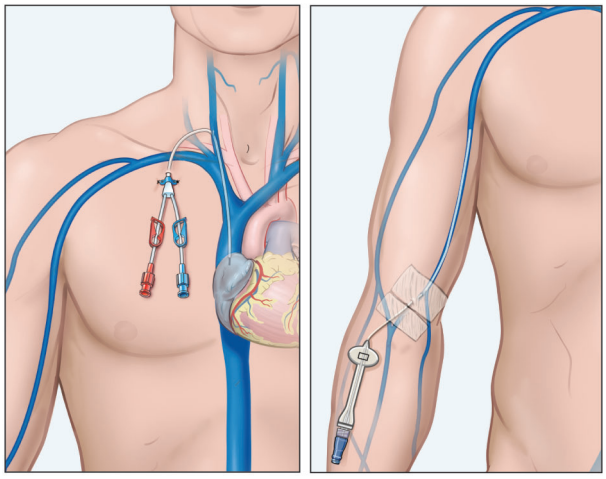

Embedded Health System Research: Studying delivery system change

Tuesday, Sept. 14, Noon-1 pm | Virtual

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Brian S. Mittman, PhD, Senior Scientist, Kaiser Permanente Southern California Department of Research and Evaluation; Co-Lead, Implementation and Improvement Science Initiative, UCLA Clinical and Translational Science Institute; Research Faculty, Suzanne Dworak-Peck School of Social Work

Grant Reed, MD, MSc, Interventional cardiologist; Director of Cleveland Clinic's STEMI Program; Quality Improvement Officer, Interventional Cardiology; Associate Program Director, Cardiovascular Medicine Fellowship

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- Define embedded health system research and understand its relevance for implementation science
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Autoimmune brain disease: Think before testing

As a rheumatologist, I have the opportunity to see many patients in consultation for the evaluation of complex and often difficult-to-define symptoms. The buzzword referral diagnosis is frequently "autoimmune." In 2021, autoimmune is seemingly the evil humor or miasma of centuries past revisited, with the added distinction that there are laboratory tests that can be ordered that, if positive, seem to provide superficial evidence for the validity of this diagnosis.

The problem is that many immune serologic tests are not specific for any defined clinical diagnosis and thus should not be used to drive therapeutic decisions. However, such testing may create significant angst and expectations in patients and their families. Indiscriminate testing often begets additional testing and specialty referrals. Obtaining an antinuclear antibody test in a patient with fatigue, brain fog, and diffuse pain as the primary symptoms—but with no diagnostically relevant basic laboratory testing or physical examination abnormalities—is invariably unhelpful to the patient[1] and, if positive, is often emotionally and financially costly.

Many of the final diagnoses, even if these autoimmune tests are positive, are not autoimmune in nature. This is because many of these serologies have little specificity (poor positive predictive value). Within this bucket of autoimmune tests are rheumatoid factor and the antinuclear antibody test and related antibody tests (anti-SSA, anti-RNP, and even to some extent anti-DNA). In a second bucket are tests that detect antibodies pathogenically linked to specific clinical syndromes, such as anti-glomerular basement membrane antibody, linked to the glomerular basement membrane subset of Goodpasture syndrome; anti-AQP4, linked to neuromyelitis optica; and anti-acetylcholine receptor, linked to myasthenia gravis. These tests are of course also susceptible to misinterpretation (false positives) if ordered indiscriminately without the appropriate clinical context. But these antibodies do have a strong pathogenic link to specific clinical disorders.

Since truly pathogenic antibodies have been identified that cause or drive heretofore unexplained complex clinical syndromes, it is no surprise that research has moved toward trying to identify additional ones. There is hope in the scientific and patient communities that such identification can result in new approaches to molecular therapy.

The 2012 autobiography by Susannah Cahalan, *Brain on Fire: My Month of Madness*, and the movie based on it relate the intense story of a young woman ultimately diagnosed with anti-*N*-methyl-D-aspartate (NMDA) receptor-associated autoimmune encephalitis—a disorder with associated antibody that has a strong pathogenic link to clinical disease. Without knowledge of the antibody to the NMDA receptor, this disorder might still remain a mystery to diagnose, and a huger challenge to treat. In this issue of the *Journal*, Abbatemarco et al present a practical discussion of recognizing and managing patients with this and other forms of autoimmune encephalitis.

As a nonneurologist, I find these syndromes striking for several reasons. There is a biology that ultimately will be teased apart to explain how these specific antibodies sort to specific syndromes. It is fairly easy to conceptualize how antibodies binding to surface

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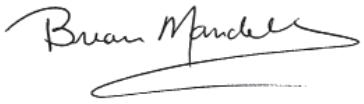
receptors can disrupt the function of the cells bearing those receptors and their associated intercellular networks. Perhaps careful clinical characterization of these syndromes will provide insight into further understanding of complex brain networking, specifically, what is the connection between characteristic focal facial seizures and encephalitis, or encephalomyelitis and sensory neuropathies? But we still have a way to go in understanding how antibodies recognizing intracellular targets are pathogenic, and why there are links between these syndromes and certain malignancies.

From the literature, I am not quite sure of the predictive value of these antibodies. For me, a takeaway from the article by Abbatemarco et al is that clinical suspicion for these rare syndromes should come first, followed by appropriate referral and subsequent thoughtful consideration for ordering these antibody panels from both blood and cerebrospinal fluid.



Brian F. Mandell, MD, PhD
Editor in Chief

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2021

AUGUST

HOSPITAL MEDICINE 2021
August 5–6
Live stream

NEUROLOGY UPDATE: A COMPREHENSIVE REVIEW FOR THE CLINICIAN
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Live stream

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August 14–15
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Virtual

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PRIMARY CARE UPDATE
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Live stream

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Pseudopathologic vertebral body enhancement

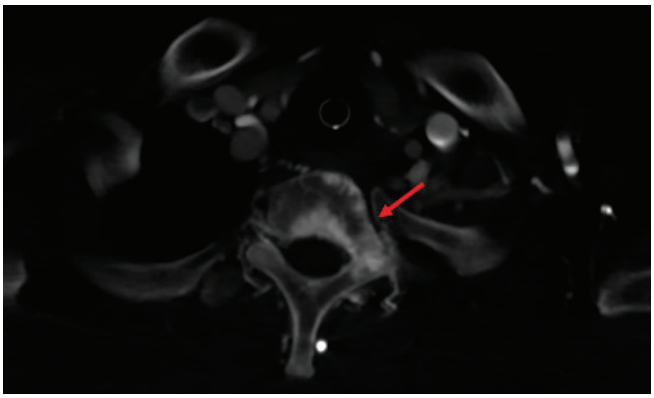

Figure 1. Contrast-enhanced thoracic computed tomography showed sclerotic enhancement of the T1 vertebral body (red arrow).

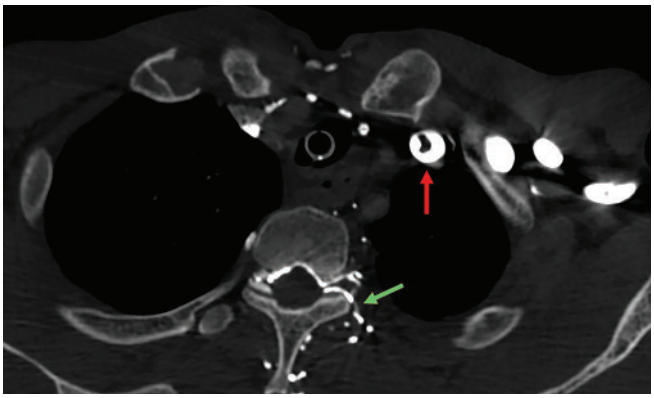

Figure 2. Contrast-enhanced computed tomography noted thrombosis in the left brachiocephalic vein (red arrow) and contrast filling of the paravertebral veins, usually occult on contrast enhancement (green arrow).

A 45-year-old man presented to the emergency department with severe dyspnea and cough that had gradually worsened over the past 3 months. His medical history was notable for stage IIA esophageal squamous cell carcinoma that had been treated with esophagectomy 15 years ago; and 13 years ago, he had developed mediastinal lymph node metastasis and had received chemoradiotherapy. He had been a heavy smoker and drinker but had quit 15 years ago.

Emergency contrast-enhanced thoracic computed tomography (CT) revealed a tumor mass in the lower trachea, sclerotic enhancement of the T1 vertebral body (**Figure 1**) and from the C2 to T2 vertebral bodies, and thrombosis in the left brachiocephalic vein (**Figure 2**). The patient rapidly developed type 2 respiratory failure (defined as a Pao_2 < 8.0 kPa and a $Paco_2$ > 6.0 kPa) and underwent bedside fiberoptic bronchoscopy, which revealed an obstructive tumor in the lower trachea that had invaded the carina and both the left and right main bronchi. Bronchoscopy-guided radiofrequency ablation was performed to relieve airway obstruction. Moderately differentiated squamous cell carcinoma was confirmed by endobronchial biopsy study.

The patient's dyspnea improved after bronchoscopic therapy. Repeat CT 5 days later showed no evidence of the vertebral body enhancement (**Figure 3**). Esophagoscopy showed an anastomotic stenosis 24 cm from the incisors and smooth mucosa in the esophagus. Anastomotic stenosis was consistent with the tumor location in the lower trachea and carina. Esophageal stenosis and smooth esophageal mucosa demonstrated external tumor compression of the esophagus, which did not support the diagnosis of esophageal carcinoma.

Based on the patient's smoking and irradiation history and the long interval between the last anticancer treatment and the appearance of the second tumor, the obstructive tumor was diagnosed as a second primary bronchogenic carcinoma.

The patient underwent disease staging with posi-

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tron emission tomography CT, which showed increased 18F-fluorodeoxyglucose uptake at the back wall of the trachea alone, indicating that the tumor was localized.

TREATMENT

The patient received 4 cycles of capecitabine and anlotinib, followed by 4 cycles of anlotinib. This achieved a partial response. At last follow-up, the patient was alive and without disease progression.

PSEUDOPATHOLOGIC VERTEBRAL BODY ENHANCEMENT

The differential diagnosis of sclerotic lesions on contrast-enhanced CT includes tumor metastasis, mastocytosis, sarcoidosis, osteomyelitis, lymphoma, Paget disease, and pseudopathologic vertebral body enhancement. For patients with a history of cancer, the leading cause is metastatic malignancy.

A limited number of case reports showed that pseudopathologic vertebral body enhancement may exist in the presence of obstruction of the superior vena cava or brachiocephalic vein. This is uncommon and easily misdiagnosed as sclerotic osseous metastasis in clinical practice.[1,2]

The mechanism of pseudopathologic sclerotic enhancement of vertebral bodies is not well characterized. However, an elevated venous pressure that induced contrast agent reflux into the intravertebral venous plexus was proposed as a main reason.[3]

In our patient, narrowing of the left brachiocephalic vein proximal to the superior vena cava resulted in elevated venous pressure and blood flow into the vertebral venous plexus, causing reflux of contrast agent.[1,4] Sclerotic enhancement of the vertebral bodies and vertebral venous collaterals, which are usually occult on CT, were seen. Eight consecutive vertebral bodies were involved, which is uncommon with metastasis. However, when the contrast agent was injected into the contralateral arm during the second CT, the vertebra enhancement disappeared (**Figure 3**).

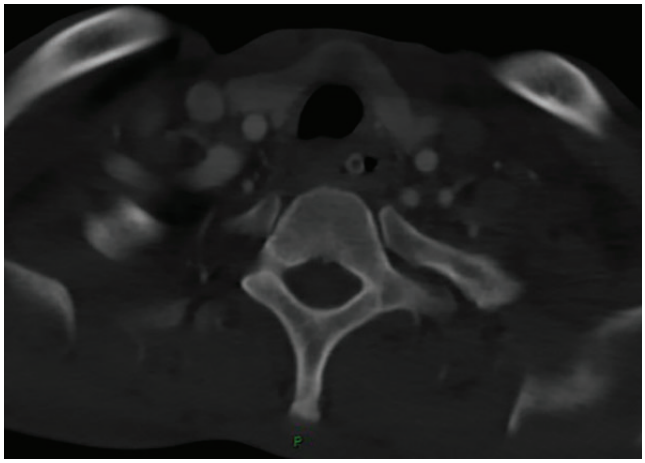

Figure 3. Repeat computed tomography showed the disappearance of the sclerotic vertebral body enhancement.

Pseudopathologic vertebral body enhancement due to brachiocephalic vein narrowing is rare. However, sclerotic bone metastasis based on contrast-enhanced CT should prompt a careful evaluation when narrowing or obstruction of the brachiocephalic vein and paravertebral collateral veins is present on imaging. Spine magnetic resonance imaging or positron emission tomography CT should be performed to confirm the diagnosis.

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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Shedding light on subungual digital mucous cysts

Transillumination is a quick and easy way to diagnose DMC and rule out other subungual masses

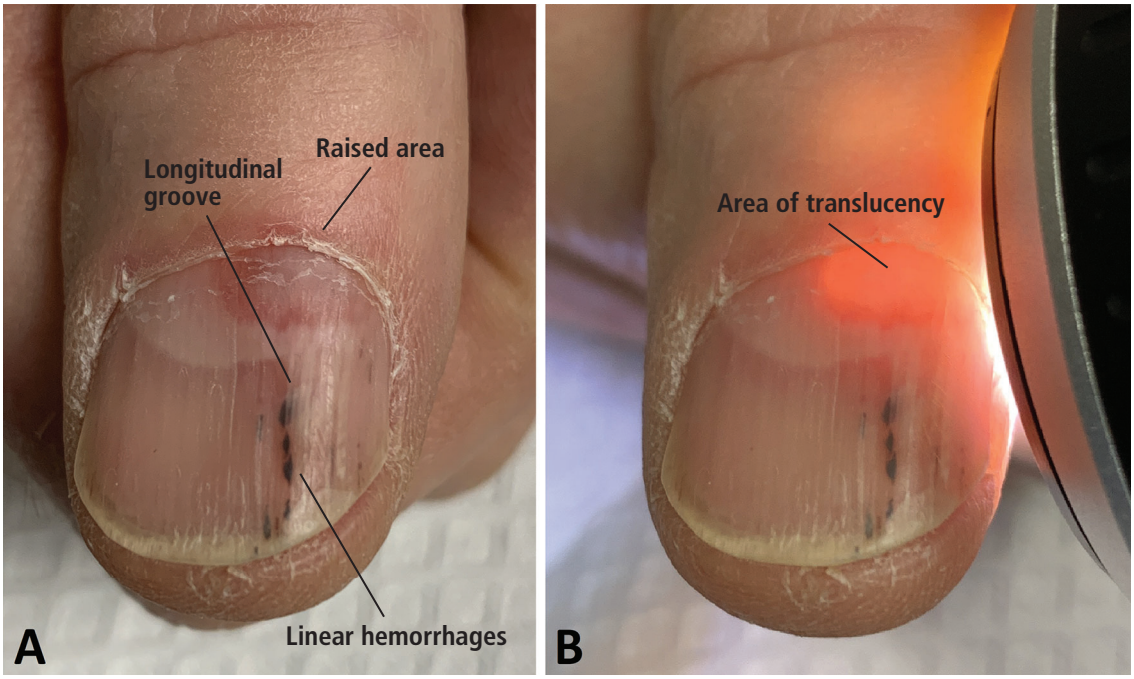

Figure 1. Subungual digital mucous cyst of the thumbnail: (A) longitudinal groove, distal linear hemorrhages, and a raised area at the proximal nail; and (B) a translucent area, 3 mm × 5 mm, beneath the nail matrix.

A 65-year-old man presented with a thumbnail deformity that had been present for 3 months. He said he had no pain and no history of trauma to the nail.

Examination of the thumbnail revealed a longitudinal groove, distal linear hemorrhages, and a raised area at the proximal end that appeared to be a subungual nodule affecting the underside of the nail plate, and transillumination showed a translucent area 3 mm by 5 mm beneath the nail matrix (**Figure 1**). Examination of all other digits was unremarkable.

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Clinically, this presentation appeared to be consistent with a subungual digital mucous cyst (DMC) causing nail deformity due to compression of the nail matrix. To confirm the diagnosis, a sterile 22-gauge needle was used to drill through the nail plate into the translucent area. A copious amount of clear, gelatinous material, characteristic of a DMC, was expressed from the puncture site.

DIFFERENTIAL DIAGNOSIS

Longitudinal grooves in the nail bed can be caused by median nail dystrophy, trauma, compression of the nail matrix from tumors,

and physiologic furrows and ridges that are accentuated in diseases such as lichen planus and Darier disease. Tumors that can affect the nail matrix include various nail fibroma, DMC, pyogenic granuloma, glomus tumor, subungual exostosis, squamous cell carcinoma, and melanoma.[1]

The translucency of this patient's subungual nodule was highly suggestive of a DMC, and the clear, gelatinous material expressed from the cyst confirmed it. In addition, a red lunula, as seen in our patient **(Figure 1)**, is a common finding in subungual DMC.[2]

DIGITAL MUCOUS CYSTS

DMC, also known as myxoid pseudocyst or synovial cyst, commonly presents as a superficial, dome-shaped, shiny, cystic nodule located near the distal interphalangeal joint on the dorsum of the fingers. The cyst is commonly diagnosed clinically based on the appearance and the history of intermittent discharge of a mucoid substance.[3] DMC is more common in people with osteoarthritis and in women.

While superficial DMC is common, the prevalence of subungual DMC is unknown, as few have been reported. The focal collection of fluid in DMC lacks a cystic lining, so DMC is not a true cyst. DMC can cause nail deformities by compressing nail matrix cells, most commonly proximal and superficial to the proximal nail fold.[1]

Subungual DMC is much more difficult to diagnose than its superficial counterpart, not only because it is less accessible, but also because it lacks the characteristic appearance of superficial DMC and does not cause intermittent mucinous discharge.[3] Though DMC is commonly asymptomatic when left untreated, subungual DMC most often requires nail avulsion and surgery to rule out other subungual masses, including malignancies.[4]

Transillumination is a quick and easy way to diagnose DMC and rule out other subungual masses, as seen in this case. The finding of a translucent cyst can spare the patient from undergoing nail avulsion and surgery. When evaluating subungual masses, all clinicians should be aware of the utility of transillumination in the diagnosis of subungual DMC. ■

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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Eruptive seborrheic keratosis: A perilous clue

An abrupt increase in seborrheic keratoses in patients with an underlying malignancy is called the Leser-Trélat sign

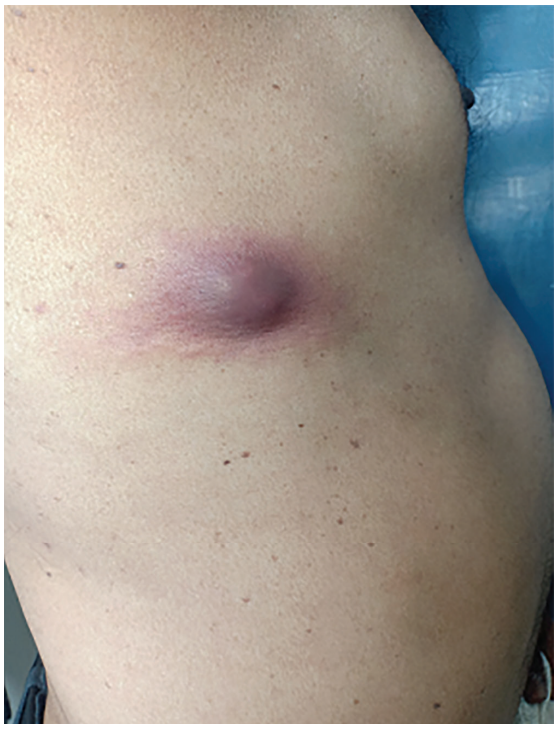

Figure 1. An erythematous, firm, nontender nodule measuring 3 cm × 3 cm in the right midaxillary line.

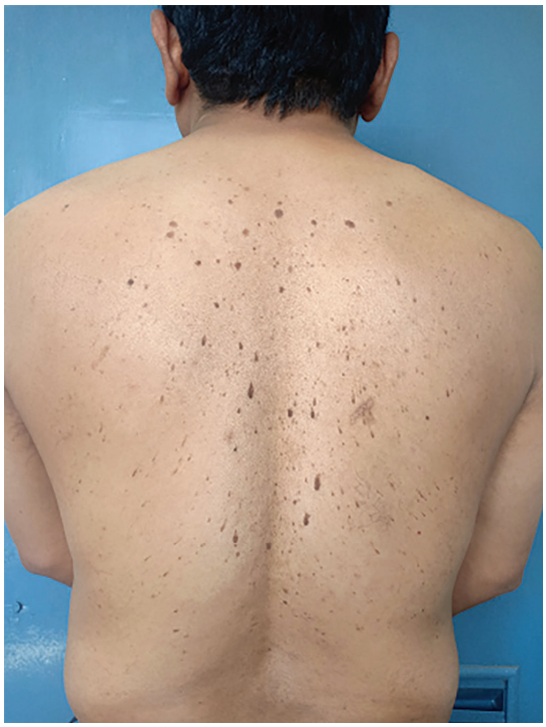

Figure 2. Multiple seborrheic keratoses of various sizes arranged in a "Christmas tree" pattern on the patient's back.

A 51-year-old man presented with a 1-month history of multiple eruptive seborrheic keratoses on his back and a single painless nodule on his chest. He reported occasional dry cough and loss of appetite over the past 3 months, but he did not seek medical care for them. He had no history of fever, weight loss, night sweats, or gastrointestinal complaints.

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The physical examination revealed an erythematous nodule measuring 3 cm by 3 cm in the right midaxillary line (**Figure 1**). The nodule was firm, mobile, and nontender on palpation, and it had a normal temperature. Also noted were multiple seborrheic keratoses of various sizes arranged in a "Christmas tree" pattern on his back (**Figure 2**). The rest of the examination was unremarkable.

A punch biopsy was taken from the nodule. The histopathology report described an

unremarkable epidermis with clusters of pleomorphic tumor cells in the dermis (**Figure 3a**) arranged in small glands inciting a desmoplastic reaction (**Figure 3b**). The tumor cells had coarse chromatin and a moderate amount of cytoplasm. Immunostaining results were positive for cytokeratin 7 (**Figure 3c**). Overall, the features suggested a possible adenocarcinoma.

The patient underwent whole-body ^{18}F-fluorodeoxyglucose (FDG) positron emission tomography with contrast-enhanced computed tomography, which revealed a soft-tissue mass lesion with speckled calcification in the right middle lobe of the lung. The lesion was FDG-avid (ie, with high uptake of FDG), heterogeneously enhancing, and lobulated. The lesion reached up to the hilum, abutting the mediastinum and encasing the right middle lobe bronchus.

There were FDG-avid lymph nodes in the right axillary and supraclavicular regions, a single FDG-avid lesion in the left adrenal gland, and multiple subcutaneous and muscular deposits distributed in the chest wall, left thigh, right gluteal region, and upper back.

Based on those results, we made a diagnosis of metastatic non-small-cell lung cancer, adenocarcinoma type, not otherwise specified. Palliative chemotherapy with paclitaxel and carboplatin was started, and the patient received oncology follow-up care. Response to chemotherapy could not be ascertained, as the patient was lost to follow-up owing to COVID-19-related lockdown.

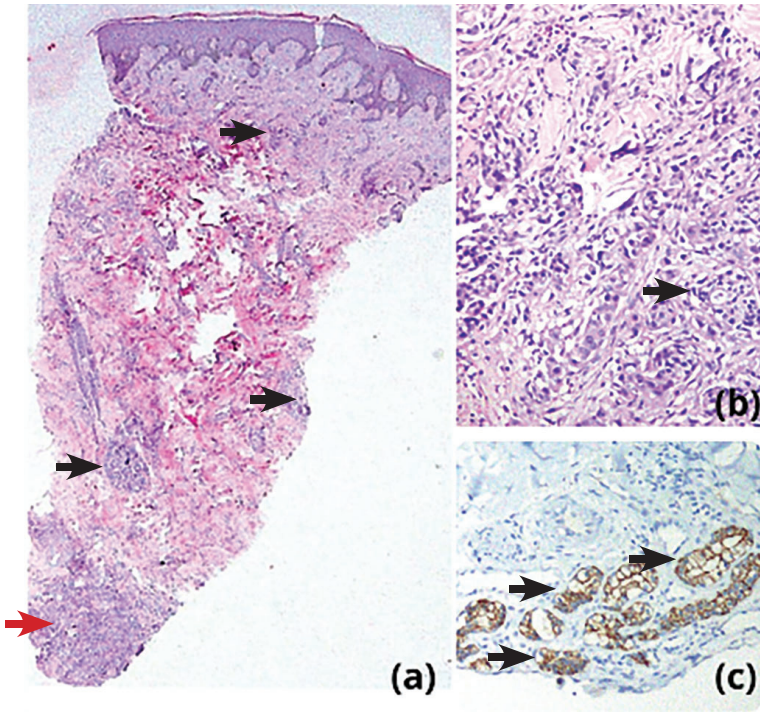

Figure 3. A: The epidermis appears relatively unremarkable. The dermis shows a mild to moderate degree of perivascular and periadnexal mononuclear inflammatory infiltrate (black arrows) along with a tumor deposit in the deep dermis (red arrow) (hematoxylin and eosin stain; magnification × 20). B: The tumor is composed of cells arranged in small glands (arrow) inciting a desmoplastic reaction. The tumor cells are moderately pleomorphic and have coarse chromatin and a moderate amount of cytoplasm (hematoxylin and eosin stain; magnification × 200). C: Immunostaining shows tumor cells positive for cytokeratin 7 (arrows) (CK 7 immunostain; magnification × 200).

ERUPTIVE SEBORRHEIC KERATOSIS

An abrupt increase in the size and number of seborrheic keratoses in patients with an underlying malignancy is called the Leser-Trélat sign. More than 50% of associated malignancies are adenocarcinomas, especially those of the stomach, colon, rectum, and breast,[1] although this sign has also been reported in other malignancies, including lung cancer.[2] The association of the Leser-Trélat sign with malignancy is debatable, with suggestions that the sign may exist independent of an underlying occult malignancy or may be associated with nonmalignant conditions such as benign neoplasms, pregnancy, or human immunodeficiency virus infection.[3,4]

The exact pathogenesis of the Leser-Trélat sign is unclear. One hypothesis attributes it to growth factors released by tumor cells, such as growth hormone, epidermal growth factor, and transforming growth factor alpha. Another suggests that extracellular matrix components, such as glycosaminoglycans released from stroma of the tumor, become incorporated in distant normal skin, causing epithelial alteration and eruption of seborrheic keratoses.[5]

The Leser-Trélat sign may be the initial presentation, or it can be detected concurrently with or after diagnosing an internal malignancy. Eruptive seborrheic keratoses can occur anywhere, but the most common sites are the back, chest, and extremities.[5]

Evaluation of a patient with the Leser-Trélat sign should begin with a detailed history and clinical examination. Special investigations should be performed to look for the occult primary malignancy.

Our patient was apparently doing well except for the relatively abrupt appearance of multiple eruptive seborrheic keratoses, which prompted us to investigate further for an occult malignancy. The nodule on his chest wall could not be explained by the Leser-Trélat sign and thus was biopsied. The results helped us reach the final diagnosis.

Despite the nonspecific nature of the Leser-Trélat sign, our case exemplifies the importance of performing a thorough evaluation in patients presenting with sudden-onset eruptive seborrheic keratoses.

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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ONE MINUTE CONSULT

BRIEF ANSWERS TO SPECIFIC CLINICAL QUESTIONS

Q: Can I place a peripherally inserted central catheter in my patient with chronic kidney disease?

A 45-year-old man is admitted to the hospital for sepsis secondary to osteomyelitis. He has diabetes mellitus, hypertension, and stage 3 chronic kidney disease (CKD), with a glomerular filtration rate of 46 mL/min/1.73m^2. He is treated with intravenous (IV) antibiotics and improves clinically. He will need 6 weeks of IV antibiotics after discharge. Should a peripherally inserted central catheter (PICC) be placed for IV access?

A: The decision to place a PICC must be individualized for the patient. Current guidelines do not provide explicit contraindications for creating permanent vascular access, but the general consensus is that poor candidates include those with advanced dementia, left ventricular ejection fraction less than 20%, poor vasculature on imaging, or terminal illness (life expectancy < 6–12 months).[1] In addition, national guidelines and the American Board of Internal Medicine's Choosing Wisely initiative recommend against PICC placement in patients expected to need permanent dialysis access in the future (CKD stages 3–5).[2]

PICC PROS: CONVENIENCE, LOW COST

PICCs have become increasingly popular in recent years due to their ease of placement, convenience for patients, and cost-effective maintenance. Up to 56% of PICCs are placed to administer IV antibiotics.[3]

PICC CONS: BLOOD VESSEL RISKS

PICCs are highly associated with phlebitis, thromboembolism, central vein thrombosis, and stenosis of the involved vessels, which may obliterate the involved veins and prevent their use for future creation of a permanent dialysis access.[4] Clinically diagnosed thrombosis has been reported to occur in 1% to 4% of patients with a PICC. However, in a 2000 study using venography to evaluate patency of the vessels, Allen et al[5] reported a much higher incidence, with thrombosis evident in 23.3% of patients after PICC insertion.

Higher rates of thrombosis are associated with larger catheter sizes, the use of cephalic veins (due to smaller size compared with basilic veins), greater number of lumens, placement of multiple catheters, and patient factors including malignancy or history of venous thromboembolism.[5,6] Central venous stenosis may also occur, although it is not as common as thrombosis.[7]

PICC insertion is also a strong independent risk factor for failure of an arteriovenous fistula, the preferred method of vascular access for hemodialysis.[7] McGill et al,[8] in a 2016 observational study, found that PICC insertion before or after initiation of hemodialysis was associated with failure to transition to a form of permanent access, with only 24.7% of patients transitioning to a working arteriovenous fistula, and 11.5% transitioning to a functioning arteriovenous graft. This is very important because the transition from central venous access to an arteriovenous fistula or graft is associated with better survival and fewer hospitalizations, due to lower risk of serious infections such as endocarditis and bacteremia.[8]

In patients such as our 45-year-old man, an end-stage kidney disease (ESKD) life plan should be created with input from a nephrologist to determine early access needs and to avoid unnecessary procedures and complications, while also considering life expectancy

PICC insertion is a strong independent risk factor for failure of an arteriovenous fistula

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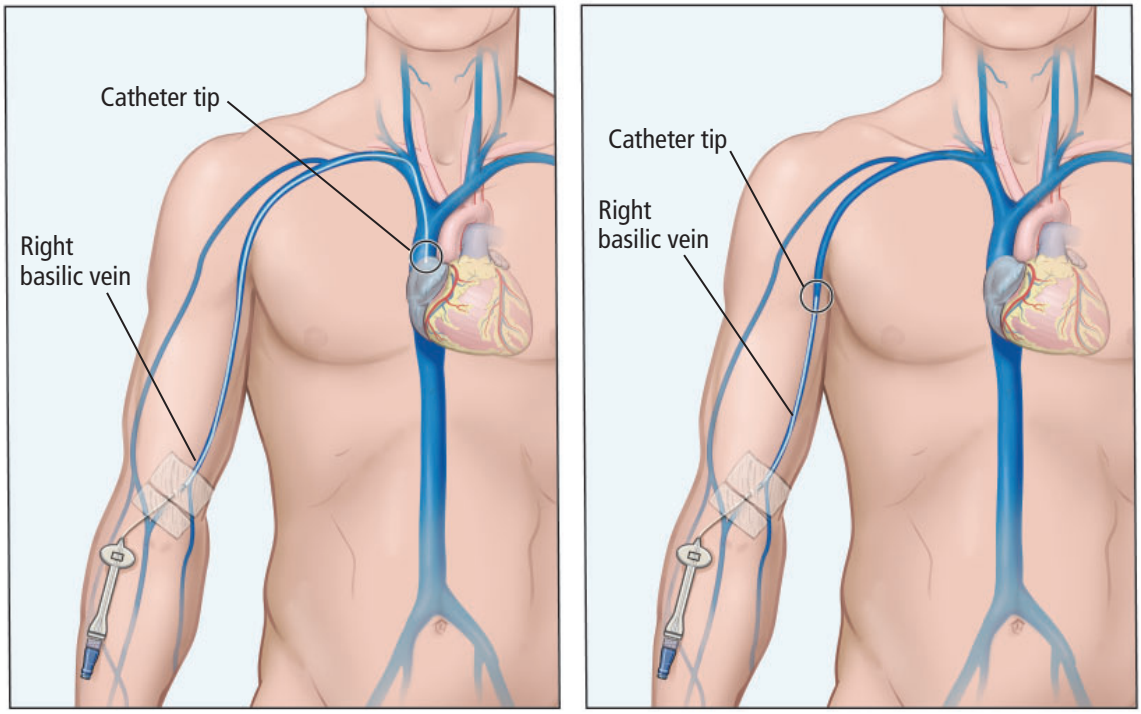

Figure 1. A peripherally inserted central catheter (left) is inserted at the right basilic vein, through the axillary and subclavian veins and into the superior vena cava. The midline catheter (right) is also inserted at the right basilic vein with the tip just below the axilla.

and kidney replacement alternatives.[2]

CASE CONTINUED

The team decides to place a PICC through the right basilic vein (**Figure 1**), and the infection resolves with 6 weeks of IV antibiotics.

However, 4 months later, he is readmitted for acute kidney injury and recurrence of osteomyelitis with a paravertebral abscess. The abscess is surgically drained, and the infectious disease consult recommends 8 weeks of IV antibiotics. After a thorough discussion with the nephrology team and the patient, the decision is made against placing a PICC.

PICC ALTERNATIVES

Unfortunately, all methods of IV access can produce venous damage, either by direct trauma at the puncture site or by device contact along the walls of the vein.[9] It has been hypothesized that the more area within a vessel that a foreign object occupies, the greater the possibility of thrombosis due to increased stasis and direct-contact damage.[3] However, midline catheters, which are also inserted into peripheral veins but occupy a smaller ending near the axilla, have also been associated with symptomatic venous thrombosis.[4] Catheter location plays an important role, with guidelines suggesting avoiding cephalic, basilic, brachial, and subclavian veins.[2,4]

A proposed alternative to a PICC is a small-bore, 4-French or 6-French tunneled internal jugular catheter (**Figure 2**). It tends to last longer and is associated with fewer complications, decreasing the risk of central venous stenosis.[10,11] A 2017 retrospective study by Bhutani et al[10] found lower rates of deep vein thrombosis in tunneled small-bore central venous catheters than with PICCs, which may be explained by the shorter length of the catheter and better catheter-to-vein size ratio. However, whether they produce less damage to the peripheral vessels or cause central vein stenosis has not been fully studied.[1]

It has also been suggested that placement of internal jugular catheters by a skilled proceduralist with ultrasonographic and fluoroscopic guidance may result in less venous trauma, reducing the risk of vessel stenosis compared with nonguided methods.[11]

But even after an arteriovenous fistula has been successfully created, patients with ESKD requiring hemodialysis must continue vessel-preservation strategies as part of their ESKD management plan.[1] If IV antibiotics are needed, it may be possible to select an agent that can be administered 3 times a week on dialysis days, using the functioning hemodialysis access. This will avoid the need for a different catheter, decreasing the risk of central venous stenosis and allowing for the creation of other arteriovenous fistulas if the current one fails.[3]

Lifelong vessel-preservation strategies

Patients who may progress to ESKD and may require hemodialysis access in the future should be identified early so that they can be provided with timely education regarding vessel preservation. This includes patients with stage 3 to stage 5 CKD, patients already on kidney replacement therapy such as hemodialysis or peritoneal dialysis, and patients who have a functional transplanted kidney. Such patients should be encouraged to advocate to preserve their vessels and work with the treatment team in balancing the risks and benefits of every intervention, including blood draws and use of IV and arterial devices.[4,9] Medical alert bracelets and signs at the bedside of hospitalized patients with CKD indicating the need to restrict needle use is essential in educating and alerting the medical community.[4]

It has also been proposed that a nephrology consult be requested before placing a PICC in patients with advanced CKD (stages 3–5).[12] Patients and health professionals are encouraged to visit the website **www.saveyourvein.org** to further educate themselves on the importance of vein preservation.[2]

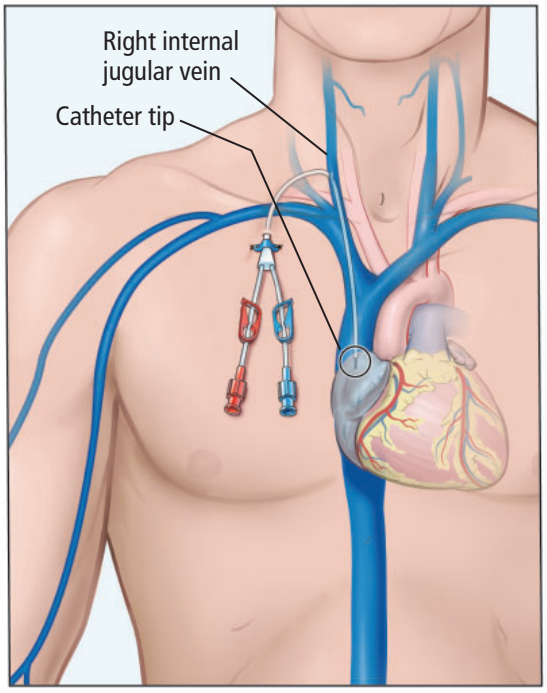

Figure 2. A small-bore (Hohn) catheter placed in the internal jugular vein is an alternative to a peripherally inserted central catheter.

DISCLOSURES

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ONE MINUTE CONSULT

BRIEF ANSWERS TO SPECIFIC CLINICAL QUESTIONS

Q: How do you effectively evaluate the elderly for alcohol use disorder?

A comprehensive patient assessment includes an in-depth history, physical examination, and other testing

A: Alcohol use disorder (AUD) is a significant problem in the elderly and one that is often undiagnosed, resulting in increasing emotional, physical, and social consequences. In 2019, Americans over age 65 accounted for 16.5% of the population (about 54 million), with a projection to reach 22% of the total population (81 million) by 2040.[1,2] It is estimated that AUD afflicts about 1% to 3% of the elderly, but in treatment settings such as doctors' offices and emergency departments, it may be 10 times more frequent. Studies from primary care settings show that alcohol problems exist in 10% to 15% of older adults, 30% of hospitalized older adults in general medicine, and about 50% of those hospitalized in psychiatric divisions.[3] Recent studies show that although the vast majority of those with alcohol use disorder see their doctors regularly for a range of issues, fewer than 1 in 10 ever gets treatment for drinking.[4]

THE PROBLEM OF UNDERDIAGNOSIS

In older adults, AUD has an atypical presentation **(Table 1)**, which contributes to the underdiagnosis in this population. Missed diagnosis has many reasons.[5]

First, there is a general lack of awareness and sensitization about AUD among physicians, with a stereotypical view of AUD as a phenomenon of young and middle-aged adults.

Second, clinicians may also be hesitant or embarrassed to screen for AUD in a senior citizen, and this can be compounded by the unwillingness of older adults to acknowledge alcohol problems, due to stigma.

Third, clinicians may fail to link coexisting medical problems with the possibility of underlying substance use such as AUD and instead attribute the problems to aging.

Fourth, clinicians may have a therapeutic nihilism about alcohol use in the elderly: "What is the point in intervening? It is okay for him to use, and besides, at this age, he deserves a break."

And finally, the widespread use of prescription medications among the elderly can hinder the detection of AUD. This is further complicated by survey data showing that only about 47% of primary care physicians ask about maximum alcohol intake, and only 13% use a formal screening tool for alcohol problems.[6]

Older adults are likely to experience more problems with relatively small amounts of al-

TABLE 1
Presentation of alcohol problems in the elderly[a]

Anxiety
Poor hygiene, urinary or fecal incontinence
Malnutrition
Confusion, memory loss, dementia, or delirium
Falls
Marital problems
Sleep problems
Depression or mood swings
Financial problems
Seizures (new-onset, idiopathic)
Worsening of chronic medical problems (hypertension, diabetes, heart failure)

[a] Note: Crime, antisocial, and substance-seeking illegal behaviors are not common in this group.

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cohol use due to changes in the pharmacokinetics and pharmacodynamics of alcohol, resulting in higher blood-alcohol levels. These are related to decreases in body water and body mass with age, hence a smaller volume of distribution, increased sensitivity, and slower metabolism. Furthermore, many older adults tend to have multiple comorbidities such as hypertension, other cardiovascular problems, and diabetes that can worsen with chronic alcohol use, as well as having drug-drug interactions from multiple medications.[7,8]

UNDERSTANDING THE TYPES OF AUD IN OLDER ADULTS

Older individuals who meet AUD criteria can be divided into 2 groups: those who developed AUD before age 60, and those who developed it after age 60. Patients with earlier onset of AUD account for about two-thirds of the elderly AUD population and have a more severe course of illness. They also tend to be predominately male and have more alcohol-related medical and psychiatric comorbidities, including being less well-adjusted and having more antisocial traits. Those with later onset of AUD tend to have a milder clinical picture and few medical problems, possibly because of the shorter exposure to alcohol. These patients also tend to be women, are more affluent, and are likely to have begun alcohol misuse after a stressful event such as the loss of a spouse, job, or home, or retirement. Hence, it is necessary to explore these areas when taking the history.

Other risk factors for development of later onset of AUD, apart from personal and family history of AUD, include onset of chronic pain, predisposition to affective or anxiety disorders, and decreased alcohol metabolism with age.[7,9,10]

SCREENING: ASK ABOUT DRINKING

The United States Preventive Services Task Force recommends screening adults age 18 and older for alcohol misuse and providing those engaged in risky or hazardous drinking (a pattern of drinking that increases the risk of physical or psychological problems) with brief behavioral counseling interventions to reduce alcohol misuse.[11] Given the high use of medical services by the elderly, clinicians are essential to identifying those who need treatment. This should be explored at every opportunity, such as visits for changes in health status or medications and after major life events such as retirement or the loss of a spouse, in addition to routine health visits.

The National Institute on Alcohol Abuse and Alcoholism (NIAAA) and the Substance Abuse and Mental Health Service Administration (SAMHSA) recommend that men and women age 65 and older consume no more than 1 standard drink per day or 7 standard drinks per week,[12,13] unlike the guidelines for adults younger than age 65, which are as follows: for women, no more than 1 standard drink per day or 7 standard drinks per week; for men, no more than 2 standard drinks per day and not more than 14 standard drinks per week.[12–15] The NIAAA defines "risky use" as exceeding the recommended limits of 4 drinks per day (56 g/d based on the US standard of 14 g of ethanol per drink) or 14 drinks per week (196 g/d) for healthy adult men ages 21 to 64, or 3 drinks per day or 7 drinks per week (42 g/d or 98 g/week) for all adult women of any age and men age 65 or older.[16] In addition, older men should not consume more than 4 standard drinks on any day. (A standard drink containing 12 to 14 g of ethanol is equivalent to a 12-oz can of beer, a 5-oz glass of wine, or about 1.5 oz of 80-proof liquor.)

Older adults can experience more problems with small amounts of alcohol

Screening questions should be asked in a confidential setting and in a nonthreatening, nonjudgmental manner. Note that a patient may have cognitive impairment that interferes with the ability to provide complete and accurate responses during the medical history, as well as to self-monitor alcohol intake and understand feedback from healthcare providers.[10] This may necessitate involving family members or friends after discussing permission with the patient.

Formal screening tools for identifying alcohol misuse should be used at every opportunity as they are brief, easy to recall, and highly sensitive and specific. They can be self-administered by the patient while waiting in the doctor's office and reviewed during the face-to-face encounter. Commonly used tools include:

- CAGE (cut-annoyed-guilty-eye), a simple 4-item yes-or-no questionnaire

TABLE 2

Short Michigan Alcoholism Screening Test—Geriatric Version (SMAST-G)

Please answer yes or no to the following questions:

1. When talking with others, do you ever underestimate how much you drink?
2. After a few drinks, have you sometimes not eaten or been able to skip a meal because you didn't feel hungry?
3. Does having a few drinks help decrease your shakiness or tremors?
4. Does alcohol sometimes make it hard for you to remember parts of the day or night?
5. Do you usually take a drink to relax or calm your nerves?
6. Do you drink to take your mind off your problems?
7. Have you ever increased your drinking after experiencing a loss in your life?
8. Has a doctor or nurse ever said they were worried or concerned about your drinking?
9. Have you ever made rules to manage your drinking?
10. When you feel lonely, does having a drink help?

Extra question (asked, but not calculated in the final score): Do you drink alcohol and take mood or mind-altering drugs, including prescription tranquilizers, prescription sleeping pills, prescription pain pills, or any illicit drugs?

Scoring: 1 point for each "yes" answer, and total the responses. A score of 2 or more points indicates an alcohol problem, and a brief intervention should be conducted.

Adapted from reference 17.

Hypertension, cardiovascular disease, and diabetes can worsen with chronic alcohol use

- AUDIT (Alcohol Use Disorder Identification Test), with good sensitivity and specificity, or its shorter version AUDIT-C questionnaire, which is good at identifying those with hazardous drinking
- MAST-G (Michigan Alcohol Screening Test–Geriatric Version) and its shorter version (SMAST-G), shown in **Table 2**.[17]

MAST-G and SMAST-G were designed for older patients who drink less and are better than the CAGE tool at identifying older adults with AUD.[18] Using more than 1 screening tool can provide more data on alcohol quantity consumed, alcohol use patterns, and alcohol-related consequences, which may help identify AUD in older patients across a wide range of demographic characteristics. SAMHSA has published a compilation of these instruments.[19]

DIAGNOSIS

According to the American Psychiatric Association, the diagnosis of AUD requires a patient to meet 2 of 11 criteria during the same 12-month period.[20] The severity of AUD is defined as mild for the presence of 2 to 3 symptoms, moderate for 4 to 5 symptoms, or severe for 6 or more symptoms.

Assessment and diagnosis provide data for a comprehensive and effective treatment plan, a process called SBIRT (screening, brief intervention, and referral to treatment). Plans range from simple brief intervention in the clinic to admission to a medically managed facility. After discharge, older patients with AUD need to participate in alcohol treatment programs with a focus specific to the elderly that incorporates both pharmacologic treatment and nonpharmacologic treatments, and to participate in support groups such as Alcoholics Anonymous. Other treatment options are cognitive behavior therapy and motivational interviewing techniques and admission to a therapeutic community.

MEDICAL HISTORY, PHYSICAL EXAMINATION, TESTS

A comprehensive patient assessment includes an in-depth medical history, physical examination, and other testing **(Table 3)**. History-

taking should inquire about falls, sleep problems, physiologic dependence and withdrawals, level of cognitive function, medical and psychiatric comorbidities, medication history with potential of drug-to-drug and drug-to-alcohol interactions, and surgical history such as bariatric surgery (especially Roux-en-Y gastric bypass), as this can increase the risk of AUD postoperatively. A psychosocial evaluation should include anxiety, presence of chronic pain, level of social activities, family dynamics (ie, level of interaction with family and friends), finances, housing, legal issues, and diet. The evaluation should also include questions about depression and suicide, as well as diagnostic tools such as the Patient Health Questionnaire 9,[21] if warranted. Also important is assessing the patient's level of readiness and motivation to change. Motivational techniques may be useful for patients exhibiting less willingness to change.

The physical examination should be thorough, assessing for intoxication and alcohol breath. Consider using noninvasive tools such as a breathalyzer or obtaining urine or blood samples to check for alcohol levels with ethyl glucuronide or ethyl sulfate testing. Also assess for alcohol withdrawal using a withdrawal scale such as the Clinical Institute Withdrawal Assessment for Alcohol.[22] The physical examination should also assess for comorbidities and complications of AUD such as hypertension, cardiomyopathy, neuropathy, myopathy, and alcoholic liver disease including cirrhosis.

Other testing should include the Mini-Mental State Examination and electrocardiography to identify arteriosclerosis, arrhythmias, and cardiomegaly. Also, include laboratory tests such as gamma-glutamyl transpeptidase, hepatic transaminases such aspartate aminotransferase and alanine aminotransferase (a 2:1 ratio pattern suggests chronic alcohol use), basic blood chemistry panel, and complete blood cell count to check for elevated mean corpuscular volume. These tests, though essential in the overall scheme, are by themselves poor screening tools for AUD in older patients and thus should be used in conjunction with results from the medical history, physical examination, and formal screening tools.[23,24]

Elevated levels on a carbohydrate-deficient transferrin test, if available, suggest recent alcohol abuse, particularly when corroborated with elevated levels of other liver-associated enzymes. Other uses of this test include long-term monitoring for early detection of relapse drinking during medical treatment, enabling early intervention.

TABLE 3

Assessment of alcohol use disorder in the elderly [a]

Previous diagnosis of alcohol-use disorder
Drinking patterns, physiologic dependence, withdrawals
Presence of intoxication
Neuropsychiatric comorbidities or manifestations including suicidal ideation
Medical comorbidities and complications including chronic pain; current medications
Psychosocial evaluation including housing, dietary issues, finances, legal issues, sociability, family
Prior treatment, including pharmacotherapy: success, failure, relapse, participation in support groups
Patient's level of motivation to change

[a] Assessment should include screening, a thorough medical and psychosocial history, physical examination, and appropriate laboratory tests.

A WORD ON TREATMENT

Even though an elaborate and in-depth evaluation of treatments for AUD in older adults is beyond the scope of this article, several studies have documented that older adults with AUD seem to do best in programs that offer age-appropriate care, including individual, group, and family therapy, and in self-help group meetings such as Alcoholics Anonymous with providers who are knowledgeable about aging-related issues. For older patients, these programs can result in higher attendance at group meetings and a greater likelihood of completing treatment than in younger patients.[25]

Older adults with AUD benefit from programs that offer age-appropriate care

Pharmacotherapy for short-term control of alcohol withdrawal includes benzodiazepines such as lorazepam and treatment of medical and psychiatric comorbidities. Treatment of acute withdrawal in patients with multiple severe comorbidities or AUD complications should be done in a medically supervised setting. Pharmacotherapy should follow the

principle of "start low, go slow" and should be closely monitored for early detection of adverse effects such as cognitive impairment, hypotension, and falls.[5]

Naltrexone

Studies have shown that pharmacotherapy such as naltrexone, which is thought to block the endogenous opioid system contribution to alcohol priming effects, can be an important ally in preventing relapse when used in conjunction with behavioral interventions and treatments.[26] The oral dose approved by the US Food and Drug Administration (FDA) is 50 mg daily, but it can be initiated at 25 mg/day with a 25-mg/day increase as often as weekly, to a maximum of 150 mg/day, using desire-to-drink and other patient symptoms as a measure of relative risk of relapse to heavy drinking.

Compared with placebo, naltrexone has been found to be well tolerated, with no significant differences in frequency of self-reported adverse effects or in liver enzyme values. But treatment has resulted in reduced craving for alcohol, as well as in fewer drinking days and relapse events.[26]

Long-acting naltrexone, available as a 380-mg dose given every 4 weeks as a deep intramuscular gluteal injection, is an alternative, especially if patients do not adhere to the daily oral regimen. Avoid long-acting naltrexone in patients taking opioids and in those with elevated levels of liver enzymes.

Acamprosate

Another medication useful in AUD rehabilitation is acamprosate, an amino acid derivative that fosters gamma-aminobutyric acid neurotransmission. It seems to interact with glutamate at the *N*-methyl-D-aspartate receptor, although its exact mechanism is unclear. It is an alternative and has an FDA-approved dosing of 1,998 mg/day, usually administered as two 333-mg capsules 3 times a day. It has been found to reduce alcohol consumption and increase abstinence rates.[27] It is renally excreted unmetabolized; thus, before prescribing it, the patient's renal function should be determined, as renal dysfunction is not uncommon in the elderly. Acamprosate is most effective at maintaining abstinence in patients who are not currently drinking alcohol.[27,28]

Disulfiram

The evidence is inconsistent on the efficacy of disulfiram, the only alcohol-sensitizing medication FDA-approved to treat AUD in the elderly. It decreases alcohol consumption by irreversibly binding with the enzyme aldehyde dehydrogenase, hence causing a disulfiram-ethanol reaction. Daily dosage ranges from 250 mg to 500 mg.

Factors that make disulfiram a less suitable choice for many older patients with AUD include problems with adherence and serious adverse effects (drowsiness, optic neuritis, peripheral neuropathy, hepatotoxicity). It is contraindicated in patients with history of seizure, psychosis, or cerebrovascular accident, and in those not willing to achieve complete abstinence.[5,28]

THE BOTTOM LINE

AUD is a significant problem in the elderly, and as this segment of the population continues to grow, we can expect to see more elderly patients with AUD. Fortunately, studies have shown that elderly patients with AUD have very good outcomes when it is diagnosed and treatment is initiated, especially with age-specific care and programming. It behooves clinicians to be knowledgeable about the presentations, screening, and assessment of AUD in the elderly, with the goal of timely interventions and referral to appropriate care.

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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Antiobesity drug therapy: An individualized and comprehensive approach

ABSTRACT

Obesity affects 42% of US adults and has a devastating impact on health. Although many patients initially lose weight with diet and exercise, long-term weight loss is difficult to achieve. Pharmacotherapy, as part of a comprehensive plan, can help patients lose weight and avoid regaining it. Choosing an antiobesity drug regimen should be an individualized, shared decision-making process that accounts for patient preferences, comorbidities, and out-of-pocket costs. We review antiobesity drugs and propose an individualized and comprehensive approach to obesity management.

KEY POINTS

Antiobesity medications as part of a comprehensive plan can help patients achieve lasting obesity control and provide independent health benefits, including decreased cardiovascular risk.

All patients suffering from obesity should be counseled to adopt a healthful low-calorie diet, exercise regularly, get adequate sleep, and manage stress.

Antiobesity management plans should include lifestyle counseling, discontinuation of obesity-inducing medications when possible, and, when indicated, weight loss surgery.

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Antiobesity medications are significantly underprescribed. Only 2% of US adults eligible for obesity pharmacotherapy receive it.[1] Contributing to this underutilization are inadequate training of prescribers and stigmatization of obesity as resulting from a perceived lack of willpower on the part of the patient.[2,3] Familiarizing clinicians with the pathophysiology of obesity and helping them provide an individualized and comprehensive plan for their patients is the purpose of this review.

OBESITY RATES ARE HIGH AND GETTING HIGHER

Obesity (body mass index [BMI] ≥ 30 kg/m^2) affects 42.4% of US adults, or more than 107 million people, and 9.2% of US adults have severe obesity (BMI ≥ 40 kg/m^2).[2,4] These rates have increased dramatically since 1999, when 30.5% of Americans were obese and 4.7% were severely obese,[2] and they continue to increase, so that it is now estimated that 51% of US adults will be obese by 2030.[5]

The prevalence of obesity is similar in both sexes, but women are more likely to be severely obese (11.5% vs 6.9%).[4] Young, middle-aged, and older adults all have similar obesity rates. The obesity rate in non-Hispanic Black people is 49.6%, which is higher than in Hispanic people (44.8%), non-Hispanic White people (42.2%), and non-Hispanic Asian people (17.4%). Rates of severe obesity are 13.8% in Black people, 9.3% in non-Hispanic White people, 7.9% in Hispanic people, and 2% in non-Hispanic Asian people.[4]

Obesity rates decrease with increasing income: 39% obesity at 130% or less of the federal poverty level vs 31.2% in those at higher than 350% of the federal poverty level.[6] Rates also decrease with college education: 27.8% in college graduates vs 40% in nongraduates.[6]

ADVERSE EFFECTS ON HEALTH

Obesity is a chronic disease characterized by a long-term positive energy balance resulting in excess adiposity.[3] Weight in relation to height (ie, the BMI) and waist circumference are surrogates for measuring adiposity.

Obesity leads to structural abnormalities such as venous stasis and hepatic steatosis, physiologic derangements such as insulin resistance and inflammation, and functional impairments such as gastroesophageal reflux disease, urinary incontinence, osteoarthritis, and disability. Obesity increases the risk of developing more than 200 other chronic diseases and thus is associated with significant rates of morbidity and death.[3]

DRUG THERAPY CAN AID WEIGHT LOSS

Obesity is influenced by genetics, epigenetics, socioeconomic status, access to food and exercise, psychological health, iatrogenic factors, and behavior, and thus it is challenging to treat. Furthermore, biological responses to loss of adipose tissue trigger a decrease in metabolic rate and increase in energy efficiency while inducing hunger and decreasing satiety.[7]

Drug therapy helps patients adhere to lifestyle changes and overcome these responses. Typically, monotherapy leads to a loss of 3% to 8% of total body weight from baseline, and combination therapy can result in even greater loss.[6,7] Moreover, some antiobesity drugs can provide independent health benefits, such as decreases in blood pressure, harmful lipid levels, waist circumference, insulin resistance, nonalcoholic fatty liver disease, risk of major cardiovascular events, and progression of diabetic kidney disease.[1,5,8–11]

CHOOSING THE RIGHT DRUG

Pharmacotherapy is indicated in patients with a BMI of 30 kg/m^2 or higher, or 27 kg/m^2 or higher with obesity-associated complications in whom a healthy low-calorie diet and regular physical activity have failed to achieve a healthy weight.[7] Choosing the right drug regimen involves an individualized, shared decision-making process that accounts for patient preferences, comorbidities, and out-of-pocket costs (**Table 1, Table 2**).

Tolerability

Adverse effects frequently limit the use of antiobesity medications.

Liraglutide and semaglutide, glucagon-like peptide 1 (GLP-1) receptor agonists that carry a US Food and Drug Administration (FDA) indication for long-term treatment of obesity, are generally well tolerated. (Semaglutide was approved in June 2021.) Gastrointestinal effects are common and include nausea, abdominal cramping, and diarrhea. Liraglutide requires daily injections, and semaglutide requires weekly injections, and although some patients find injections undesirable, they rarely discontinue this therapy because of its mode of administration. Semaglutide is available in an oral formulation, but this is not approved for the treatment of obesity.

Phentermine-topiramate, another FDA-approved drug, is also well tolerated. The combination can achieve higher weight loss at lower doses of each medication, thus lessening the chance of dose-dependent adverse effects. Irritability, insomnia, neuropathy, problems with memory, and changes in taste are the adverse effects most frequently reported. Patients often find soda drinks less appealing, which can help their weight management.

By 2030, 51% of US adults may be obese

When patients experience severe topiramate-associated effects such as neuropathy, or phentermine-associated effects such as irritability, one can consider prescribing the other medication by itself. Generally, phentermine is very well tolerated, and side effects wane with continued use. However, the clinician may recommend as-needed use for patients who experience significant adverse effects. For example, if a patient tends to eat excessively during the weekends, phentermine can be taken just on weekends.

Phentermine carries a theoretical potential for abuse and addiction, but this concern is not supported in the literature. Topiramate is generally less well tolerated, with frequent neurologic and psychiatric adverse effects.

TABLE 1

Drugs approved for long-term treatment of obesity

Drug and class	Ideal candidates	Adverse effects	Contraindications[a]	Average wholesale price[b]
Liraglutide **Semaglutide** (GLP-1 receptor agonist)	Patients with coronary artery disease, prediabetes, and diabetes	Constipation, diarrhea, nausea, headache, fatigue, and injection site reactions. Serious but rare: increased heart rate, renal impairment, pancreatitis, and suicidal ideation. Potential risk of thyroid C-cell tumor. Semaglutide is associated with an increased incidence of diabetic retinopathy complications, probably attributable to rapid correction of hyperglycemia in patients with diabetes.	Family or personal history of medullary thyroid cancer or multiple endocrine neoplasia type 2. Use with caution in patients with severe chronic kidney disease and history of pancreatitis.	Liraglutide $1,619 Semaglutide $1,022
Naltrexone-bupropion (opioid receptor antagonist and DNRI)	Patients with depression, those interested in smoking cessation, and those with food addiction and strong cravings	Glaucoma, hepatotoxicity, increase in heart rate and blood pressure, headache, nausea, constipation, vomiting, dry mouth. Serious but rare: suicidal ideation and a lower seizure threshold.	Uncontrolled hypertension, seizures, anorexia, bulimia, drug or alcohol withdrawal, or chronic opioid use.	$365
Orlistat (lipase inhibitor)	Patients who do not want to take a systemic drug, or patients who eat a moderate- or high-fat diet	Headaches, flatulence, cramping, fecal incontinence, oily spotting, decreased absorption of medications and fat-soluble vitamins. Gastric disturbances can be reduced by taking with psyllium. Serious but infrequent: liver injury, cholelithiasis, nephrolithiasis.	None, but not recommended for patients with malabsorption (eg, after gastric bypass surgery).	$108
Phentermine-topiramate ER[c] (sympathomimetic amine and GABA receptor modulator)	Patients with chronic migraines	Increased heart rate, dizziness, neuropathy, insomnia, anxiety, depression, cognitive impairment, and dry mouth. Serious but rare: suicidal ideation, acidosis, hypokalemia, rise in serum creatinine, myopia, or glaucoma. Minimal risk of seizures with rapid discontinuation.	Uncontrolled anxiety or depression, cardiovascular disease, uncontrolled hypertension, hyperthyroidism, glaucoma, and history of substance dependence.	$239

[a] All antiobesity medications are contraindicated in pregnancy. Because of potential teratogenicity of many antiobesity drugs, a pregnancy test should be done before prescribing, and women should be counseled on effective birth control.

[b] Lexicomp average wholesale price for 30-day supply of maximum doses as of May 2021.

[c] A controlled substance.

DNRI = dopamine-norepinephrine reuptake inhibitor; ER = extended release; GABA = gamma aminobutyric acid; GLP-1 = glucagon-like protein-1

TABLE 2

Other drugs used for treating obesity

Drug and class	Ideal candidates	Side effects	Contraindications[a]	Average wholesale price[b]
Lisdexamfetamine[c] (amphetamine prodrug)	Patients with attention deficit hyperactivity disorder	Insomnia, irritability, anxiety, dry mouth, increased heart rate and blood pressure. Controlled substance with theoretical potential for abuse and dependence.	None, but we recommend against using in patients with cardiovascular disease.	$402
Phentermine[d] (sympathomimetic amine)	N/A	Headaches, increased blood pressure and heart rate, irritability, insomnia, constipation, diarrhea, impotence, dizziness. Controlled substance with theoretical potential for abuse and dependence. Serious but rare: pulmonary hypertension, valvular disease.	Uncontrolled anxiety and hypertension, cardiovascular disease, hyperparathyroidism, glaucoma, and history of drug dependence.	$21.30
Topiramate[e] (GABA receptor modulator)	Patients with chronic migraines	Insomnia, xerostomia, constipation, paresthesias, dizziness, anxiety, depression, drowsiness, language and memory impairments. Very rare: seizures with rapid discontinuation.	Hyperthyroidism, glaucoma.	$10
Metformin[e,f] (biguanide)	Patients with diabetes and prediabetes	Diarrhea, nausea, abdominal pain. Serious but rare: lactic acidosis.	Severe chronic kidney disease.	$5
Pramlintide[e,f] (amylin analogue)	Patients with type 1 or type 2 diabetes	Hypoglycemia, headaches, nausea, vomiting.	Gastroparesis and hypoglycemic unawareness.	$694
SGLT-2 inhibitors[e,f]	Patients with type 2 diabetes, hypertension, heart failure, cardiovascular disease, diabetic kidney disease	Genitourinary infections, hypovolemia, increased low-density lipoprotein cholesterol, and hyperkalemia. Serious but rare: diabetic ketoacidosis, bone fractures, amputations, Fournier gangrene.	Severe chronic kidney disease and ketogenic diet (concern for euglycemic ketoacidosis).	$600–$700

[a] All antiobesity medications are contraindicated in pregnancy except for metformin in patients with diabetes. Because of the potential teratogenic effect of many antiobesity medications, a pregnancy test should be obtained before prescribing, and women should be counseled on effective birth control.
[b] Lexicomp average wholesale price for 30-day supply of maximum doses as of May 2021.
[c] Approved for treatment of binge-eating disorder.
[d] Approved for short-term use; however, it is often prescribed long-term in US states where this regulation is not strictly enforced.
[e] Off-label use.
[f] Occasionally prescribed for patients who do not have diabetes or another US Food and Drug Administration indication for their use; however, this is not our practice.

GABA = gamma aminobutyric acid; SGLT-2 = sodium-glucose cotransporter-2

Naltrexone-bupropion, another FDA-approved option, is usually well tolerated, with constipation, headaches, irritability, anxiety, and insomnia being commonly reported. These can be ameliorated by reducing doses, eg, skipping the afternoon dose to reduce sleep disturbance. A stool softener or coprescription with metformin can be considered to promote more regular bowel movements.

Lisdexamfetamine, FDA-approved for treating binge-eating disorder but not obesity per se, has very infrequent side effects. It

has potential for abuse and dependence, but whether this actually occurs in patients taking it for binge-eating disorder is not well established.

Metformin, a diabetes drug frequently used off-label to treat obesity, is also well tolerated. Its most common adverse effects include abdominal pain, nausea, and diarrhea. These are lessened when using extended-release formulations and when taken with meals. Dose reduction is often required to manage adverse effects.

Orlistat, FDA-approved for treating obesity, is poorly tolerated, with abdominal pain, nausea, bloating, flatulence, and diarrhea being very common and bothersome effects. Gastric disturbances can be reduced when this drug is taken with psyllium.

COST

Antiobesity drugs are not frequently covered by insurance, and their cost limits patients' choices.

Most expensive

Liraglutide and semaglutide. Liraglutide, average wholesale price (30-day supply of maximum dose) $1,619, and semaglutide (average wholesale price $1,022) are the most expensive choices, have no generic alternatives, and are often not covered by insurance. Lower doses are more affordable. These drugs are usually covered by insurance when prescribed for diabetes, but when prescribed for this indication, the doses are lower and thus there is less effect on weight loss.

Depending on insurance coverage, other GLP-1 receptor agonists may be more suitable for patients with diabetes and obesity.

Obesity is multifactorial and thus is difficult to treat with lifestyle modifications alone

Intermediate cost

Naltrexone-bupropion, average wholesale price $365, has no generic option and is not usually covered by insurance. However, its individual components are available as generic formulations and can be prescribed separately at much lower cost (average wholesale price $50 for naltrexone 25 mg plus bupropion XL 300 mg). Bupropion can also be prescribed alone for obesity management and is usually covered by insurance (average wholesale price $16.50).

Phentermine-topiramate, average wholesale price $239, has no generic formulation and is usually not covered by insurance. Its individual components are available generically and can be prescribed separately, in combination or individually (average wholesale price $21.30 for phentermine 18.75 mg plus topiramate 100 mg).

Despite the listed prices, both phentermine and topiramate can be bought very inexpensively at certain retailers at less than $10 per month. Phentermine-topiramate can be used alternatively with phentermine alone to reduce overall costs.

Phentermine is FDA-approved for short-term use only—3 months of therapy with 6 months between courses. This is not strictly enforced in all US states. Phentermine is the most commonly prescribed antiobesity drug in the United States.[5]

Orlistat, average wholesale price $108, has no generic formulation and often is not covered by insurance. It is available over the counter at a lower dose.

Lisdexamfetamine, average wholesale price $402, has no generic alternative but is often covered by insurance when prescribed for binge-eating disorder.

Most affordable

Metformin, average wholesale price $5, is an economical option available in generic form and covered by insurance. Phentermine and topiramate are also affordable at less than $10 per month, and bupropion is another affordable option.

Very frequently, manufacturers offer customer-assistance programs, but these programs often exclude patients with Medicaid and Medicare insurance.

EFFICACY IN WEIGHT LOSS

Semaglutide is the most effective agent. Phentermine-topiramate, naltrexone-bupropion, liraglutide, lisdexamfetamine, and pramlintide are also associated with a high percentage of total body weight loss. Orlistat, topiramate alone, metformin, and sodium-glucose cotransporter-2 (SGLT-2) inhibitors are associated with a more modest weight loss. Further, orlistat is effective only in those who consume a moderate- or high-fat diet. **Table 3** lists percentages of total body weight loss observed in randomized controlled trials of the various drugs.[10–29] Of note, not all available dosages of the medications today were included in

TABLE 3

Weight loss in randomized, double-blind, placebo-controlled trials

Medication	Patients	Dose	% TBWL vs placebo
Liraglutide[10]	Diabetes, body mass index (BMI) ≥ 27 kg/m^2	1.8 mg 3.0 mg	2.7 4.0
Liraglutide[11]	Prediabetes, BMI ≥ 30 or ≥ 27 with hypertension or dyslipidemia	3.0 mg	5.4
Liraglutide[12]	No diabetes, BMI ≥ 30 or ≥ 27 with hypertension or dyslipidemia, who lost ≥ 5% total body weight with a low-calorie diet	3.0 mg	6.0
Naltrexone-bupropion[13]	Diabetes, BMI ≥ 27	32/360 mg	3.2
Naltrexone-bupropion[14]	No diabetes, BMI ≥ 30 or ≥ 27 with hypertension or dyslipidemia	16/360 mg 32/360 mg	3.7 4.8
Naltrexone-bupropion[15]	No diabetes, BMI ≥ 30 or ≥ 27 with hypertension or dyslipidemia	32/360 mg	5.2
Naltrexone-bupropion[16]	No diabetes, BMI ≥ 30 or ≥ 27 with hypertension or dyslipidemia	32/360 mg	4.2
Orlistat[17]	BMI 30–43	120 mg TID	3.0
Orlistat[18]	BMI 30–44	120 mg TID	3.7
Orlistat[19]	Type 2 diabetes, clinically stable on oral sulfonylureas, BMI 28–40	120 mg TID	1.9
Phentermine-topiramate ER[20]	No diabetes, BMI ≥ 35, blood pressure ≤ 140/90 mm Hg	3.75/23 mg 15/92 mg	3.5 9.3
Phentermine-topiramate ER[21]	BMI 27–45 with at least 2 of the following: hypertension, dyslipidemia, diabetes, prediabetes, abdominal obesity	7.5/46 mg 15/92 mg	8.0 10.8
Phentermine-topiramate ER[22]	BMI 27–45 with at least 2 of the following: hypertension, dyslipidemia, diabetes, prediabetes, abdominal obesity	7.5/46 mg 15/92 mg	7.1 8.5
Phentermine-topiramate ER[23]	BMI 30–45	7.5/46 mg 15/92 mg	6.8 7.5
Lisdexamfetamine[24]	Adults with binge eating disorder, BMI 25–45	30 mg 50 mg 70 mg	3.3 5.2 5.3
Phentermine[23]	BMI 30–45	7.5 mg 15 mg	3.7 4.4
Topiramate[23]	BMI 30–45	46 mg 92 mg	3.4 4.7
Metformin[25]	No diabetes, BMI ≥ 24 (≥ 22 in Asian Americans), elevated fasting glucose or impaired glucose tolerance	850 mg BID	2.3
Pramlintide[26]	No diabetes, BMI 30–50	120 µg TID 360 µg TID	5.6 6.8
Canagliflozin[27]	No diabetes, BMI 27–50	50 mg 100 mg 300 mg	0.9 1.6 1.4
Semaglutide[10]	No diabetes, BMI ≥ 30, or ≥ 27 with at least 1 obesity-associated comorbidity	2.4 mg/week	12.4
Semaglutide[11]	Diabetes, BMI ≥ 27	2.4 mg/week	6.2

BID = twice a day; ER = extended release; TID = three times a day; TBWL = total body weight loss

the trials, and all studies included lifestyle modifications in addition to pharmacotherapy.

IN PATIENTS WITH DIABETES

Weight loss can help patients improve glycemic control, and certain diabetes drugs have the added benefit of helping patients lose weight.

GLP-1 receptor agonists and SGLT-2 inhibitors are great choices for patients with high BMI and diabetes, as they lower hemoglobin A1C and carry a low risk of hypoglycemia. Some agents—liraglutide, semaglutide, dulaglutide, empagliflozin, canagliflozin, and dapagliflozin—offer cardiovascular benefits in these already high-risk patients. Use is limited by high copays. Further, most of the GLP-1 drugs are injectable and have frequent adverse gastric effects. Semaglutide is an ideal choice because it has been shown to produce more weight loss than others in this category, requires only weekly injection, and is the only GLP-1 receptor agonist available in oral formulation.

SGLT-2 inhibitors are usually well tolerated, with frequency of urination being the most commonly reported adverse effect. Urinary tract and vaginal infections are also common in these patients, who are already at risk for infection. Canagliflozin should likely be avoided in patients with known or suspected peripheral artery disease, as it is associated with a modest yet higher risk of amputations. Some studies have shown canagliflozin to be associated with a higher incidence of fractures, making other SGLT-2 inhibitors potentially more suitable for those with osteoporosis or frequent falls.

Multiple agents or combination agents, off-label and on-label, are sometimes required for clinically significant weight loss

Metformin is a more affordable option that promotes weight loss, lowers hemoglobin A1C, and has low potential for hypoglycemia. However, metformin has not been shown to provide additional cardiovascular benefits. Metformin should be avoided in patients with severe chronic kidney disease (glomerular filtration rate < 30 mL/min/1.73 m^2).

Pramlintide is FDA-approved for type 1 and type 2 diabetes, but its use is limited by multiple daily injections and a tendency to cause hypoglycemia.

GLP-1 receptor analogues (other than liraglutide and semaglutide), SGLT-2 inhibitors, and pramlintide are sometimes prescribed for weight loss in patients without diabetes or another FDA-approved indication. This is not our practice.

Orlistat and naltrexone-bupropion can also be considered in this group since they have been shown to improve insulin sensitivity.

IN PATIENTS WITH CARDIOVASCULAR DISEASE

Several antiobesity drugs have shown a positive impact on cardiometabolic risk factors such as blood pressure, waist circumference, insulin sensitivity, and lipid profile. These drugs include liraglutide, semaglutide, naltrexone-bupropion, and orlistat. Naltrexone-bupropion is contraindicated in patients with uncontrolled hypertension but is a suitable choice for this patient group once blood pressure control is established.

Phentermine-topiramate has also been shown to improve cardiometabolic markers, but due to its stimulant effect on the heart, it should be avoided in patients with known or suspected coronary artery disease, to avoid infarction. Lisdexamfetamine should similarly be avoided in these patients. In patients at high risk for cardiovascular disease, such as those with multiple metabolic comorbidities, smoking history, and family history of coronary artery disease, a thorough history and examination should be performed before prescribing stimulants.

ONCE A DRUG IS CHOSEN, FOLLOW-UP IS ESSENTIAL

Once a medication is chosen, patients should be evaluated for weight loss and adverse effects at least monthly for the first 3 months, then at least every 3 months. If the medication is effective (≥ 5% total body weight loss at 3 months), safe, and tolerable, it should be continued indefinitely.[7,30] Multiple or combination agents, off-label and on-label, are sometimes required for clinically significant weight loss.

BEYOND DRUG THERAPY

All patients suffering from obesity should be counseled to adopt a healthful low-calorie

diet, exercise regularly, get adequate sleep, and manage stress.

The clinician should also eliminate or replace the patient's current obesity-inducing medications with more favorable ones whenever appropriate. For example, the clinician may consider bupropion instead of paroxetine, amitriptyline, nortriptyline, or mirtazapine in patients with depression or anxiety. Second-generation antihistamines can be prescribed instead of first-generation ones.

Beta-blocker use should be limited to those with an indication (such as an arrhythmia). When beta-blockers are indicated, carvedilol and nebivolol are associated with less weight gain.[1,7]

For contraception, oral contraceptive pills and intrauterine devices should be considered over medroxyprogesterone acetate.[1]

In treating patients with diabetes, metformin, pramlintide, SGLT-2 inhibitors, and GLP-1 receptor agonists should be considered, as they promote weight loss. Thiazolidinediones, sulfonylureas, and insulin can cause patients to gain weight, and thus should be limited to those with specific indications (such as insulin for type 1 diabetes mellitus), those unable to tolerate or afford preferred medications, or those whose blood glucose remains uncontrolled. Basal insulin is more favorable than preprandial or biphasic insulin.[1,7] Analogue insulins are recommended over human insulin.[31]

When treating patients with chronic inflammatory diseases, disease-modifying antirheumatics and biologics are preferred over steroids in patients who tolerate them and are able to afford them.

Bariatric weight loss surgery is indicated in patients who have not achieved a healthy weight though lifestyle changes and who meet one of the following criteria[1,30]:

- BMI 40 kg/m^2 or greater
- BMI 35 kg/m^2 or greater, with obesity-associated complications
- BMI 30 kg/m^2 or greater in patients with diabetes.

A substantial body of evidence has demonstrated that weight loss surgery is more effective in promoting long-term weight loss and in improving associated comorbid conditions than intensive lifestyle modifications and pharmacotherapy.[32] Weight loss surgery also achieves superior glycemic control and reduction of cardiovascular risk factors in patients with diabetes and obesity.[30] However, despite its effectiveness and safety, only 0.5% of eligible patients receive this treatment.[33] The reasons behind this underutilization are not fully understood but likely include an overestimation of the surgical risks and an underestimation of the potential benefits by primary providers, who in turn fail to make an initial recommendation.[33]

Another potential barrier is a lack of knowledge by primary providers regarding bariatric surgery options and qualifying patient characteristics. Lastly, underutilization may also be due to variable coverage for bariatric surgery across insurances.

TAKE-HOME POINTS

- Obesity, a chronic disease with devastating health consequences, is exceedingly prevalent and affects certain groups disproportionately, including women, non-Hispanic Blacks, and people with lower education and income.
- The prevalence of obesity has increased in the past 20 years, and it is expected to worsen.
- Obesity is multifactorial and thus difficult to treat with lifestyle modifications alone.
- Pharmacotherapy, as part of a comprehensive plan, can help patients achieve meaningful and lasting obesity control. It can also provide independent health benefits, including decreased cardiovascular risk.
- Despite its benefits, antiobesity drug therapy is significantly underutilized.
- Choosing a drug for weight loss should be an individualized, shared decision-making process that accounts for patients' preferences, comorbidities, and out-of-pocket expenses.
- A comprehensive antiobesity management plan should also include lifestyle counseling, discontinuation of obesity-inducing medications when possible, and weight loss surgery, when indicated.

Weight loss surgery can result in superior glycemic control and reduction of cardiovascular risk factors in patients with diabetes and obesity

DISCLOSURES

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REVIEW

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The obesity paradox in heart failure: What is the role of cardiorespiratory fitness?

ABSTRACT

The obesity paradox describes a survival benefit for higher body mass index in patients with heart failure. But other factors like cardiorespiratory fitness may play a role in heart failure development, severity, and survival. Although more research is needed to better understand the relationships between body mass index and fitness in patients with heart failure, evidence indicates that recommending weight loss and an exercise program is appropriate for most patients.

KEY POINTS

Obesity increases the risk of developing heart failure regardless of fitness level, but better fitness attenuates the risk.

Weight appears to be only part of the obesity paradox story. Evidence indicates that cardiorespiratory fitness is a major factor influencing the paradox.

Fitness modifies the obesity paradox in patients with heart failure and reduced ejection fraction, with the paradox remaining strongest in patients who are less fit.

Although more research is needed on risk reduction for heart failure, evidence indicates that intentional weight loss and increased fitness are advisable for select patients.

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Obesity is a well-established and important predictor of morbidity and mortality in patients with cardiovascular (CV) disease and other conditions, including chronic kidney disease and chronic obstructive pulmonary disease. Yet some studies report obesity is associated with lower mortality in patients with heart failure—a finding known as the obesity paradox.

Though not fully understood, several possible reasons for the obesity paradox have been proposed (**Table 1**).[1–9]

Understanding the obesity paradox has important clinical implications given the high prevalence of obesity in patients with heart failure (42% of those with preserved ejection fraction [HFpEF] and 36% of those with reduced ejection fraction [HFrEF]).[10] What should patients be advised about weight management? What should patients be advised about cardiorespiratory fitness, a major factor influencing the paradox?

This review summarizes current understanding of the roles of cardiorespiratory fitness and body mass index (BMI) in patients with heart failure and its development. It also discusses how to advise patients about fitness and body mass in light of the obesity paradox.

BENEFIT OF FITNESS IN CARDIOVASCULAR DISEASE

The effect of cardiorespiratory fitness on CV outcomes is an active area of clinical research. The standard for measuring cardiorespiratory fitness is cardiopulmonary exercise testing, using

TABLE 1

Select theoretical mechanisms of the obesity paradox

Greater metabolic reserves
Less cardiac cachexia
Increased concentration of tumor necrosis factor receptors
Earlier presentation owing to greater functional impairment
Attenuated response to renin-angiotensin-aldosterone system
Higher blood pressure leading to greater use of cardioprotective medications

Adapted from reference 6.

an incremental treadmill or upright cycle protocol. Numerous studies have found associations between poor CV disease outcomes and low peak exercise oxygen uptake (peak Vo_2).[11,12]

Low fitness predicts poor outcomes

In 1996, Blair et al[13] were among the first to quantify the effects of cardiorespiratory fitness on cardiovascular disease outcomes. After following 25,341 men and 7,080 women in a preventive medicine clinic for about 9 years, they found that low fitness was independently associated with increased all-cause mortality in both men (relative risk [RR] 1.52, 95% confidence interval [CI] 1.28–1.82) and women (RR 2.10, 95% CI 1.36–3.21). Low fitness was associated with statistically significant increased cardiovascular disease mortality risk in men (RR 1.70, 95% CI 1.28–2.25), although the difference was not statistically significant in women. In both sexes, low fitness was a more significant prognostic factor than other traditional cardiac risk factors. Interestingly, elevated BMI (> 27 kg/m^2) was not found to be significantly associated with increased mortality in either sex.

Low fitness is a strong independent predictor of cardiovascular disease mortality

Fitness may be more important than weight

A 1999 prospective observational study by Wei et al[14] also found that low cardiorespiratory fitness is a strong independent predictor of cardiovascular disease mortality in the general population, and perhaps more so than BMI. The study assessed nearly 26,000 men for cardiorespiratory fitness, cardiovascular disease, and risk factors for cardiovascular disease development, with follow-up for about 10 years. Cardiorespiratory fitness was determined using maximal treadmill exercise testing with age-based metabolic equivalent (MET) values for fitness levels. Participants also were stratified by BMI using standard thresholds for normal weight (18.5–24.9 kg/m^2), overweight (25.0–29.9 kg/m^2), and obesity (> 30 kg/m^2).[14]

Results showed that cardiovascular disease mortality increased with increasing BMI levels.[14] Expectedly, the lowest risk for cardiovascular disease mortality was a combination of normal weight and high fitness. However, the relative risk of cardiovascular disease mortality in the obese high-fitness cohort was half that in the low-fitness normal-weight cohort, suggesting that fitness is a more important predictor of cardiovascular disease mortality than body weight. The effect of low cardiorespiratory fitness on cardiovascular disease mortality was also higher than the presence of diabetes, dyslipidemia, hypertension, or current smoking across all BMI levels.[14]

HEART FAILURE DEVELOPMENT: CARDIORESPIRATORY FITNESS AND BMI

The mechanisms related to obesity that contribute to the development of HFpEF and HFrEF include hemodynamic alterations that may predispose the patient to changes in cardiac morphology and ventricular function.[10]

Possible mechanisms

The mechanisms related to low cardiorespiratory fitness that contribute to the development of heart failure are not well understood. Low cardiorespiratory fitness may indirectly affect development of cardiovascular risk factors (ie, reduced cardiorespiratory fitness is associated with a low level of physical activity),[15] which may accelerate the development of heart failure risk factors including diabetes, hypertension, and coronary artery disease. Alternatively, cardiovascular symptoms such as angina or dyspnea on exertion may limit habitual physical activity, in turn leading to reduced cardiorespiratory fitness.

Even in the absence of traditional cardiovascular disease risk factors, studies demonstrate that sedentary aging leads to increased stiffness of the left ventricular myocardium, a potential substrate for heart failure.[16] Higher

TABLE 2

Studies assessing BMI and cardiorespiratory fitness: Effect on heart failure development

Study	N	Design[a]	End point	Main findings
Pandey et al[19] Cooper Center Longitudinal Study	19,485	Patients stratified by BMI and peak METs into quintiles	Long-term risk of hospitalization for HF	Higher midlife BMI was significantly associated with greater risk of hospitalization for HF in older age. This association was attenuated after adjusting for cardiorespiratory fitness.
Kenchaiah et al[20] Physicians' Health Study	21,094	Patients stratified by BMI and vigorous physical activity	New onset HF	Compared with lean participants, overweight and obese participants had increased HF risk. Vigorous physical activity conferred decreased HF risk. No interaction was found between BMI, vigorous physical activity, and HF risk.
Hu et al[21]	59,178	Patients stratified by physical activity and indicators of adiposity (eg, BMI, waist circumference, waist-to-hip ratio)	New onset HF	Higher BMI, waist circumference, or waist-to-hip ratio was associated with increased HF incidence in men and women. The protective effect of physical activity on HF risk was consistent in participants at all levels of BMI.
Kokkinos et al[22]	20,254	Patients stratified by BMI and cardiorespiratory fitness in quartiles	New onset HF	Increased cardiorespiratory fitness was associated with progressively lower HF risk regardless of BMI. After adjusting for fitness, BMI was not a significant predictor of HF risk.
Pandey et al[23] Look AHEAD trial	5,109 (with DM)	Patients stratified by BMI and cardiorespiratory fitness into tertiles	New onset HF	High cardiorespiratory fitness was associated with lower risk of developing HFpEF. Sustained long-term improvement in fitness was associated with lower risk of HF after 4 years.

[a] All studies are retrospective.

AHEAD = Action for Health in Diabetes; BMI = body mass index; DM = diabetes mellitus; HF = heart failure; HFpEF = heart failure with preserved ejection fraction; METs = metabolic equivalents

levels of physical activity are associated with beneficial effects on cardiovascular measures, including improved early diastolic filling time and favorable cardiac remodeling.[17] In addition, an animal study showed a direct and favorable effect of exercise training on cardiac structure and function, leading to a delayed onset of heart failure.[18]

Study comparing fitness and BMI

The combined impact of cardiorespiratory fitness and BMI on heart failure development is gaining increasing attention, and many studies have been conducted (**Table 2**).[19–23]

Data from the Cooper Center Longitudinal study[19] indicated that cardiorespiratory fitness may be at least as important as BMI for developing heart failure. The study stratified nearly 20,000 participants by standard BMI thresholds and cardiorespiratory fitness levels (low, moderate, and high as determined by calculated METs achieved with treadmill exercise testing). A higher BMI during midlife was associated with a significantly greater risk of heart failure hospitalization in older patients (age 65 and older), even after adjusting for other established heart failure risk factors. When adjusted for cardiorespiratory fitness, this association was attenuated, such that cardiorespiratory fitness accounted for 47% of the heart failure risk associated with BMI. Furthermore, the BMI-associated risk of hospitalization for heart failure was more pronounced in participants who had low fitness or were moderately fit.

A subgroup of about 9,000 participants underwent repeat measurements of cardiorespiratory fitness and BMI at a median follow-up of 4.2 years. Increased cardiorespiratory fitness, but not BMI, was significantly associated with decreased risk of heart failure hospitalization in older patients (hazard ratio [HR] 0.91, 95% CI 0.84–0.98 per 1 MET increase).[19]

Data from the Physicians' Health Study showed that participation in self-reported vigorous activity (defined as "working up a sweat") 1 to 3 times a month conferred a 26% decrease in new-onset heart failure development.[20] In contrast, a 1-kg/m^2 increase in BMI increased the risk of heart failure by 13%. Adjusting for vigorous physical activity did not alter the risk of heart failure associated with elevated BMI.

Hu et al[21] studied the relationship between physical activity, heart failure risk, and indicators of adiposity (ie, BMI, waist circumference, and waist-to-hip ratio) in nearly 60,000 Finnish participants who were free of heart failure at enrollment. During a mean follow-up of 18.4 years, the risk of developing heart failure directly increased with BMI and other measures of adiposity for men and women. Moderate or high levels of physical activity were associated with a reduced risk of heart failure in both sexes at all levels of BMI and waist-to-hip ratio.

Cardiorespiratory fitness may be at least as important as BMI for developing heart failure

In a study published in 2019, Kokkinos et al[22] stratified 20,000 US men by standard BMI thresholds and cardiorespiratory fitness. Fitness thresholds were based on quartiles following age and sex-specific MET adjustments. After a mean follow-up of 13.4 years, they found that heart failure risk increased progressively with decreasing fitness in each BMI category. Although age, BMI, and cardiorespiratory fitness were strong independent predictors of heart failure risk, the association between BMI and heart failure risk was no longer statistically significant after adjusting for fitness. Each increase of 1 MET was associated with a 16% lower risk of heart failure (HR 0.84; 95% CI 0.83–0.86; $P < .001$).

Clues from patients with diabetes

A recent post hoc analysis of the Look AHEAD (Action for Health in Diabetes) trial[23] also examined the impact of fitness and BMI on heart failure development. It found that intensive lifestyle modification did not lower the risk of heart failure more than diabetes support and education groups (HR 0.96, 95% CI 0.75–1.23).

However, a pooled multivariate analysis found a statistically significant, graded, inverse association between baseline cardiorespiratory fitness and heart failure incidence in participants who were moderately or highly fit. Interestingly, this association was only observed for heart failure with preserved but not reduced ejection fraction. Also, the association of BMI with heart failure was not stastistically significant after adjusting for baseline cardiorespiratory fitness and traditional risk factors. In a subset of patients who underwent repeat assessment of cardiorespiratory fitness and BMI at 1 and 4 years, there was a statistically significant association between improved fitness and lower risk of overall heart failure at 4 years (HR 0.86, 95% CI 0.79–0.94).[23]

More information needed on women and type of heart failure

Other than in a study by Hu et al,[21] which included comparable numbers of men (1,921) and women (1,693), women are vastly underrepresented in the studies. The Physicians' Health Study[20] consisted entirely of men, and in the Cooper Center Longitudinal Study,[19] women accounted for less than 10% of participants in the overweight category and less than 11% in the obese category. Given the known differences between men and women, especially body fat distribution, more studies that include women are essential.

Another criticism is that only the Look AHEAD trial[23] determined the risk for specific heart failure phenotypes (ie, HFrEF vs HFpEF). In most studies, the primary outcome was defined by a combination of International Classification of Diseases codes, limiting overall interpretation.

Bottom line

Despite limitations, these studies, taken as a whole, have two important implications for heart failure prevention:

- BMI and cardiorespiratory fitness both affect heart failure development, but fitness is likely the more significant factor
- Increased fitness is associated with a reduced risk of heart failure hospitalization as one ages.

TABLE 3

Studies assessing BMI and cardiorespiratory fitness: Effect on heart failure prognosis

Study	N[a]	Average LVEF of target groups	Design[b]	End point	Main findings
Lavie et al[24]	2,066	High fit = 30.1% Low fit = 26.0%	Patients stratified by BMI and peak Vo_2	Overall mortality	In patients with low cardiorespiratory fitness, BMI ≥ 30 kg/m² was a significant predictor of better survival. No obesity paradox seen at the high fitness level.
Clark et al[7]	1,675	High fit = 23.4% Low fit = 23.2%	Patients stratified by BMI and peak Vo_2	Death, urgent status 1A heart transplant, or VAD placement.	BMI of obesity class was associated with a significantly lower risk of death, urgent transplant, or device placement than with normal BMI in the group with low peak Vo_2. In the high peak Vo_2 group, no difference was seen for BMI and survival.
Piepoli et al[27] MECKI Score Research Group	4,623	BMI (kg/m²) < 25 = 31% 25 to 30 = 33% > 30 to ≤ 35 = 33% > 35 = 33%	Patients stratified by BMI and peak Vo_2	All-cause mortality and CV death	Higher BMI and peak Vo_2 were significant positive predictors of longer survival. When patients in a BMI category were matched according to age, sex, LVEF, and peak Vo_2, the protective role of BMI disappeared.
McAuley et al[26] FIT Project	774	High fit = 41% Low fit = 40%	Patients stratified by BMI and peak METs	Overall mortality	Significant positive association between BMI category and survival for exercise capacity < 4 METs, but not ≥ 4 METs.

[a] All patients had established heart failure.
[b] All studies were retrospective.

BMI = body mass index; CV = cardiovascular; FIT = Henry Ford Exercise Testing; LVEF = left ventricular ejection fraction; MECKI = Metabolic Exercise test data combined with Cardiac and Kidney Indexes; METs = metabolic equivalents; VAD = ventricular assist device; Vo_2 = exercise oxygen uptake

HEART FAILURE PROGNOSIS: CARDIORESPIRATORY FITNESS AND BMI

Studies have been conducted in patients with heart failure to determine the impacts of fitness and BMI, and whether fitness affects the obesity paradox (**Table 3**).[7,24–27]

Clark et al[7] also found that higher fitness levels likely mitigate the obesity paradox in patients with heart failure. They assessed almost 2,000 patients referred for heart transplant evaluation. Participants were stratified by BMI and fitness, as determined by cardiopulmonary exercise testing. After 2 years of follow-up, a high BMI (≥ 30 kg/m²) was a significant predictor of improved survival in the low-fitness group but not in the high-fitness group.

The Henry Ford Exercise Testing (FIT) Project[26] followed nearly 800 participants with heart failure and a BMI of at least 18.5 kg/m². Participants were grouped into standard BMI categories and then stratified by fitness (< 4 or ≥ 4 METs) based on treadmill stress testing. After a mean follow-up of 10 years, the authors concluded that the higher the BMI, the lower the mortality in those with a low level of fitness, but not in those with a high level of fitness. Thus, exercise capacity should be considered when stratifying risk.

HFrEF: Higher fitness may negate the obesity paradox

In the MECKI Score Research Group study,[27] 4,623 patients with HFrEF underwent maximum cardiopulmonary exercise testing at enrollment and were followed for a median of 3 years. The population was divided according to BMI and peak Vo_2. On univariate analysis, groups with higher BMI and peak Vo_2 had lower mortality. However, when groups were matched for age, sex, left ventricular ejection fraction (LVEF), and predicted peak Vo_2, the protective role of BMI disappeared.

Fitness: An obesity paradox modifier

The above studies support an obesity paradox-

cardiorespiratory fitness dichotomy in established heart failure: obesity is predominantly protective in patients with low fitness but not in highly fit patients. Hence, high fitness can be thought of as a modifier of the obesity paradox.

A strength of the data is the wide range in the mean age of each low-fitness obese cohort (50.8–63 years),[8,27] indicating that the protective effect of obesity is not limited to younger patients. Studies also have included a range of mean LVEF (23.6%–40%),[2,7,27] suggesting that cardiorespiratory fitness is likely an obesity paradox modifier in patients with reduced LVEF (< 40%), mid-range LVEF (40%–50%), and preserved LVEF (> 50%).

HFpEF: Does the obesity paradox hold?

The obesity paradox is not as consistently reported for heart failure patients with preserved ejection fraction as it is for those with reduced ejection fraction. Aerobic exercise capacity has been examined in patients with preserved ejection fraction in relation to indices of obesity and adiposity.[28,29] In those trials, BMI predicted lower exercise capacity but did not correlate with cardiac-specific functional and prognostic parameters, including measures of left ventricular function.

Vigorous activity 1 to 3 times a month conferred a 26% decrease in new-onset heart failure development

A retrospective analysis of the Treatment of Preserved Cardiac Function Heart Failure With an Aldosterone Antagonist (TOPCAT) trial[30] indicated that the obesity paradox may not hold for HFpEF. It found that a higher baseline level of physical activity was associated with lower risk of adverse cardiovascular events through the duration of the trial (median follow-up 2.4 years), independent of BMI and other risk factors.

It is possible that the apparent lack of an obesity paradox in HFpEF may be because obesity itself is a risk factor for HFpEF. Also, patients with HFpEF and obesity are more likely to have other cardiovascular risk factors such as hypertension, diabetes, and obstructive sleep apnea that may attenuate any protective effect of obesity.[31]

What about heart failure with mid-range ejection fraction?

Heart failure with mid-range ejection fraction (LVEF 40%–50%) is a more recently characterized group that is not well defined or understood.[32,33] It is possible that the mechanisms underlying fitness as an obesity-paradox modifier in these patients are similar to those with reduced ejection fraction, but that is not well established. It is unclear if beneficial interventions in one group are relevant to the other.

Obesity definitions vary by study

Most of the above studies defined obesity broadly as a BMI greater than 30 kg/m^2, limiting the generalizability of conclusions. Only the MECKI Score study[27] subdivided patients based on obesity classes. Certain BMI thresholds may exist for which protective effects of obesity become deleterious.

IMPACT OF WEIGHT LOSS

A meta-analysis by Mahajan et al[4] found that weight loss induced by bariatric surgery resulted in significantly improved measures of cardiac function and morphology (diastolic function, left ventricular mass index, and left atrial size). However, clinical outcomes (eg, heart failure incidence) were not assessed. Furthermore, patients did not have a diagnosis of heart failure at baseline, so the effect of bariatric surgery in established heart failure was uncertain.

Other studies have not found improved cardiac function with weight loss. Kitzman et al[34] found that left ventricular mass and relative wall thickness decreased after diet-induced weight loss, but resting cardiac function did not improve.

A Swedish registry study with nearly 40,000 participants without heart failure at baseline evaluated the effects of weight loss from either intensive lifestyle intervention or bariatric surgery.[35] Baseline weight and BMI did not differ between the cohorts. Surgery led to 18.8 kg more weight loss than lifestyle interventions at 1-year follow-up and 22.6 kg more at 2 years. After a median follow-up of 4.1 years, surgery was associated with lower heart failure incidence than lifestyle modification (4.1% vs 7.6% per 10,000 person-years; HR 0.54, 95% CI 0.26–0.81). A 10-kg weight loss from both cohorts combined resulted in decreased heart failure incidence (HR 0.77, 95% CI 0.60–0.97).

Bariatric surgery may also help mitigate established heart failure. In a population-based study,[36] 524 patients with heart failure were followed after bariatric surgery, with a

composite of emergency department visits or hospitalizations for heart failure exacerbation as the primary outcome measure. In the 13 to 24 months after surgery, heart failure exacerbations were significantly reduced (odds ratio 0.57, 95% CI 0.39–0.82). There were 184 heart failure events (43% systolic and 57% diastolic). No information on body weight reduction was reported, so it is unclear if more weight loss correlated with fewer events.

In contrast, a study by Zamora et al[37] of 1,000 patients with ambulatory chronic HFrEF were followed for 3 years to determine the impact of significant weight loss (defined as more than 5% of body weight over 1 year) on the mortality rate. Mortality was higher in patients who lost significant weight (27.6%) than in patients without significant weight loss (15.3%). Among obese patients, significant weight loss was associated with a higher risk of all-cause death (adjusted HR 2.38, 95% CI 1.31–4.32) than in nonobese patients (adjusted HR 1.83, 95% CI 1.16–2.89).

Does unintentional weight loss explain the obesity paradox?

Intentional vs unintentional weight loss likely explains the different heart failure outcomes following weight loss, particularly in patients with HFrEF.

When evaluating candidates for intentional weight loss via bariatric surgery or lifestyle modifications, medical clearance for participation requires a certain level of baseline functional status. However, unintentional weight loss in patients with advanced HFrEF may be the result of sarcopenia and cardiac cachexia, leading to poor baseline metabolic reserves and adverse clinical outcomes. Thus, the obesity paradox may simply reflect the severity of heart failure, with lower BMI occurring in end-stage heart failure and obesity, indicating a better baseline metabolic reserve.

Body composition is also important

Patients with HFpEF and obesity also have sarcopenia and adipose infiltration of muscle,[31] indicating a highly inflamed and catabolic state. This highlights one of the limitations of using BMI as a surrogate of adiposity, and it demonstrates the need to further describe body composition when evaluating heart failure outcomes.

More attention is being focused on the effect of lean mass on cardiorespiratory fitness. Lean mass is used as a surrogate for skeletal muscle mass, which is independently associated with cardiorespiratory fitness, possibly via endothelial and mitochondrial dysfunction and respiratory muscle abnormalities.[28,38] In a 2017 review, reduced lean mass contributed to impaired cardiorespiratory fitness, independent of cardiac function.[39] BMI reductions occur with loss of lean mass, which may partially account for the obesity paradox in heart failure.[40]

Osman et al[41] prospectively studied 225 consecutive ambulatory patients with chronic systolic heart failure who were referred for cardiopulmonary exercise testing. They found that adjusting peak Vo_2 to lean mass provided greater prognostic strength than adjusting by body weight, particularly in people with obesity.

The pattern of regional tissue deposition, especially increased proportions of intra-abdominal fat, may play a key role in exercise intolerance in patients with HFpEF. Haykowsky et al[42] found that patients with HFpEF had higher ratios of intermuscular fat to skeletal muscle mass than healthy controls, and this was significantly related to reduced peak Vo_2. This evidence suggests that body composition indices such as lean mass play an important role in cardiorespiratory fitness regardless of BMI.

In patients with established heart failure, obesity is predominantly protective in patients with low fitness

Drug-induced weight loss: The evidence is unclear

There is little evidence to demonstrate the safety and efficacy of pharmacologic weight loss in patients with heart failure. A recent post hoc analysis of the Functional Impact of GLP-1 (glucagon-like peptide-1) for Heart Failure Treatment (FIGHT) trial[43] found that in patients with reduced ejection fraction, there was a treatment-related 4.1-lb weight loss for liraglutide vs placebo (95% CI −7.94 to −0.25; $P < .04$), but no effect was found in worsening heart failure, making the clinical implications unclear. More research is needed to determine whether pharmacologic weight loss is an effective strategy to improve clinical outcomes in this patient population.

WHAT TO ADVISE PATIENTS?

Studies support 2 major themes:

- Obesity and low cardiorespiratory fitness are risk factors for the development of heart failure

TABLE 4
The obesity paradox: What we know and what we don't

Setting	Established study findings	Current limitations	Research questions
Patients with heart failure	BMI appears to be protective predominantly in patients with low fitness.	Different obesity classes have not been specifically evaluated. No separate evaluation of patients with either preserved or mid-range ejection fraction; they are largely grouped with reduced ejection fraction.	Is cardiorespiratory fitness an obesity paradox modifier in specific classes of obesity? Is cardiorespiratory fitness an obesity paradox modifier in HFpEF and HFmrEF?
Heart failure prevention	Improving cardiorespiratory fitness may be more important for risk reduction than lowering BMI. In patients with established diabetes, improved fitness may decrease the risk of developing HFpEF. Increasing BMI and specific measures of adiposity correlate with increased risk of developing heart failure. Even small amounts of physical activity decrease risk of developing heart failure. Physical activity appears to have a dose-dependent effect on heart failure risk, with the lowest risk associated with highest frequency of physical activity.	No differentiation between types or duration of physical activity. Limited specificity of type of heart failure as end point (ie, HFpEF, HFmrEF, or HFrEF). Women underrepresented.	What type of physical activity leads to the lowest risk of heart failure development? How do BMI and cardiorespiratory fitness (and interventions) affect development of different types of heart failure? Are findings relevant for women?
Weight loss	Either surgical or lifestyle-based weight loss may reduce morbidity from heart failure. Unintentional weight loss indicates acute illness and contributes to poor metabolic reserve, leading to worse outcomes.	Lack of clinical outcomes data after intentional weight loss for patients with heart failure and obesity. Limited data on specific exercise training programs in heart failure outcomes or prevention.	How does medical vs surgical weight loss affect heart failure morbidity and mortality rates, particularly with newer medical therapies for obesity? How does supervised exercise for patients with heart failure and obesity affect fitness, weight loss, and outcomes?

BMI = body mass index; HFmrEF = heart failure with mid-range ejection fraction; HFpEF = heart failure with preserved ejection fraction; HFrEF = heart failure with reduced ejection fraction

- Obesity in people with low fitness is protective for those with established heart failure.

How can clinicians use this knowledge to advise patients regarding weight loss and exercise training? The answer is unclear. The most recent American and European heart failure guidelines give only limited guidance on obesity management in patients with established heart failure.[44,45] A 2018 position paper from the Heart Failure Association of the European Society of Cardiology advocates cardiopulmonary exercise testing only for assessing the risk of heart failure.[46]

Bottom line: Advise to increase fitness and consider weight loss

Although large-scale clinical trials are needed to better assess and define the risks and ben-

efits of weight loss in patients with heart failure, particularly in those with reduced ejection fraction, recommending moderate weight loss may be appropriate. Lifestyle interventions aimed at weight loss and improving cardiorespiratory fitness—such as with a phase 2 (outpatient) cardiac rehabilitation program—should be considered, as studies suggest they reduce heart failure risk by improving fitness in patients with obesity and heart failure. And no data suggest harm.

For heart failure prevention, weight loss through dietary and lifestyle changes can be recommended, given that evidence shows a lower BMI predicts reduced risk of heart failure development. In patients with established heart failure and reduced ejection fraction, it appears that intentional weight loss through lifestyle modification or bariatric surgery may be beneficial,[35] although unintentional weight loss appears to be detrimental.[36] Thus, when advising weight loss to obese patients with heart failure, it is important to consider the individual's clinical profile.

FUTURE DIRECTIONS FOR RESEARCH

Understanding the overlapping impact of obesity and cardiorespiratory fitness in heart failure is important to identify gaps in evidence and assess future research directions (**Table 4**).

A high priority for future studies is to better evaluate the impact of obesity on different heart failure phenotypes. Distinct pathophysiologic differences exist between heart failure with reduced, mid-range, or preserved ejection fraction, with each responding differently to therapeutic interventions. Grouping all patients with heart failure together in analyses may blur results. Current literature has consistent findings in reduced ejection fraction, but dedicated analyses of preserved and mid-range ejection fraction are needed.

Similarly, it is likely that there are certain BMI thresholds where the protective effects of obesity become deleterious, but different obesity classes are commonly considered together in studies. Future research should examine if fitness modifies the obesity paradox in heart failure when assessing individuals with class II (BMI 35–39.9 kg/m^2) or class III (> 40 kg/m^2) obesity.

Other major gaps in evidence include the specific weight reduction interventions that result in better heart failure outcomes in patients with obesity. Metabolic surgery has been studied the most. How do pharmacological therapies compare? How do supervised exercise programs (particularly cardiac rehabilitation) impact risk in patients with established heart failure? Which is more important, weight loss or increased cardiorespiratory fitness? Future studies should assess relative risk reduction of specific exercise training combined with metabolic surgery or pharmacotherapy-induced weight loss in patients with heart failure.

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Antibody-mediated autoimmune encephalitis: A practical approach

ABSTRACT

Antibody-mediated autoimmune encephalitis (AE) is a heterogeneous group of inflammatory central nervous system disorders. Symptoms typically include subacute, progressive neuropsychiatric symptoms with associated cognitive dysfunction, movement disorders, and autoimmune seizures. The diagnosis should be based on objective neurologic dysfunction in combination with autoantibody testing. Treatment with immunotherapies requires both short-term and long-term strategies depending on the specific syndrome and potential for relapse. In this paper, we review key features of AE, focusing on syndromes involving cell surface and synaptic proteins, and share a practical approach to the diagnosis and management, including common pitfalls associated with nonspecific antibody findings.

KEY POINTS

AE is an umbrella term for a group of inflammatory central nervous system disorders associated with neuronal autoantibodies or other biomarkers of central nervous system autoimmunity.

Common clinical presentations include progressive neurocognitive symptoms with concomitant movement disorders, seizures, and autonomic dysfunction that worsens over weeks to months.

Objective clinical findings are needed to make the diagnosis of AE, including changes on magnetic resonance imaging, electroencephalography, and cerebrospinal fluid analysis.

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The spectrum and understanding of antibody-mediated autoimmune encephalitis (AE)—an umbrella term for a group of noninfectious, inflammatory central nervous system diseases—have expanded dramatically over the past few years. Familiarity with AE syndromes ensures prompt diagnosis and treatment. Practitioners need to stay abreast of developments in this field as the breadth of immune-mediated disorders of the nervous system continues to evolve.

In this paper, we will focus on the clinical features of common central nervous system cell surface and synaptic antibody syndromes in adults and on the emerging evidence in this area that has led to rapid changes in management and treatment over the past decade. We will also briefly comment on antibody-negative AE.

Antibody-related syndromes such as intracellular neuronal antibody-associated encephalitis and encephalitis occurring with demyelinating disorders are less commonly encountered in clinical practice and are beyond the scope of this article.

GENERAL FEATURES OF AUTOIMMUNE ENCEPHALITIS

Potential associations of AE encompass paraneoplastic, parainfectious triggers along with adverse events related to various immunotherapies.[1–3]

Onset of AE is usually subacute over weeks to months, with progressive neurocognitive symptoms including encephalopathy, cognitive dysfunction, neuropsychiatric symptoms, and seizures. Other features may include brainstem syndromes, dysautonomia, and movement disorders.

The prevalence and incidence are increasing as testing becomes more widely available. A recent study in Olmsted County, MN, showed a prevalence of AE of 13.7 per 100,000, similar to that of infectious encephalitis.[4]

HOW IS AUTOIMMUNE ENCEPHALITIS CLASSIFIED?

Over the past few decades, there has been rapid growth in the discovery of antibody-associated neurologic diseases. Autoantibodies that target neuronal antigens can cause a diverse set of neurologic disorders. This has significantly raised awareness of the wide spectrum of disease presentations that may have an underlying autoimmune component.

Antibodies associated with AE are commonly divided into 2 groups depending on the location of the antigen. The traditional "well-defined" syndromes (eg, anti-Hu or ANNA-1, anti-Ri or ANNA-2) target intracellular neuronal antigens.[5] And more recently, a new group of neuronal cell surface/synaptic proteins has been described in association with AE. This distinction is important for diagnosis and prognosis. Intracellular antibody-mediated syndromes appear to be driven primarily by a CD8+ T-cell cytotoxic response and usually have a poorer prognosis, with a limited response to immunotherapy (**Table 1**). In contrast, cell surface/synaptic antibodies appear to be directly pathogenic and are more responsive to multimodal immunotherapies (**Table 2**).[1,5] Detailed discussions of the pathophysiology of AE have been published by Bradshaw and Linnoila[6] and by McKeon.[7]

A 2018 study found the prevalence of autoimmune encephalitis was similar to that of infectious encephalitis

Though the terms paraneoplastic syndrome and AE are sometimes used interchangeably, not all AE syndromes are paraneoplastic. Paraneoplastic syndromes are defined as neurologic syndromes occurring in the setting of cancer, sometimes preceding the diagnosis of neoplasm by months or years.[1] Paraneoplastic disorders are usually related to intracellular neuronal antibodies. Cell surface/synaptic antibody-mediated syndromes, however, may also be associated with cancer, though they are usually classified as phenotypes of low to moderate risk, as these disorders can occur with or without cancer. The strength of association with an underlying neoplasm varies depending on the specific antibody or antibodies.[5]

WHEN SHOULD I CONSIDER THE DIAGNOSIS?

AE may be considered in patients presenting with subacute onset (over 1 to 3 months) of cognitive or memory deficits, alterations in consciousness, seizures, movement disorders, or other neuropsychiatric symptoms.[8] Accompanying neurologic or systemic symptoms suggestive of a specific antibody-mediated syndrome can increase clinical suspicion for AE. Examples include the following:

- Dystonia-chorea for anti-*N*-methyl-D-aspartate (anti-NMDA) receptor encephalitis
- Hyperekplexia (exaggerated startle reflex) for anti-glycine receptor (Gly-R) antibody syndrome
- Faciobrachial dystonic seizure (focal or lateralized coordinated contractions of an arm and the face) for anti-leucine-rich glioma-inactivated protein 1 (LGI1) encephalitis
- Peripheral nerve hyperexcitability (diffuse involuntary motor-unit activity due to hyperexcitability of the motor nerve or its terminal)[9] for anti-contactin-associated protein-like 2 (Caspr2) syndrome
- Weight loss accompanying gastrointestinal symptoms for anti-dipeptidyl-peptidase-like protein 6 (DPPX) encephalitis.[5,10]

While certain autoantibody disorders have a specific phenotype, a number of patients with AE do not present with classic "limbic encephalitis" and can present with a range of central nervous system and peripheral nervous system involvement.[11] **Table 3** provides a list of potential clinical and radiographic findings suggestive of AE.

It is also important to recognize that AE can be antibody-negative. Antibody-negative AE may occur due to limitations of currently available testing, especially as novel autoantibodies are being discovered. However, objective clinical and radiologic criteria exist to aid diagnosis.[8]

Despite the challenges, the diagnosis of AE should be driven by the patient's clinical presentation and diagnostic evaluation. This approach includes a detailed clinical history

TABLE 1

Autoantibody biomarkers of autoimmune encephalitis: Intracellular autoantibodies

ANTIBODY TARGET	CENTRAL NERVOUS SYSTEM FEATURES	PERIPHERAL NERVOUS SYSTEM FEATURES	OTHER	ASSOCIATED MALIGNANCY
High-risk paraneoplastic autoantibodies				
ANNA-1 (Hu)	Limbic encephalitis Encephalomyelitis Cerebellar ataxia	Sensory neuropathy	Gastrointestinal dysmotility	SCLC Rare: neuroblastoma
ANNA-2 (Ri)	Encephalomyelitis Cerebellar ataxia Rhombencephalitis		Jaw dystonia Laryngospasm	SCLC Breast carcinoma
ANNA-3	Limbic encephalitis Encephalomyelitis Cerebellar degeneration	Sensory and sensorimotor neuropathies		SCLC
Amphiphysin	Stiff-person spectrum disorder			SCLC Breast or ovarian carcinoma
CRMP-5	Limbic encephalitis Cerebellar ataxia Chorea Myelopathy Cranial neuropathies (optic neuritis)	Polyradiculoneuropathy		SCLC Thymoma carcinoma
GAD65	Stiff-person spectrum disorder Limbic encephalitis Cerebellar ataxia			Rare
GFAP	Meningoencephalitis Myelitis Optic neuritis			Ovarian teratoma Adenocarcinomas of various sites
PCA-1 (Yo)	Cerebellar ataxia			Breast or ovarian carcinoma
PCA-2	Limbic encephalitis Cerebellar ataxia	Polyneuropathy		SCLC
PCA-Tr (DNER)	Limbic encephalitis Cerebellar ataxia			Hodgkin lymphoma
Ma 1 and Ma 2 (Ta)	Diencephalitis Limbic encephalitis Brain stem encephalitis Cerebellar degeneration			Ma1: Common, diverse Ma2: Testicular seminoma

ANNA = antineuronal nuclear antibody; CRMP-5 = collapsin response mediator protein 5; DNER = delta/notch-like epidermal growth factor-related receptor; GAD = glutamic acid decarboxylase; GFAP = glial fibrillary acidic protein; PCA = Purkinje cell cytoplasmic antibody; SCLC = small-cell lung cancer

Negative antibody testing does not rule out autoimmune encephalitis

TABLE 2

Autoantibody biomarkers of autoimmune encephalitis: Cell-surface and synaptic antibodies

ANTIBODY	CENTRAL NERVOUS SYSTEM FEATURES	PERIPHERAL NERVOUS SYSTEM FEATURES	OTHER FEATURES	ASSOCIATED MALIGNANCY
AMPAR	Limbic encephalitis			SCLC Breast carcinoma Thymoma
Caspr2	Limbic encephalitis	Peripheral nerve hyperexcitability		Rare, but thymoma carcinoma reported
DPPX	Encephalopathy Myelopathy		GI dysmotility Sleep disorder	Rare, but lymphoma reported
D2R	Parkinsonism Encephalitis			
GABA A receptor	Encephalitis Status epilepticus			Thymoma
GABA B receptor	Limbic encephalitis Status epilepticus Opsoclonus myoclonus			SCLC
GQ1b	Bickerstaff brain stem encephalitis	Guillain-Barré-like illness		
IgLON5	Sleep disorder Dementia		Dysphagia Respiratory failure	Rare
LGI1	Limbic encephalitis Faciobrachial dystonic seizures			Thymoma
NMDA-R	Limbic encephalitis Status epilepticus Movement disorders Psychosis Catatonia			Ovarian teratoma
mGluR1	Cerebellar ataxia		Dysgeusia	Hodgkin lymphoma
mGluR5	Limbic encephalitis			Hodgkin lymphoma
Glycine receptor	Stiff-person spectrum disorder			Rare

AMPAR = 2-amino-3-(5-methyl-3-oxo-1,2-oxazol-4-yl) propanoic acid receptor; Caspr2 = contactin-associated protein-like 2; D2R = dopamine 2 receptor; DPPX = dipeptidyl-peptidase-like protein 6; GABA = gamma-aminobutyric acid; GI = gastrointestinal; LGI1 = leucine-rich glioma-inactivated 1; mGluR = metabotropic glutamate receptor; NMDA-R = anti-*N*-methyl-D-aspartate receptor; SCLC = small cell lung cancer

Ruling out an infectious process is important, given that immunotherapies can worsen infection

including a personal or family history of autoimmunity, identifying infectious risk factors (ie, exposure and travel history) while excluding other conditions in the differential diagnosis.[8] It should also be noted that a patient with AE may not exhibit all the disease characteristics discussed below. For example, normal findings on magnetic resonance imaging (MRI) and electroencephalography (EEG) are not uncommon in anti-LGI1 encephalitis.[12]

TABLE 3

Clinical, diagnostic, and radiographic clues to autoimmune encephalitis

FINDINGS	COMMENTS
Subacute clinical course	1–3 months of symptoms
Viral-like prodrome	Fever, malaise, headache, gastrointestinal symptoms, etc
Neurocognitive deficits	Agitation, apathy, catatonia, delusions, irritability, mania, psychosis, and paranoia
Neurologic examination abnormalities	Ataxia, brain stem abnormalities, myoclonus, tremor, or myelopathy
New-onset focal seizure disorder or status epilepticus	Often not responsive to antiepileptic medications
New focal electroencephalogram abnormalities	Focal epileptic or slow-wave activity particularly arising from the temporal lobes
Subacute movement disorder	Dyskinesias, dystonia, or choreoathetosis
Subacute sleep disturbance	Central sleep apnea, central neurogenic hypoventilation, or narcolepsy
Subacute autonomic dysfunction	Hyperhidrosis, tachyarrhythmias, labile blood pressure, central hypoventilation, gastrointestinal dysmotility, urinary dysfunction
Brain MRI abnormalities	Bilateral T2-weighted FLAIR hyperintensities in the medial aspect of the temporal lobes, although multifocal changes involving the gray and white matter are also possible
Inflammatory cerebrospinal fluid	Mild to moderate pleocytosis (white blood cell count 5–100/μL)
Previous or current oncologic disorder or risk factors for malignancy such as smoking	Increased risk of a paraneoplastic disorder

FLAIR = fluid-attenuated inversion recovery; MRI = magnetic resonance imaging

WHAT ARE THE COMMON CELL-SURFACE/SYNAPTIC ANTIBODY SYNDROMES IN AUTOIMMUNE ENCEPHALITIS?

Anti-NMDA receptor encephalitis

Anti-NMDA receptor encephalitis was initially characterized in 12 women showing a characteristic progression of psychiatric symptoms ranging from subtle behavioral changes, such as irritability, to frank psychosis. These symptoms were followed by movement disorders, autonomic dysfunction, hypoventilation, seizures, and coma.[13] Anti-NMDA is one of the most frequently identified neuronal autoantibodies in AE.[1] Anti-NMDA receptor encephalitis frequently affects young adults, with a strong female predominance (4:1), though it has been described in all ages including children and the elderly, with variable phenotypes.[14] The median age is 20.

Viral-like prodrome. Some patients experience a viral-like prodrome that includes headache or fever during the initial 1 to 2 weeks of the illness (**Figure 1**). Soon after, subacute psychiatric symptoms develop including anxiety, personality changes, hallucinations, paranoid ideas, and frank psychosis. It is not unusual for patients to alternate between hyperactive and catatonic states. Concomitant movement disorders such as dyskinesia (typically orofacial or limb), dystonia, and choreoathetosis are common. From 60% to 75% of adult patients have been reported to experience behavioral problems or movement disorders during the first month of the disorder.[15]

Autonomic dysfunction. As the disease progresses, autonomic dysfunction becomes more prominent and commonly necessitates monitoring in an intensive care unit.

Potential complications include tachyarrhythmias, hypotension, and central hypoventilation requiring mechanical ventilation. Approximately 80% of patients require ICU admission.[15]

Seizures can occur at any time and are

NMDA receptor encephalitis: Typical clinical course

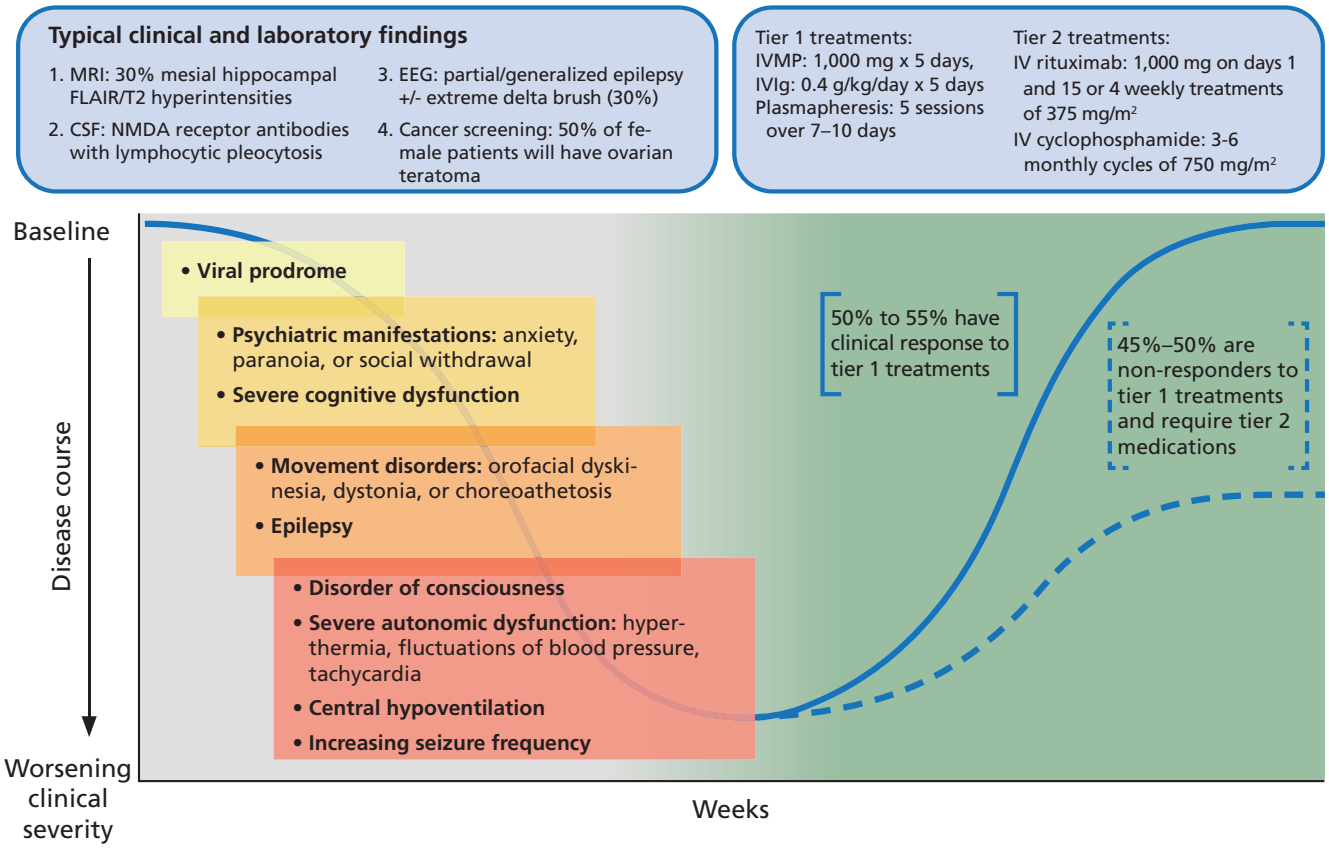

Figure 1. Typical clinical course associated with anti-NMDA receptor encephalitis.

CSF = cerebrospinal fluid; EEG = electroencephalography; FLAIR = fluid-attenuated inversion recovery; IV = intravenous; IVIg = intravenous immunoglobulin; IVMP = intravenous methylprednisolone; MRI = magnetic resonance imaging; NMDA = anti-*N*-methyl-D-aspartate receptor

Based on information in reference 15.

often not responsive to antiepileptic medications alone. In a case series of 75 patients with anti-NMDA receptor encephalitis, almost 80% suffered from generalized tonic-clonic seizures, and 74% had focal seizures without impaired awareness.[16] There has been some evidence to suggest antiepileptic drugs with sodium channel-blocking properties (eg, carbamazepine, oxcarbazepine, lacosamide, phenytoin) may be more effective, though seizure freedom is usually achieved only when paired with immunotherapies.[16,17]

NMDA receptor immunoglobulin G (IgG) testing should always be done with cerebrospinal fluid (CSF), as serum testing is less reliable (100% sensitivity for CSF vs 85% for serum).[15] CSF analysis usually reveals a moderate lymphocytic pleocytosis, elevated protein, and intrathecal antibody production.

Patterns on EEG can vary and often simply demonstrate slowing.[11] Approximately one-third of patients develop extreme delta brush; this is described as slowing with delta activity 1–3 Hz and superimposed bursts of rhythmic activity (beta activity 20–30 Hz) on these slow waves and may be a poor prognostic sign.[18]

MRI findings. MRI is usually normal but may show subtle mesial hippocampal fluid-attenuated inversion recovery (FLAIR) hyperintensities. Titulaer et al reported that 76% of patients had a CSF pleocytosis, one-third of the cohort had an abnormal brain MRI, and 90% had changes on EEG including slowing.[15]

Teratomas. Anti-NMDA receptor encephalitis may be associated with ovarian

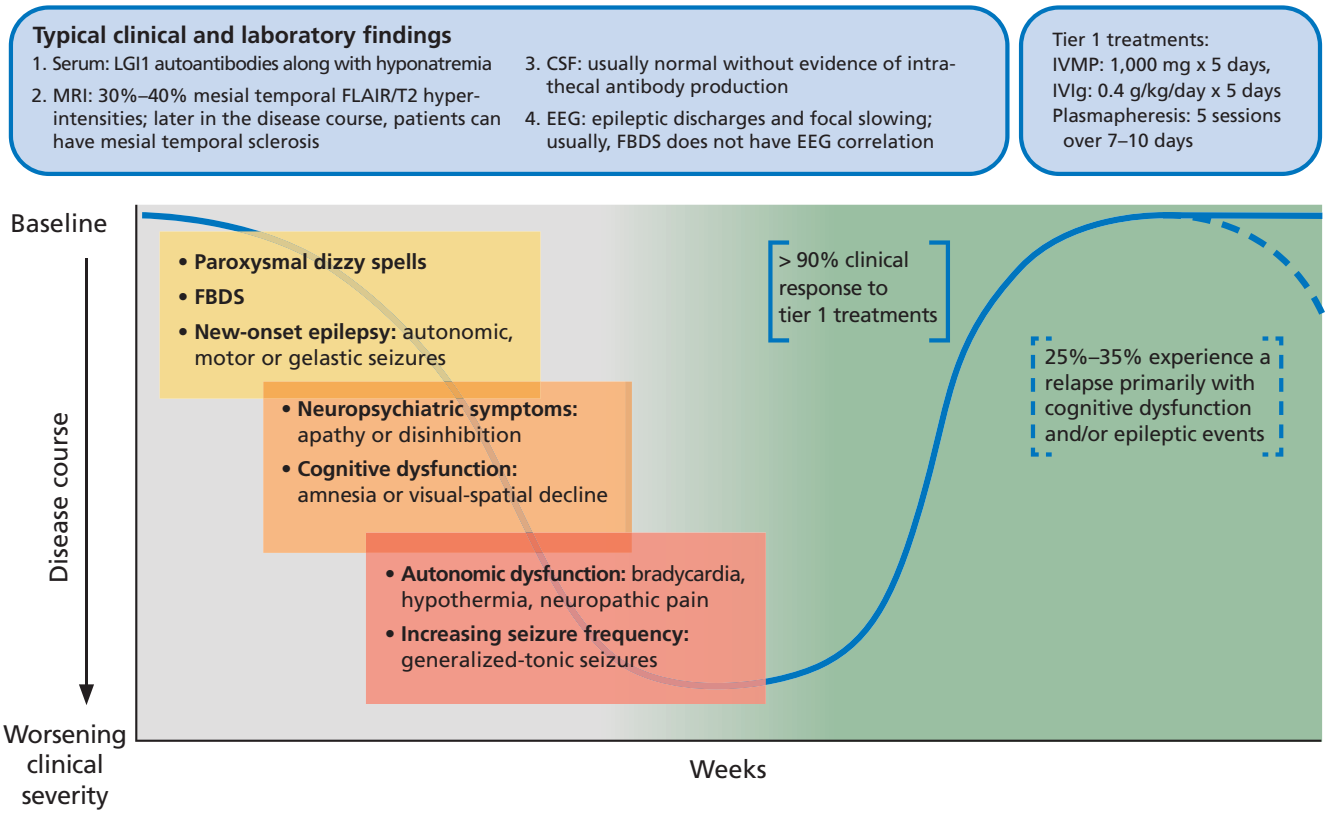

Figure 2. Typical clinical course associated with anti-LGI1 encephalitis.

CSF = cerebrospinal fluid; EEG = electroencephalography; FBDS = faciobrachial dystonic seizures; FLAIR = fluid-attenuated inversion recovery; IVIg = intravenous immunoglobulin; IVMP = intravenous methylprednisolone; LGI1 = leucine-rich glioma-inactivated 1; MRI = magnetic resonance imaging

or extraovarian teratomas in 30% to 40% of patients, particularly in young women. It requires prompt surgical treatment.[15]

Infection. Herpes simplex virus infection of the central nervous system can also trigger the production of NMDA receptor IgG.[19] In a large prospective study, 27% of patients with herpes simplex encephalitis developed anti-NMDA receptor antibodies within 16 weeks of completing their acyclovir treatment.[19] None of the patients had NMDA receptor IgG at the index admission. Interestingly, 3 patients (6%) developed CSF NMDA receptor IgG without clinical correlation, but the antibody production was not detectable at 1-year follow-up.[19] There have been reports of pediatric anti-NMDA receptor encephalitis developing after Japanese encephalitis infection, but no other clear postinfectious or vaccination pattern has emerged in the literature.[20,21]

Immunotherapy. Anti-NMDA receptor encephalitis responds to immunotherapy, but the response can be slow. In the largest study to date of patients with anti-NMDA receptor encephalitis, 81% had significant recovery at 24 months, but only 53% had clinical improvement within 4 weeks of diagnosis.[15]

From 10% to 25% of patients have a clinical relapse, though symptoms are less severe than in the initial presentation.[1,22]

Maintenance immunotherapy can be used to optimize acute treatment response while preventing relapses.[15] Commonly used agents include oral corticosteroids, intravenous immunoglobulin (IVIg), and steroid-sparing agents such as mycophenolate mofetil, azathioprine, rituximab, and cyclophosphamide.[23]

Anti-LGI1 encephalitis

Anti-LGI1 encephalitis was first characterized in 2010.[24] In contrast to anti-NMDA receptor encephalitis, it typically occurs in men over age 60, presenting with subacute cognitive dysfunction and behavioral changes.

About 50% of patients also develop faciobrachial dystonic seizures characterized by focal or lateralized rapid coordinated movements of an arm or the face that may occur hundreds of times a day. These dystonic seizures are very specific for anti-LGI1 encephalitis but are not universally present. Most patients will have normal surface activity on EEG even if the faciobrachial seizure events are captured during the recording. The exact reason for this is unclear, but it may reflect subcortical seizure origin, as some of these patients have contralateral basal ganglia lesions on MRI.[25]

Other associated seizure subtypes include subtle autonomic focal seizures and generalized tonic-clonic seizures (**Figure 2**).[12] Autonomic hyperactivity has also been reported. This includes hyperhidrosis, tachycardia, blood pressure lability, and urinary dysfunction.[26]

The initial workup for anti-LGI1 encephalitis includes MRI, EEG, and CSF analysis but is usually unrevealing aside from a mild hyponatremia on basic metabolic testing. CSF-specific oligoclonal bands may be seen, but CSF can also be non-inflammatory. Initial brain MRI can occasionally demonstrate T2-FLAIR hyperintensity of the hippocampus.[27] Unlike in anti-NMDA receptor encephalitis, CSF is less sensitive than serum for the detection of LGI1 antibodies (serum 100% vs CSF about 88%).[27,28]

Treatment response. This syndrome characteristically responds briskly to tier 1 treatments (corticosteroids, intravenous immunoglobulin, plasmapheresis), but 20% to 30% of patients may experience a relapse necessitating long-term immunosuppression.[22] In one small randomized control trial, IVIg treatment was associated with a significant reduction in seizure burden and can be considered a steroid-sparing agent.[29]

Malignancy. From 5% to 15% of patients have an underlying malignancy, most commonly thymoma.[30] Patients may have residual cognitive deficits despite initial recovery.

Viral infections usually cause a more profound CSF pleocytosis

WHAT TESTING SHOULD I CONSIDER FOR AE DIAGNOSIS?

When AE is highly suspected (**Table 3**), initial testing should include an antibody panel. Both serum and CSF should be tested for antibodies since CSF is more sensitive and specific for certain antibodies such as NMDA receptor IgG, GAD65 IgG, and GFAP IgG, whereas serum is more sensitive for other antibodies such as LGI1 IgG and Caspr2 IgG.

Antibody panels are preferred over specific antibody tests, given the often overlapping clinical syndromes and the possibility of multiple positive antibodies.

Common testing sites include Mayo Clinic or Associated Regional and University Pathologists (ARUP) laboratory. Antibody panels include:

- Mayo ENS-2 panel in serum (www.mayocliniclabs.com/test-catalog/Overview/92116)
- Mayo ENC-2 panel in CSF (www.mayocliniclabs.com/test-catalog/Overview/92117)
- ARUP Autoimmune Encephalitis Extended Panel in serum (https://ltd.aruplab.com/Tests/Pub/3001431).

Encephalitis has a broad differential diagnosis

The differential diagnosis for encephalitis is very broad and includes infections, toxic-metabolic encephalopathy, mitochondrial disorders, nutritional deficiencies, vascular disorders, malignancy, and demyelinating disorders. Clinicians should be particularly concerned about ruling out an infectious process given the immunotherapies utilized to treat AE. Infections to consider include herpes simplex virus encephalitis, human herpesvirus 6, human immunodeficiency virus, fungal infection (eg, cryptococcal), mycobacterial infection, Whipple disease, and neurosyphilis.

In general, viral infections usually cause a more profound CSF pleocytosis (a white blood cell count of 50–100/μL). Bacterial or mycobacterial infections can have a lower of CSF glucose concentration, whereas AE usually has normal glucose levels.[31]

Overall, careful examination usually reveals subtle neurologic deficits that should prompt further evaluation for AE. Diagnos-

tic red flags include newly occurring epileptic seizures, movement disorders, and neurocognitive symptoms, especially in the setting of MRI or CSF abnormalities.

It should be mentioned that the prevalence of primary psychiatric disorders is much higher than the prevalence of AE. For example, the overall prevalence of schizophrenia, with incidence peaking in young adults, is estimated to be 2.7 to 8.3 per 1,000,[32] whereas the overall prevalence of AE is 13.7 per 100,000.[4] Thus, in a young patient with new mood disorder, a primary psychiatric diagnosis remains more likely than AE.

While patients with a preexisting psychiatric disorder can develop a concomitant autoimmune condition, it should also be mentioned that a specific isolated psychiatric AE phenotype has not emerged in the literature despite extensive investigations.[21]

A COMPREHENSIVE EVALUATION FOR AUTOIMMUNE ENCEPHALITIS

A comprehensive evaluation for suspected AE includes a range of laboratory studies and imaging.

Serum testing

Serum testing with an AE antibody panel to human immunodeficiency virus, thyroid-stimulating hormone, vitamin deficiency (B_1, B_{12}, E, folic acid).

Evaluation for other disease markers

Patients with autoimmune encephalitis are at increased risk of having a second autoimmune disorder. Choice of any specific testing should be based on clinical suspicion.[7,33]

Cerebrospinal fluid testing

CSF studies include an AE antibody panel, routine studies, CSF IgG index, CSF-specific oligoclonal bands, and comprehensive infectious evaluations with specific attention to viral agents (ie, herpes simplex virus type 1, varicella-zoster virus, West Nile virus, John Cunningham virus, and human herpesvirus 6).

Urine toxicology screen

A urine toxicology test should include screening for marijuana and cocaine.

Magnetic resonance imaging

MRI of the brain with and without gadolinium contrast is appropriate. Consider completing an epilepsy protocol, which may vary between institutions but usually consists of standard T1- and T2-weighted images, FLAIR, gradient-echo (T2) sequences, and diffusion-weighted sequences. Imaging sequences should also include contiguous, thin slices to ensure that hippocampal and temporal lobe lesions can be identified.[34]

Consider spinal cord MRI if neurologic abnormalities suggest concomitant myelitis. Symptoms could encompass motor, sensory, and autonomic (bladder, bowel, sexual) dysfunction that localizes to the spinal cord. An example could be a well-defined truncal sensory level below which the sensation is altered.[35]

Electroencephalographic monitoring

Continuous monitoring with EEG can clarify the cause of motor symptoms, identify suggestive patterns such as extreme delta brush, and characterize seizure burden.

Positron emission tomography

Brain fluorodeoxyglucose-positron emission tomography with computed tomography (FDG-PET/CT) may illustrate either hypometabolism that may correlate with impairment of neuronal activity even in the absence of structural disturbance[36] or hypermetabolism that could correlate with increased glucose metabolism caused by synaptic dysfunction or ongoing seizure activity.[37] Overall, PET may be a sensitive marker for AE but is limited by its higher cost, lack of diagnostic specificity and clinical availability.[36]

Body FDG-PET/CT can be done to screen for malignancy.[38]

Paraneoplastic syndromes sometimes precede a cancer diagnosis by months or years

WHICH AUTOANTIBODY FINDINGS SHOULD BE INTERPRETED CAUTIOUSLY?

The development of broad antibody panels has led to some unintended consequences, particularly as these panels may include disorders of the central nervous system and the peripheral nervous system.[39] In addition, the specificity and sensitivity can vary for the different autoantibodies and the association with AE. Therefore, interpretation of autoantibody

testing should be combined with a comprehensive clinical evaluation as outlined above in the section "A comprehensive evaluation for autoimmune encephalitis."[8]

Caution is particularly needed when interpreting tests for autoantibodies that have low specificity for AE. For example, anti-voltage-gated potassium channel (VGKC) antibodies were initially detected in peripheral nerve hyperexcitability disorders such as neuromyotonia and Morvan syndrome. Further laboratory evaluation has elucidated that LGI1 and Caspr2 are the usual targets of these complex antibodies and not the VGKC itself. VGKC antibodies alone are not specific for AE and can be seen in 5% of healthy controls.[40] In VGKC-positive patients without LGI1 and Caspr2 antibodies, additional testing is not usually warranted, as there is no clear evidence that VGKC titers are indicative of an autoimmune disorder.[30]

Hashimoto encephalopathy, also known as steroid-responsive encephalopathy associated with autoimmune thyroiditis, has been historically linked to elevated serum levels of thyroid peroxidase antibodies.[41] In the era of more neuronal-specific antibodies, thyroid peroxidase antibodies have been found to have limited diagnostic value. An extensive evaluation to exclude other causes of AE should be pursued in cases with elevated thyroid peroxidase antibody titers, given the unclear clinical significance of these antibodies in neurologic disorders.[42,43]

Anti-NMDA receptor encephalitis is associated with ovarian or extraovarian teratomas

WHAT IS THE INITIAL TREATMENT FOR AUTOIMMUNE ENCEPHALITIS?

Current treatment guidelines for AE are based on a combination of expert opinion, case series, and case reports, and evidence from high-quality multicenter randomized trials is lacking.[29] But existing evidence suggests that early initiation of therapy and prompt escalation to second-line immunotherapy may lead to improved clinical outcomes.[15,22]

Still, unanswered questions include the time frame associated with a response to the first-line immunotherapy and the optimal duration of sustained immunotherapy. A comprehensive evaluation for malignancy is also vital as early detection and treatment are important for improved patient outcomes.

An important caveat for all clinicians is that although response to corticosteroid therapy is a typical feature of AE, it does not confirm the diagnosis of AE. Disorders such as lymphoma and vasogenic edema associated with a brain tumor can also respond dramatically to steroids. Additionally, some AE patients do not respond to corticosteroids but require prolonged treatment with other immunotherapies.[8]

Initiation and escalation of treatment depend on the pretest probability of AE along with the clinical severity. If there is a high pretest probability of a known syndrome, waiting for the results of antibody testing should not delay treatment. For example, a case of refractory autoimmune-mediated status epilepticus in the intensive care unit requires prompt and aggressive treatment. Caution should be used when the diagnosis is less certain.[8]

First-line treatments

First-line treatment for AE involves corticosteroids combined with either IVIg or plasmapheresis[22,44]:

- Methylprednisolone 1 g daily for 5 days, followed by oral prednisone 1 mg/kg (maximum dose 60–80 mg daily, with a prolonged taper over 3–6 months)
- IVIg 400 mg/kg/day for 5 days
- Plasmapheresis, with 5 exchanges over 7 to 8 days.

Second-line treatments

Second-line treatments can be given as monotherapy or in combination for refractory disease activity 1 to 2 weeks from completion of first-line treatment[22]:

- Rituximab 1,000 mg IV, with a repeat dose in 2 weeks, or 375 mg/m^2 weekly IV infusion for 4 weeks
- Cyclophosphamide 750 mg/m^2 IV monthly for 3 to 6 months.

Maintenance treatments[45]

- Rituximab, repeat every 6 months, same dosing schedule as second-line therapy
- IVIg 0.4 g/kg every 2 to 4 weeks
- Mycophenolate mofetil 500 to 3,000 mg/day
- Azathioprine 1 to 3 mg/kg/day
- Cyclophosphamide 1 to 2 mg/kg/day orally.

HOW DO I MONITOR RESPONSE TO TREATMENT IN AE?

There are no validated biological markers to assess treatment response in AE. Although some studies have suggested that early reduction in titers can correlate with better clinical outcomes, antibodies can remain positive even in patients with good outcomes.[46] Further, the change in antibody titers does not consistently correlate with risk of relapse.[47] Therefore, serum or CSF antibody titers in isolation are not reliable for monitoring treatment response in AE.

Imaging, when abnormal, can be repeated to look for improvements over time. Unfortunately, even after appropriate treatment is initiated for AE, brain MRI may show irreversible changes such as generalized or focal atrophy on follow-up.

Monitoring of the treatment response is therefore primarily based on the clinical examination. We urge clinicians to use objective measures to determine the true efficacy of a given treatment. For example, clinicians can use the Scale for the Assessment and Rating of Ataxia (SARA),[48] Symbol Digit Modalities Test, or the Montreal Cognitive Assessment (MoCA)[49] for reliable scores to measure the success of a trial and the utility of long-term treatments. Formal neuropsychological testing is also a valuable tool to document the extent of cognitive damage and to evaluate immunotherapy response.

WHAT ONCOLOGIC EVALUATION IS APPROPRIATE FOR PATIENTS WITH AE?

Paraneoplastic AE can occur in association with an underlying malignancy. In particular, small-cell lung cancer, non-small-cell lung cancer, and neuroblastoma trigger the production of paraneoplastic autoantibodies.[50] The neurologic sequelae can occur prior to detection of the cancer allowing for early discovery and oncologic treatment.

Though treating the cancer is the main goal in these patients, they may still require short-term or long-term immunotherapy for the paraneoplastic disorder. Immunotherapies that may have dual benefit to treat the cancer and autoimmune disorder, such as cyclophosphamide, can be considered.

All treatment decisions must be made in coordination with the treating oncologist.[6] Additionally, patients may have permanent neurologic deficits with relatively little hope for recovery.

The type and frequency of screening for malignancy depends on the specific antibody syndrome.[50] If a patient is diagnosed with an autoantibody commonly associated with paraneoplastic syndromes, frequent monitoring is recommended. In those cases, we typically order surveillance testing every 6 to 12 months for at least 3 to 5 years. If the patient has an antibody with a low likelihood of an underlying neoplasm, we consider reevaluating once a year for 3 years after the index diagnosis.[50]

Based on the 2011 European Federation of the Neurological Societies guidelines, we will utilize either whole-body FDG-PET or CT of the chest, abdomen, and pelvis as a screening measure for certain AE patients, with clinical consideration of the known cancer associations, cancer risk factors, or family history of cancer.[50]

In particular, the nature of the antibody determines the risk and type of an underlying malignancy and therefore the investigation. For example, anti-Yo autoantibody has a greater than 90% association with breast or ovarian malignancy, so an extensive evaluation should be pursued to identify the underlying neoplasm.[50]

In addition, sex-specific tests such as pelvic ultrasonography, mammography, and testicular ultrasonography should be considered if the initial evaluation is unrevealing. Further, all patients should complete routine age- and sex-appropriate screening measures including screening for breast, colorectal, cervical, and prostate cancer, along with lung cancer when applicable, based on US Preventive Services Task Force recommendations.

Anti-NMDA receptor encephalitis responds to immunotherapies, but response can be slow

TAKE-HOME MESSAGE

Our understanding of AE has expanded dramatically over the past few years. Familiarity with different AE syndromes will ensure prompt diagnosis and treatment. In cases that are less clear, a sound diagnostic approach anchored on objective clinical or radiographic findings is important for optimizing outcomes. Clinicians

need to stay abreast of developments in this field as the breadth of immune-mediated disorders of the nervous system continues to evolve.

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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