Synapse
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Comprehensive Stroke Center Certification Raises the Bar for Complex Case Management

Lucian Maidan, MD

The technology and protocols recognized for optimal treatment of complex stroke cases have advanced considerably in recent years. Incorporating such breakthroughs into a hospital's practice routine requires significant investment in resources, staff and training. In September 2012, to recognize this level of commitment, The Joint Commission (in collaboration with the AHA/ASA) established the advanced certification of **Comprehensive Stroke Center**.

Rising to meet these heightened standards is no small feat. In the year or so since the Comprehensive Stroke Center Certification was established, few hospitals have been successfully certified. As of this writing, there are only five Comprehensive Stroke Centers in all of Southern California. In Northern California, there are two in San Jose, one in Stanford and none in San Francisco or the East Bay.

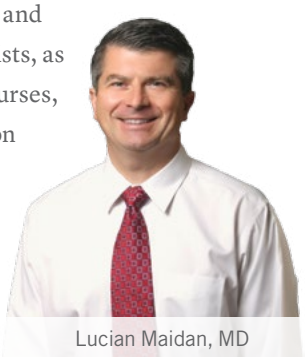
In July 2014, Mercy San Juan Medical Center became the first and only certified Comprehensive Stroke Center north of the San Francisco Bay Area.

To attain Comprehensive Stroke Center certification, organizations must meet not only all of the general eligibility requirements for Disease-Specific Care and Primary Stroke Center certification, but also:

- Have dedicated neurointensive care unit beds for complex stroke patients that provide neurocritical care 24 hours a day, seven days a week
- Have in-house access to advanced imaging capabilities, including catheter, CT, MR angiography and a host of others
- Provide 24/7 microsurgical clip ligation or endovascular treatment of cerebral aneurysms, carotid endarterectomy (CEA) or carotid angioplasty and stenting, and endovascular treatment of acute stroke
- Meet minimum patient volume requirements for providing care to patients with a diagnosis of subarachnoid hemorrhage, performing endovascular coiling or surgical clipping procedures for aneurysm, and administering IV tPA
- Deliver mandatory nurse and ED staff training
- Coordinate post-hospital care for patients
- Actively participate in IRB-approved stroke research
- Use a peer review process to evaluate and monitor the care provided to ischemic stroke and subarachnoid hemorrhage patients

Standards for the new Comprehensive Stroke Center Certification were derived from the Brain Attack Coalition's "Recommendations for Comprehensive Stroke Centers," (Stroke, 2005) and "Metrics for Measuring Quality of Care in Comprehensive Stroke Centers," (Stroke, 2011), and on recommendations from a multidisciplinary advisory panel of experts in complex stroke care.

Neurointensive care is unique in its concern with comprehensive multisystem treatment and the interface between the brain and other organ systems in the setting of critical illness. Given the complexity of severe stroke and potential complications, a neurointensivist works closely with multidisciplinary teams composed of neurosurgeons, neurointerventional radiologists, neurologists, emergency medicine and other medical and surgical specialists, as well as pharmacists, critical care nurses, respiratory therapists, rehabilitation therapists and social workers.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The effectiveness of such comprehensive care in lessening the rates of mortality and

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First-Line Treatments of Neuropathic Pain

Andrew Linn, MD

The International Association for the Study of Pain (IASP) defines neuropathic pain (NP) as pain "initiated or caused by a primary lesion or dysfunction in the nervous system." NP often coexists with other pain conditions, and there can be significant overlap of symptoms, making diagnosis difficult. Treatment can be frustrating because medications are unpredictable in efficacy between patients, often have significant adverse effects (AEs), especially among the elderly where prevalence of many NP syndromes is highest, and onset of analgesic effect may be delayed. This article will focus on non-narcotic medication management of neuropathic pain. Opioids, which in some instances could be considered a first-line treatment, are excluded from this discussion.

Assessment should focus on accurately identifying and treating the underlying disease processes and peripheral or central nervous system lesions causing NP. Unfortunately, effective treatments of nervous system lesions or dysfunction causing NP are often not available, and we are left to treat the consequence. In these cases, medication management is generally the primary option. For chronic NP, medications are best considered trials, with a goal of titration to satisfactory relief of pain or to a certain dose. If an adequate trial of one medication fails to adequately relieve pain or causes intolerable AEs, treatment should be discontinued and a different medication should be selected. If a medication is well tolerated and provides partial pain relief, it should be continued and a second first line medication with a different mechanism of action added. When considering which of the medications to use, care should be given to patient comorbidities, potential drug interactions, including alcohol and possible illicit drugs, and the common AEs associated with the medication.

First Line Medications

Secondary amine tricyclic antidepressants (TCAs), dual reuptake inhibitors of both serotonin and norepinephrine (SNRIs), Calcium channel $\alpha 2\text{-}\delta$ ligands, and topical lidocaine should be considered the first line treatment of neuropathic pain.

Antidepressants

The secondary amine tricyclic antidepressants—nortriptyline and desipramine—increase activation of inhibitory pathways in the spinal cord through blocking presynaptic reuptake of serotonin and norepinephrine. They may have NMDA receptor antagonism and ion channel blocking properties as well. Tertiary amines—amitriptyline, imipramine—are not considered first line therapies as their effect on pain is similar to the secondary amines, and risk for AEs are greater.

TCAs are well-studied, and have been proven efficacious in many types of neuropathic pain. Sedation, anticholinergic effects, and orthostatic hypotension are common. Caution is necessary in patients with ischemic heart disease, glaucoma, seizure history, amphetamine use, or with concurrent use of tramadol or other medications that increase serotonin levels. TCAs should be started at a low dose and titrated carefully to either efficacy or adverse effect. The usual starting dose is 25mgqhs (10mg in the elderly), titrating up every five to seven days. A six- to eight-week trial at 100mg to 150mg is generally an acceptable trial period.

Duloxetine, a SNRI, has been shown to be an effective treatment of peripheral neuropathies. It has a much more favorable side effect

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profile than TCAs, with nausea the most common complaint. Cost can be a disadvantage, though duloxetine has recently been available as generic formulation. Caution should be given when prescribing to patients with hepatic dysfunction, bleeding abnormalities, or alcohol abuse. To mitigate nausea, duloxetine is often scheduled for nighttime dosing of 30mg, and titrated up to 60mg over one week. Use in doses of 90mg to 120mg is not supported by the scientific literature, and risks increase for AEs. A four-week trial is generally deemed adequate.

Venlafaxine has properties similar to duloxetine. It has a longer initial titration schedule and must be titrated down before discontinuation. Caution should be used in patients with ischemic heart disease or concurrent use of amphetamines or tramadol. A withdrawal syndrome may occur with abrupt discontinuation. The usual starting dose of venlafaxine is 37.5mg twice daily, titrating up every seven days to maximum dose of 225mg/d. A four- to six-week trial is generally deemed acceptable.

Calcium Channel α2-δ Ligands

Gabapentin and pregabalin are both antagonists of α2-δ subunit of voltage-gated calcium channels, decreasing the release of pronociceptive neurotransmitters. Both have been shown to be efficacious in a wide variety of neuropathic conditions.

Neither gabapentin nor pregabalin have significant drug-interactions, and AEs of sedation and peripheral edema are common to both. Pregabalin has been shown efficacious in anxiety disorders, a potential benefit for chronic pain patients. Additionally, pregabalin has a faster titration schedule, and some patients have relief with the usual initial dosing of 150mg/d. Gabapentin is often started at 100mg to 300mg at night, and titrated up to three times daily dosing with maximum of 3600mg/d. If there is no symptom relief at 1800mg/d, however, consideration should be given to discontinuing the medication. The dose of both gabapentin and pregabalin should be adjusted for renal impairment.

Topical Lidocaine

The 5% lidocaine patch has been shown to be efficacious in post herpetic neuralgia (PHN), and other NP with allodynia (pain in response to stimulus which does not normally cause pain). The most common AE is skin irritation, but it has limited AEs and little risk of drug interaction due to the low systemic effect. Lidocaine gel 5% is also efficacious in NP with allodynia.

Assessment of associated comorbid conditions that may be improved or exacerbated by, or effect the therapy of, NP is important. The presence of coexisting depression and poor sleep hygiene, both of which are impacted by and contribute to pain in a cyclical fashion, should be evaluated. Several of the first-line treatments have the potential to serve a dual function in this respect, improving sleep as well as pain. Realistic expectations should be discussed with patients. Elimination of pain, in particular neuropathic pain that has become chronic, is often not an achievable goal. Focus should be on lessening the impact of neuropathic pain on physical and emotional well-being of the patient. Where appropriate, non-pharmacological treatments of pain including relaxation techniques/biofeedback, talk therapy, physical therapy, injection therapies, and surgery should be included in the armamentarium of the provider treating NP. ■

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Comprehensive Stroke Center Certification—continued from page 1

morbidity after stroke is demonstrated in numerous studies, and the positive effects and impact of improved outcomes are well supported by evidence.

It is anticipated that, over time, municipalities and regions will develop a formal referral network so the most complicated cases can be treated at the centers best equipped to provide the specialized care that can lead to better outcomes.

In addition to improving the quality of care provided to patients, a Comprehensive Stroke Center Certification provides hospitals a framework for organizational structure and management, standardizes performance measures, and demonstrates commitment to a higher standard of service. ■

Metastatic Brain Tumors: A Shifting Treatment Paradigm?

Dominique Rash, MD

In patients with brain metastases, stereotactic radiosurgery (SRS) has emerged as a viable treatment alternative to whole brain radiation therapy.

First developed in 1949 by Swedish neurosurgeon, Lars Leksell, MD, SRS was initially defined as a "single high dose fraction of radiation stereotactically directed to an intracranial region of interest," with the intent of treating benign functional disorders and arteriovenous malformations. The role of SRS quickly expanded to include the treatment of other spherical lesions including brain tumors and metastases. Over time the machines used to deliver SRS have evolved and include both the Gamma Knife, which employs a Cobalt 60 radioactive source, and Linac-based radiosurgery, which involves a modified linear accelerator adapted for both conventionally fractionated and stereotactic radiotherapy.

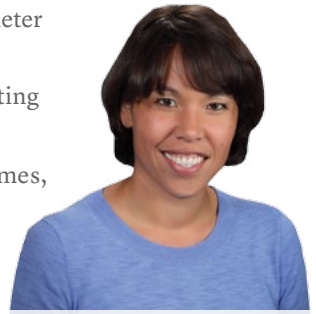
With the evolution of technology, our expectations for the management of cancer patients with intracranial disease have also changed. Advances in radiographic imaging have led to the early detection of brain lesions which are often asymptomatic. Additionally, the development of genetic/molecular markers across cancer subtypes has enabled us to identify patients with a more favorable prognosis, despite harboring brain metastases. Among such patients, the goal of therapy is to prevent intracranial progression and potential neurologic deterioration, while extracranial disease is controlled with systemic therapy.

The new Radiosurgery Suite at Mercy Cancer Center's C Street location offers sub-millimeter accuracy and continuous tumor tracking, allowing for real-time synchronization between imaging, patient positioning, motion management, beam shaping, and dose delivery.

Treatment progress is therefore defined by our ability to effectively treat brain metastases in a timely fashion, while minimizing side effects and toxicity.

Whole brain radiation therapy (WBRT) for brain metastases is well established as a means to reduce the rate of, and delay the time to, intracranial relapse, which may minimize the risk of neurological deterioration secondary to new brain lesions. Indeed, the primary advantage of WBRT over SRS is the ability to address micrometastatic disease. However, the recently published EORTC 22952-26001 randomized clinical trial comparing the use of SRS or surgery alone versus SRS or surgery and WBRT failed to demonstrate an improvement in functional independence or overall survival with the eradication of micrometastatic disease by WBRT. Complementary data from Chang et al. in 2009 highlighted an increased risk for memory decline at four months among patients treated with SRS and WBRT compared to SRS alone. Therefore, in carefully selected patients the use of SRS with serial MRI imaging every three months allows early detection of new asymptomatic lesions amenable to repeat SRS. It also reduces the risk of neurologic decline associated with WBRT, which remains a valid concern especially for the cohort of patients with a good Karnofsky Performance Status (KPS), extracranial disease control, and favorable cancer histology.

The new Varian Edge™ treatment machine, now in operation at the Mercy Cancer Center's C Street location, represents the latest in cutting edge technology designed for SRS. As a linear accelerator, it may be used to treat both intracranial and extracranial sites. Greater degrees of articulation and freedom of positioning enable us to deliver high doses of radiation to sites previously inaccessible or abutting critical normal structures with submillimeter accuracy. By using a frameless positioning system and incorporating technological innovations that dramatically reduce treatment times, the Edge is unique in its ability to improve the SRS experience for the patient, which remains our ultimate goal. ■



Dominique Rash, MD

Metastatic Brain Tumors: A Brief Review

Hamid Aliabadi, MD

Metastases to the brain are the most common intracranial tumors in adults. They occur in 20 to 40% of all patients with cancer with 30 to 40% presenting as a single metastasis. It is estimated that 170,000 new cases of metastatic brain tumor are diagnosed in the United States each year, and the incidence continues to rise as a result of advances in cancer diagnosis and management. In particular, the use of MRI has led to the detection of small metastases which would not have been visualized in the past. However, the prognosis for patients with metastases to the brain remains poor.

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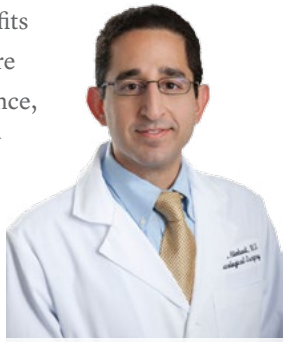
Proper clinical and radiological evaluation is important in determining the optimum treatment strategy for patients with brain metastases. This includes assessing the extent and control of systemic disease and assigning the appropriate cancer stage. This evaluation, be it with CT/PET scans of the body or radionuclide bone scans, is critical since patient prognosis is most accurately based on the extent of systemic disease. The extent of intracranial disease is assessed by contrast-enhanced MRI.

In a study by Patchell et al. in 1990, it was found that treatment outcomes for cerebral metastases were better when surgical resection was combined with whole-brain radiation therapy (WBRT). Recurrence at the original site was reduced in these patients when compared with those receiving only WBRT. Furthermore, the patients who underwent resection plus radiation survived longer with a better quality of life. However, WBRT has also been associated with an acute detriment in quality-of-life measures, potentially delayed neurocognitive deficits, and in some studies, a lack of overall survival benefit.

An alternative approach, post-operative stereotactic radiosurgery (SRS), is used at many institutions in lieu of WBRT for treatment of brain metastases. This focal radiation technique offers several potential advantages and may avoid the acute and delayed effects of WBRT, including neurocognitive decline. In addition, SRS requires a much shorter elapsed time for treatment and reduces the volume of normal brain parenchyma irradiated. SRS is often offered to patients with a good Karnofsky Performance Status (KPS) score and three or fewer metastases of <4 cm in maximum dimension. When it is selected as the treatment modality, the neurosurgeon, radiation oncologist, and radiation physicist work together to perform target delineation, dose selection, and radiosurgical planning.

In a retrospective study by Soltys et al. published in 2008, post-resection, adjuvant SRS yielded a local control rate that was comparable to that of post-operative WBRT. The local failure rate at 12 months was 21% when using SRS to the resection cavity, 46% with surgery alone, and 10 to 20% in patients with surgical resection followed by WBRT. Similarly, Patchell et al. in 1998 demonstrated that when an isolated metastasis is removed and treated with post-operative WBRT versus no additional therapy, the WBRT decreased the rate of local failure at the original tumor site from 46% to 10%. An additional advantage of WBRT is that it reduces the rate of appearance of distant brain metastases. However, given early detection of brain metastases, effective intracranial salvage therapy, and improved systemic control of malignant disease, one could argue that it would be equally appropriate to treat a solitary metastasis with surgery followed by SRS.

Although the long-term prognosis for patients with metastatic brain tumors is poor, advances in early detection, accurate cancer staging, and post-operative radiation therapy are producing benefits to the patient. Both WBRT and SRS are effective tools to reduce local recurrence, prolong survival, and improve quality of life after primary tumor resection. Optimal outcomes are most likely to be achieved through a team-based approach to the selections of appropriate treatment options. ■



Hamid Aliabadi, MD

Amyotrophic Lateral Sclerosis (ALS)

Ryan Armour, DO

Amyotrophic lateral sclerosis (ALS) is a neuromuscular disorder that is typically characterized by degeneration of both upper and lower motor neurons in the brain and spinal cord. Presentation is variable, but symptoms typically consist of progressive loss of muscle strength and bulk. Fasciculations are often present. Ultimately the disease will progress with loss of the ability to swallow and respiratory failure. Weakness usually will begin in one region of the body or a single limb and then spread to other areas over time. The incidence is estimated to be 1.8/100,000 with an average age of onset of 60 years. Life expectancy after diagnosis is approximately three years. Approximately 5 to 10% of cases are familial. Genetic testing is currently not performed except for research purposes since it has little bearing on the diagnosis or treatment of disease.

The diagnosis is made on clinical examination and electrodiagnostic studies (EMG and nerve conduction) based on the revised El Escorial World Federation of Neurology criteria, or more recently proposed Awaji ALS criteria. Patients should have evidence of combined upper and lower motor neuron degeneration with progressive spread of signs and symptoms.

The most common concerning mimics of ALS are benign fasciculations and cramps, which may affect up to 70% of people at some point in their lives. Less common conditions including inflammatory or hereditary myopathies, post-polio syndrome, hereditary spastic paraplegia, and myasthenia gravis may also mimic the symptoms of ALS, particularly early in the course of disease. Evaluation by providers who have experience with complex neuromuscular disorders is preferred when the diagnosis of ALS is considered.

Workup for ALS consists mainly of serial neurological examinations, electromyography, and nerve conduction studies. Blood tests and imaging studies are often performed to rule out other diseases. Ultimately, the diagnosis is made by physical examination with or without supportive data from electrodiagnostic testing. There is no laboratory test or imaging modality alone that can reliably provide diagnosis of ALS.

Riluzole is the only FDA-approved treatment available to slow the progression of the disease. This medication provides only modest benefit, can be expensive, and requires clinical and laboratory monitoring. Other medications may be prescribed for symptomatic relief of muscle cramps, excessive salivation, or other issues that may develop through the course of the illness.

Less commonly known are the non-motor manifestations of the disease. Patients with ALS will frequently experience uncontrollable emotions that can be more debilitating than the motor manifestations in the course of the disease. This symptom is known as pseudobulbar affect and can be effectively treated with dextromethorphan-quinidine capsules or tricyclic antidepressants. ALS patients may also develop frontotemporal dementia and a clear genetic link between these two diseases has been established.

"Evaluation by providers who have experience with complex neuromuscular disorders is preferred when the diagnosis of ALS is considered."

Patients with ALS are best cared for with frequent visits with a multidisciplinary clinic of specialists with experience in treating this disease. During these visits, patients will often see one or more physicians, occupational therapists, speech therapists, respiratory therapists, and a social worker in the course of a single morning or afternoon. Early percutaneous gastrostomy (PEG) placement and non-invasive mechanical ventilation has been shown to prolong survival and improve quality of life, but not all patients opt to proceed with these interventions.

In summary, ALS is a progressive disease causing severe weakness of the limbs, bulbar, and respiratory muscles. Especially since it is invariably fatal, examination should be made by a physician experienced with the disease and the necessary workup to excluded mimics. Unfortunately, treatment to slow progression is not very effective, but management in a multidisciplinary ALS clinic provides critical guidance to the patient and family, and facilitates optimal care. ■

Ryan Armour, DO

Restless Legs Syndrome

Robert Dias, MD

Restless legs syndrome (RLS) affects 5 to 10% of adults in the US and can significantly impact quality of life. Large population-based studies have found positive associations between RLS and cardiovascular and cerebrovascular disease. RLS is a clinical diagnosis, characterized by an urge to move the legs that is worse in the evening, worse at rest, better with movement, and not solely accounted for by another medical or behavioral condition such as myalgia, venous stasis, leg edema, arthritis, leg cramps, positional discomfort, or habitual foot tapping. RLS is typically, but not always, accompanied by an uncomfortable, unpleasant sensation in the legs, but may also involve the arms or other parts of the body. The unpleasant sensations may be described as creeping, crawling, itching, pulling, aching, drawing, stretching, or may be difficult to describe. Most patients seek medical attention given difficulties falling and/or staying asleep.

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Precipitating factors for RLS include iron deficiency, pregnancy, chronic renal failure, prolonged immobility, and certain medications, including centrally-acting antihistamines, most antidepressants (with the exception of buproprion, with its dopamine-promoting activity), and some centrally active dopamine receptor antagonists (antipsychotics, dopamine-blocking antiemetics such as metoclopramide). Peripheral neuropathy may also be a comorbid condition. RLS often occurs in the absence of any of these risk factors.

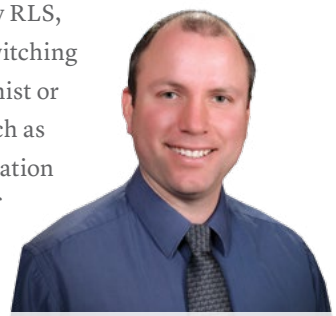
Early-onset RLS (age < 45 years) often includes a positive family history and is typically characterized by slow progression of symptoms in about two thirds of cases, with most of the remaining third of cases reporting stable symptoms, and in some cases remission. In late-onset RLS, rapid progression and precipitating factors are more common.

Primary factors in the pathophysiology of RLS include brain iron deficiency (iron is a cofactor for dopamine production and synaptic density, as well as in myelin synthesis and energy production), central nervous system dopamine regulation, and genetics.

Treatment of RLS is first directed at addressing potential precipitating factors. Repletion of iron stores, when serum ferritin levels are below 50-75mcg/L, has been demonstrated to alleviate RLS symptoms, and Vitamin C helps with absorption of iron. Review of the patient's prescription and over-the-counter medications may reveal a potential trigger for RLS, particularly over-the-counter sleep aids containing antihistamines. Avoiding caffeine, nicotine, and alcohol, as well as sleep hygiene measures, exercise, leg massage, applied heat, and short daily dialysis for patients in renal failure, may help alleviate RLS.

If the symptoms occur predominantly while the patient is asleep and do not disturb going to sleep, a sleep study may be helpful to evaluate potential periodic limb movements during sleep (PLMS) and secondary causes. More than 90% of patients with RLS, when multiple nights are sampled, have 5 or more periodic limb movements per hour. However, PLMS are not specific for RLS, and in the majority of cases, PLMS are attributable to alternative causes, such as obstructive sleep apnea (OSA) or medication effect. PLMS are also common in patients with REM sleep behavior disorder and narcolepsy.

If symptoms persist in spite of the above measures, medications to treat RLS/PLMS include dopamine agonists, such as pramipexole and ropinirole. With dopaminergic therapy, there is risk over time of augmentation, in which RLS symptoms can become more severe and occur earlier in the day and spread to other body parts, including the trunk and arms. Pregabalin and gabapentin are alternative treatment options with less risk of augmentation, and also helpful if there is a comorbid peripheral neuropathy or pain syndrome. For refractory RLS, the following may be helpful: switching to an alternative dopamine agonist or different class of medication such as gabapentin/pregabalin; combination therapy with different classes of medication; the Rotigotine transdermal patch; or as a last resort, opioid therapy. ■



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