Recent Advances in Neurology

**Patient 1**
This 70-year-old man has restless leg syndrome (RLS), a clinical diagnosis. RLS affects 5-10% of the adult population of European ancestry, though likely only 2-3% come to clinical attention. The cause of RLS is not clear but it is associated with low central iron stores. This is supported by evidence from autopsy studies, CSF analysis, gradient echo MRI and transcranial ultrasound. A family history of RLS is reported in 63-92% of individuals suggesting a strong genetic component as well.

RLS is typically separated into intermittent symptoms, defined by fewer than twice/week over a year and chronic symptoms. When symptoms are only bothersome intermittently, such as a long plane flight, medications such as carbidopa/levodopa 25/100 can be very effective, however use more than twice weekly can lead to augmentation.

Benzodiazepines and hypnotics are also recommended only for as needed use.

Periodic limb movements (PLMs) occur in up to 80% of patients with RLS and are diagnosed by polysomnography. These are stereotyped kicking movements and patients are usually unaware of their presence though bed partners may complain. A small subset of those with PLMs are thought to have periodic leg movement disorder (PLMD), defined by PLMs causing either night time or daytime impairment. Other causes of insomnia and hypersomnia must be ruled out and those with RLS cannot have a diagnosis of PLMD. PLMs are of unclear clinical significance and may be a part of normal aging or an epiphenomenon. RLS and PLMs are commonly confused. RLS is a sensation during wake in contrast to PLMs which are a movement during sleep.

**References**

Patient 2:
This 20-year-old woman has delayed sleep-wake phase disorder (DSPD). DSPD is far more common in adolescents but can last throughout life. This patient reports daytime sleepiness which may be due to not sleeping aligned with her internal clock, but can also be related to several other factors including excessive time in bed, mood disorder, or another sleep disorder such as obstructive sleep apnea. We focused in the case presentation on how to use melatonin and light as treatment. Other interventions that are important for this patient include using the bed for sleep and sex only, going to bed only when tired, maintaining a consistent wake time (unless actively working with tools discussed to change sleep schedule) and getting out of bed when not sleeping for about 20 minutes. Management of co-morbid considers such as migraine and chronic pain should be simultaneously addressed for best results.

Melatonin phase response curve summary:
- To advance the circadian clock (sleepier earlier) give 2-8 hours before bedtime
- To maximally advance give 0.5mg 5 hours before bedtime
- To delay the circadian clock (sleepier later) give at core body temperature minimum (about 2 hours before wake) to midday
- To maximally delay give 0.5mg within 4 hours after habitual wake
- Melatonin taken around bedtime until 3 hours after mid sleep midpoint has minimal effect on the circadian clock

Light phase response curve summary:
- To advance the circadian clock (sleepier earlier) use bright light shortly after the core body temperature minimum (typically two hours before awakening) until early afternoon
- To delay the circadian clock (sleepier later) use bright light at time of dim light melatonin onset (typically two hours before bedtime) until two hours before wake
- The most effective duration is 6.7 hours of bright white though 60 minutes will provide about 40% of the shifting power

References:
1. Auger RR, Burgess HJ, Emens JS, Deriy LV, Thomas SM, Sharkey KM. Clinical practice guideline for the treatment of intrinsic circadian rhythm sleep-wake disorders: advanced sleep-wake phase disorder (ASWPD), delayed sleep-wake phase disorder (DSWPD), non-24-hour sleep-wake rhythm disorder (N24SWD), and


Patient 1: Peri-Ictal Imaging Changes in Brain Tumor Patients

With increased frequency of brain imaging in the setting of acute neurological changes, it has become increasingly appreciated within the neurology community that there can be acute peri-ictal MRI changes that can mimic other pathology\(^1\), including stroke\(^2\) or recurrent tumor\(^3\). This can be a particular concern in patients with a known history of glioma, for whom an abrupt increase in seizure activity may herald tumor recurrence.

While a high index of suspicion should be maintained for the possibility of recurrent tumor as a trigger for breakthrough seizures, it is now recognized that a pattern of focal cortical/leptomeningeal enhancement likely represents peri-ictal changes rather than tumor progression. T2/FLAIR imaging, diffusion-weighted imaging, and perfusion imaging findings can all be variable in the peri-ictal setting, adding to the challenge of recognizing this uncommon entity.

References:

\(^1\)Cole AJ: Status Epilepticus and Periictal Imaging. Epilepsia 45:72-77, 2004
L4-5 Spondylolisthesis with Dynamic Instability and Referred Pain to the Legs

Neurologists frequently see patients with low back pain radiating to a leg. While the cause is often nerve root injury, there are many instances in which the cause is unknown. Many of these patients eventually find their way to pain management physicians or programs and the focus of clinical care shifts to pain control, improved function, and (hopefully) improved quality of life. While it may be accurate to tell the patient there is no spinal cord, nerve root or nerve etiology for the pain, both the physician and patients are routinely and understandably frustrated by the lack of a more specific diagnosis or specific curative management.

From a diagnostic point of view, there are useful patient history indicators that low back pain radiating to the leg may suggest referred pain rather than radicular pain:
1) Pain that crosses multiple dermatomal distributions (e.g.-from the groin down the anterior thigh to the anterior knee crosses the L1, L2, and L3 dermatomes);
2) Pain lacking a burning or electrical quality by history (neuropathic symptoms) is less likely to be due to nerve root injury;
3) Leg pain not originating in the back, but in the buttock or upper thigh. When these findings are combined with the absence of focal findings on exam, then probability of a non-neurologic etiology for the pain increases substantially.

The patient presented today is one example of a specific, curable cause of chronic low back and leg pain that is within the diagnostic reach of the neurologist. The pain was chronic, shifted sides (!), and was precipitated by different changes in posture over time (initially worse with sitting and later worse with standing) suggested the lack of a structural injury to the peripheral nervous system. The lack of focal neurologic findings raised this probability further.

Spondylolisthesis refers to slippage of one vertebral body on another and comes in two varieties: 1) A fixed deformity apparent on sagittal images but not moving on flexion or extension x-rays; 2) A dynamic deformity that moves when comparing flexion and extension x-rays. The radiology group at UCSF uses the phrase *dynamic instability* when reporting this dynamic deformity and quantifies the severity of the slip in millimeters. Dynamic instability, found in the context of appropriate clinical symptoms as described by this patient, should almost always prompt a spine surgery referral for consideration of fusion at the mobile spine segment.

A precise and singular source of spine in the context of dynamic instability may not be obvious. Movement at the facet joints, tethering of the nerve roots in the foramina (usually accompanied by focal neurologic deficits), or tension on the adjacent disk during the dynamic movement are all potential pain generators. On some occasions, the patient will report pain over many years that then resolved. Spine
imaging may show bridging osteophytes connecting the adjacent vertebrae at the previously dynamic segment (auto fusion).

References
Patient X: Arterial Ischemic Stroke due to Focal Cerebral Arteriopathy-Inflammatory subtype (FCA-i)

The differential diagnosis for an *acute* onset hemiparesis in a child includes migraine with aura, post-ictal Todd’s hemiparesis, and stroke, ischemic or hemorrhagic. Brain tumors very rarely will present with acute hemiparesis due to bleeding into a tumor, or peritumoral edema encroaching on the motor strip. Demyelinating diseases more typically cause subacute onset hemiparesis (progressive over days). It can be impossible to distinguish stroke from migraine or post-ictal Todd’s on a clinical basis. Headache or seizure at stroke ictus is common in both hemorrhagic and ischemic stroke in children. A family history of migraine can be falsely reassuring, as ischemic stroke can trigger a migraine in a child with such a genetic predisposition. Hence, any child with a first-time acute hemiparesis—even with migraine features or a preceding seizure—should have urgent head imaging to rule out a stroke. Approximately half of childhood strokes are hemorrhagic, most often due to an underlying vascular malformation (brain arteriovenous malformation, AVM; or cavernous malformation); half are ischemic, mostly arterial ischemic stroke. As in adults, CT is insensitive to acute ischemic stroke, but highly sensitive to hemorrhage. MRI scans with DWI (diffusion weighted imaging) sequences are needed to rule out an acute infarction. Fortunately, DWI is relatively resistant to movement artifact, so usually can be accomplished without anesthesia in even young children.

Arterial ischemic stroke (AIS) affects 2.4 per 100,000 children, or almost 2,000 U.S. children, per year. While chronic conditions like congenital heart disease and sickle cell disease are risk factors for childhood AIS, most strokes occur in previously healthy children, and the majority are caused by an arteriopathy of the cervical or cerebral vessels. Arteriopathies confer a high risk of recurrent stroke in children—one in five children with arteriopathic stroke will have a second stroke within the year. Childhood arteriopathies include arterial dissection, moyamoya (which can be primary/idiopathic or secondary to diseases like Down syndrome and NF-1), and a unique disease called “focal cerebral arteriopathy—inflammatory subtype” (FCA-i; also known as transient cerebral arteriopathy, or TCA). FCA-i is a poorly understood focal vasculitis of the distal internal carotid artery (ICA) or its proximal branches (middle cerebral artery and anterior cerebral artery). FCA-i appears to be a monophasic illness, with rapid progression of the arteriopathy within the first days to weeks, followed by non-progression and some degree of improvement after 6 months. Old histopathology studies demonstrate that it can be caused by direct invasion of varicella zoster virus (VZV); more recent epidemiological studies implicate other herpes viruses, including herpes simplex virus type 1 (HSV-1). Current management includes aspirin and supportive care to prevent flow-related ischemic events; children can require ICU management with IV pressors until pial collaterals become established. The role for corticosteroids and anti-viral therapy (acyclovir) has not yet been established. Surgical revascularization is rarely indicated.
References


Recent Advances in Neurology

Case Summary

A 45 year old, otherwise healthy, man was referred for neck "spasms" and involuntary movements. First symptoms occurred at age 27, with mild posturing of his limbs. This dystonia very slowly progressed to his neck and became more disabling only age 40-45, when it began to impair his gait. By presentation, he had minimal parkinsonism on examination, but dystonic posturing of his legs, trunk, and neck led to gait impairment with occasional falls. Levodopa helped somewhat. Genetic testing was sent for Dopamine-responsive Dystonia (DRD) panel, and familial Parkinson’s disease (PD) panel. Patient was found to be PARK2 (+), with homozygous deletion of exon 4 in the parkin gene. Therefore, diagnosis was consistent with Young-Onset Parkinson’s disease (YOPD). Please note, since the time of this patient’s genetic test, a new system for nomenclature for genetic movement disorders has been proposed, with new names designated by the protein involved. Therefore, PARK2 is now called PARK-Parkin, (Marras et al).

YOPD is defined as Parkinson’s disease in which first symptoms occur before the age of 40 years. Mutations in the parkin gene are the most common genetic cause in YOPD, and is found in the majority of Autosomal Recessive PD. Parkin-associated PD commonly presents in childhood with dystonia in the legs, as with this case. It is slowly progressive, usually over decades, and involves more mild non-motor symptoms (minimal cognitive and autonomic burden) with the exception of behavioral features (which were seen in this patient). It also tends to be very responsive to treatment, with good outcomes in medical and surgical management.

YOPD is frequently misdiagnosed. Several reasons may account for this. (1) As only 10% of case of PD occur before the age of 50, physicians are not expecting PD in this young population. (2) When tremor is present in YOPD, there is commonly a large postural component which may lead to a diagnosis of Essential Tremor (which is more common in younger populations). (3) Finally, the YOPD syndromes frequently have a large dystonic component which can make diagnosis difficult by confounding the examination of parkinsonism, and by leading physicians on a large diagnostic expedition, given the large differential diagnosis of dystonia.

References
Spinal Cord tumors:

Spinal cord tumors can occur within or adjacent to the spinal cord. Primary spinal cord tumors account for 2-4% of all primary CNS tumors, and 1/3 are one-third are located in the intramedullary compartment. Spinal cord tumors can be classified according to their anatomic location. Intramedullary tumors arise within the spinal cord itself and are usually ependymomas, astrocytomas, or less commonly metastases. Intradural-extramedullary tumors arise within the dura but outside the spinal cord and are most commonly meningiomas and nerve sheath tumors. Extradural tumors are most commonly metastatic. This patient on imaging had evidence of an intramedullary mass. The majority of intramedullary spinal cord tumors are ependymomas, followed by astrocytomas, and rarely metastases or lymphoma. This particular lesion also had cauda equina involvement making a glioblastoma very unlikely. Ependymomas are intramedullary tumors that can occur anywhere is the spinal cord; approximately ½ are located in the lumbosacral region. Ependymomas are classified into four major groups including ependymoma, myxopapillary ependymoma, subependymoma, and anaplastic ependymoma.

Ependymomas are the most common intramedullary tumors in adults with a peak age of presentation between ages 30-40. Typically patients present with localized back pain, followed by neurologic symptoms that can include spasticity, loss of pain and temperature sensation, lower extremity and truncal sensory changes, and gait ataxia. Most commonly, ependymomas occur centrally within the spinal cord and can be associated with a tumor-associated cyst or syrinx. Typically, these lesions are enhancing on MRI. These are typically treated with surgery and in many cases gross total resection can be achieved. Although there is no randomized data, if a gross total resection is not achieved treatment with radiation should be considered. Rarely, ependymomas have more aggressive features on histologic examination including necrosis, mitosis, vascular proliferation and cellular pleomorphism, and can be classified as anaplastic. These tumors have ependymomas have a higher recurrence rate and poorer survival and radiation should be considered even in the setting of a gross total resection. Myxopapillary ependymomas most commonly arise in the lumbosacral spinal cord and filum terminale and are biologically and morphologically distinct from other ependymomas. They are slow-growing glial tumors that typically present in young adults and in men more commonly than woman. There presenting feature is usually pain without neurologic deficits. They do have a possibility of disseminating, and therefore complete brain and spine MR imaging and cerebrospinal fluid analysis should be performed. Management is surgical resection with a goal of a gross total resection. If a subtotal resection is achieved, consideration of radiation is recommended.

Astrocytomas can occur throughout the spinal cord and can either be pilocytic or infiltrative. Pilocytic astrocytomas are typically well circumscribed, low grade and are slow growing, but d enhance on contrast MRI. Infiltrative astrocytomas include low grade (grade II) astrocytomas, and high grade (grade III and IV, anaplastic astrocytoma and glioblastoma respectively). They are typically non-encapsulated lesions that enhance minimally or heterogeneously on MRI. About 50% of the high grade tumors have mutations in the histone coding genes, H3K27M which have been shown in highly aggressive midline tumors. Treatment for gliomas is typically surgical resection, followed by radiation with chemotherapy if high grade or residual tumor.
Glioproliferative lesion:

This patient underwent biopsy of his intramedullary mass that also had cauda equina involvement. The pathology demonstrated a highly cellular glial mass with a high rate of proliferation. However, when the DNA of the cells within the mass was compared to the patient, the majority of cellular DNA was not of the patient’s origin and therefore likely was introduced from endogenous stem cells. Furthermore, next generation sequencing did not reveal any typical mutations seen in cancer cells. Therefore, it was determined that this was a glioproliferative lesion, but was not a true cancer. The patient was treated with radiation and did achieve some symptomatic relief with pain, but he did not have any improvement in neurologic function. The lesion remains stable on MRI scan 1 year following radiation treatment.

Stem cells have been proposed to be the origin of cancer, and do have tumorigenic potential. Treatment with stem cells at this point is unregulated and can be harmful to patients. There is ongoing research on the benefit of stem cell therapy to patients especially with neurologic disease, but this research should be done in a controlled manner to limit negative consequences as was seen with this patient.

References
Recent Advances in Neurology: Difficult Diagnosis
A 61-year-old man with exercise-induced muscle spasms

Case Discussion: Neuromyotonia

Neuromyotonia (Isaacs syndrome) is a rare, treatable form of severe peripheral nerve hyperexcitability (PNH) characterized by muscle stiffness and, on needle EMG examinations of affected muscles, runs of extremely rapid electrical discharges. Milder examples of peripheral nerve hyperexcitability include myokymia, cramps, and fasciculations. There are wide variety of triggers for neuromyotonia (and PNH syndromes in general) that include toxins, infections, autoimmune factors, and even genetic disorders.

The clinical manifestations of neuromyotonia include muscle twitches, cramps, muscle stiffness, hyperhidrosis, muscle hypertrophy, and pseudo-myotonia. The muscle stiffness and muscle hypertrophy are consequences of the very frequent nerve discharges. Sometimes the muscle activity produces pseudo-athetoid finger movements. Pseudomyotonia refers to the slow relaxation of muscles after voluntary contraction. In this patient, pseudomyotonia was a prominent feature, though this feature is only present in a minority of patients. It can affect the limbs, eye, and mouth/jaw region. Occasionally, patients have weakness and occasionally sensory disturbances in the distal limbs.

Some patients with neuromyotonia have cerebral disturbances that include seizures, hallucinations, delusional episodes, and insomnia. This has been referred to as Morvan’s fibrillary chorea. In general, however, most patients with neuromyotonia do not manifest symptoms or signs of significant cerebral dysfunction. Likewise, patients with potassium–channel antibody–associated limbic encephalitis (characterized by memory loss, confusion, and seizures) usually do not manifest neuromyotonia, either neuro-physiologically or clinically.

Neuromyotonic discharges consist of spontaneous motor unit action discharges firing at extremely high frequencies (150–300 Hz). The runs of activity begin and end suddenly. The amplitude of the signals may vary, thus imparting a myotonic-like quality to the activity. It is the very high frequency of the discharges that is the key distinguishing feature from myotonic runs. Neuromyotonic discharges may be interspersed with myokymic runs as well as isolated doublet, triplet, or multiplet discharges. Standard motor nerve conduction studies may show afterdischarges trailing the compound muscle action potential.
Impairment of nerve potassium conductance underlies neuromyotonia. Most often the disease has an autoimmune basis, but, as mentioned earlier, there are multiple associated triggers/causes. Many different autoimmune disorders have been associated with neuromyotonia, including myasthenia gravis, Hashimoto’s thyroiditis, pernicious anemia, and celiac disease.

Approximately 40% of patients have antibodies to the voltage-gated potassium channel (VGKC). VGKCs are expressed in the peripheral, autonomic, and central nervous systems. Blockade of these channels increases nerve excitability and the repetitive nerve discharges. Recently, antibodies have been identified to components of the potassium channel complex, including leucine-rich glioma–activated protein 1 (LGI1) and contactin–associated protein 2 (Caspr2). Antibodies to LGI1 are associated with limbic encephalitis but not neuromyotonia. Patients with antibodies to Caspr2 may have neuromyotonia as well as CNS symptoms. In many cases despite recent advancements, the precise antigenic target responsible for neuromyotonia remains unknown.

In most cases, the generator site for the nerve discharges is the distal nerve arborization of the motor unit. At these sites, the potassium channels are not protected by the blood–nerve barrier.

Neuromyotonia responds to sodium-channel blocking drugs such as phenytoin and carbamazepine. Acetazolamide and gabapentin have also been reported to be effective. If symptomatic therapy is not enough, immune therapies can be effective. No controlled trials have been done. Anecdotally, plasma exchange is more effective than IVIG. Prednisone and azathioprine have also been used with success.

References:

Acquired Ataxia Case

Background. Late onset sporadic cerebellar ataxias represent a heterogeneous group of disorders including autoimmune (paraneoplastic and non-paraneoplastic), toxic, infectious and vitamin deficiency causes.

Cases of autoimmune ataxia have been associated with paraneoplastic and non-paraneoplastic disorders caused by antibodies that target ion channels or synaptic receptors in the brain. Paraneoplastic neurological syndromes (PNS) are rare manifestations of malignancies and may precede tumor diagnosis by years, thus follow-up is essential in cases of a clinically suspected paraneoplastic etiology with tumor screening every 3–6 months for up to 5 years. By definition they are not caused by direct effects of the tumor itself, metastasis or side effects of chemotherapy.

Paraneoplastic cerebellar degeneration (PCD) is one of the most common PNS. Its clinical presentation is usually of subacute onset and rapid progression leading to severe disability within weeks to months. Initial symptoms include vertigo, nausea and gait imbalance and as the syndrome progresses dysarthria, limb ataxia and nystagmus become more apparent. There are two categories of autoantibodies associated with PCD. The first group are antibodies directed against intracellular antigens (onconeural) and show frequent association with specific tumor types. The most frequent onconeural antibodies in PCD are anti-Yo (38 %), anti-Hu (36 %), anti-Ri (12 %) and anti-Tr (12 %). Example of tumors associated with specific antibodies includes small cell lung cancer (Hu, Ri, CV2, VGCC, Amphiphysin), breast and ovarian cancer (Yo, Ri) and Hodgkin lymphoma (Tr, mGluR1).

The second category of autoantibodies associated with PCD target cell surface antigens. These occur less frequently in PCD and include the metabotropic glutamate receptor 1 (anti-mGluR1) and voltage-gated calcium channel (anti-VGCC). Contrary to the onconeural antibodies, they are considered to be directly pathogenic and have shown a lower association to underlying malignancies. There are case reports of PCD with anti-VGCC that can present with isolated cerebellar ataxia, but more frequently these cases are complicated by coexisting Lambert–Eaton myasthenic syndrome, diffuse encephalopathy or peripheral neuropathy. Tumors associated with anti-VGCC include lung, breast and ovarian cancer.

In addition there have been case reports of anti-VGCC in the literature that have not found evidence for an underlying malignancy. Cases of anti-VGCC ataxia associated with cerebellar degeneration are confirmed by a typical clinical presentation in association with the detection of a specific paraneoplastic antibody and/or a tumor. Findings in CSF include mild inflammation with predominantly lymphocytic pleocytosis, elevated protein levels and elevated immunoglobulin synthesis. Imaging is necessary to exclude alternative diagnoses and to evaluate for the presence of cerebellar atrophy.

A prompt diagnosis and rapid initiation of treatment for the underlying tumor are essential for stabilizing PCD. In addition treatment with immunosuppressive agents has shown benefit in early disease with improvement in some cases or stabilization of the deficits. Commonly use first line therapies include steroids, intravenous immunoglobins (IVIG) and plasmapheresis. In more refractory cases, empiric treatment with rituximab, cyclophosphamide...
and other immunosuppression therapies such as tacrolimus and mycophenolate mofetil have been reported. Neurological outcome is usually poor especially in patients with persisting symptoms and development of cerebellar atrophy.

**Case report.** Our case describes a 59 yo white woman with subacute progressive ataxia. Negative family history of ataxia or other neurological disease. She has repeatedly had high titer +VGCC antibodies in serum (no CSF antibodies or inflammation). No Lambert-Eaton physiology on EMG-NCS or clinically. No lung cancer on body imaging including PET-CT. Her MRI at UCSF showed moderate atrophy involving the bilateral cerebellar hemispheres and central pons with abnormal signal intensity in the bilateral middle cerebellar peduncles. These findings are nonspecific, however can be seen in the setting of a toxic, metabolic, genetic or neurodegenerative process. She tested negative for Fragile X and had no toxic exposures.

She had perhaps a small, but not profound, clinical response to steroids or IVIG. She received empiric treatment with IV cyclophosphamide with stabilization of her symptoms after third treatment. In parallel, genetic testing with the complete autosomal dominant and recessive panels for ataxia evaluation reported a pathogenic heterozygous frameshift mutation in SYNE1 and an additional heterozygous missense mutation in SYNE1 (although unclear if on the same allele because her parents could not be tested), which was predicted to be a variant of unknown significance that is more likely benign.

**Summary.** Thus, our patient has +VGCC antibodies, 1 pathogenic SYNE1 allele in addition to another mutation in SYNE1 determined to be a variant of unknown significance. Immunologic therapy resulted in stabilization. Case reports of SYNE1 mutations have demonstrated cerebellar atrophy but not signal change in the MRI (and signal change is unusual for autoimmune ataxia as well). MSA C continues to be a possibility as the RBD and her findings on MRI scan are relatively strong markers for MSA.

**References**

3. Synofzik et al. SYNE1 ataxia is a common recessive ataxia with major non-cerebellar features: a large multi-centre study. BRAIN 2016: 139; 1378–1393